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"The Influence of Physical and Mechanical Factors in Tablet Making"

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Dedicated

to

My Dear Parents
The experimental work in connection with these investigations has been carried out at the School of Pharmacy of the Swiss Federal Institute of Technology, Zürich and partly at the Swiss Federal Institute of Materials Testing (E. M. P. A.), Zürich, under the guidance of Prof. Dr. K. Münzel. I wish to express my sincere thanks to my teacher, Prof. Dr. Münzel for providing me with the facilities to carry out this work and for his valuable advice throughout the course of this work.

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PREFACE

The tablet is to-day the most common form of medication for the administration of drugs in a dry state. Its preparation constitutes an important part of modern "Pharmaceutical Technology." Unfortunately there exists but very inadequate published data in pharmaceutical literature on the systematic scientific investigations made in this field.

In recent years, a systematic study on the subject was initiated at the School of Pharmacy, Swiss Federal Institute of Technology, Zürich, and a work was presented by W. Kägi as his Doctoral thesis in the year 1953 under the title:

"Ueber die Beeinflussung der Eigenschaften von Tabletten durch Arzneistoffe, Hilfsstoffe und Herstellungsverfahren".

In this study, Kägi investigated chiefly the influence of various auxiliary additions and the different methods of preparation on the properties of the tablets.

In the present work, these investigations have been carried further. Particular consideration has been given to the influence of various physical and mechanical factors in the preparation of the tablets and on the properties of the tablets produced.
INTRODUCTION

From a purely physical point of view, the technique of tablet making or 'tabletting' may be defined as a process whereby a known volume of a drug in a finely divided state is subjected to pressure in a die between two punches. A compact of well defined state known as a tablet thus results. A tablet shows definite properties of mechanical strength and is also characterised by a definite rate of disintegration when brought into contact with water.

It is generally observed that tablets can be made easily from certain drugs, such as sodium chloride and the other alkali halides, etc., even without the addition of auxiliary substances. For some other drugs, such as lactose, the addition of auxiliary substances is found to be necessary to overcome certain difficulties in their tabletting. The technique of tablet making has been based largely on the empirical knowledge derived from practice. Such knowledge has mostly been gained in the laboratories of commercial firms and has remained closely guarded as individual 'trade secrets.' Consequently, there does not exist much literature on fundamental studies of the technique of tablet making. Apart from certain investigations reported in the Danish pharmaceutical literature (1), it is only recently that various fundamental aspects of the tabletting process have been studied at some of the University laboratories. Higuchi and coworkers (2) and Münzel and coworkers (3) are among the pioneers in many aspects of this field. A considerable amount of work of fundamental nature on compressional processes, in many respects similar to that of tabletting, has been done in "powder metallurgy" and allied fields of plastics and ceramics. In the absence of sufficient fundamental information on tabletting, it is useful to draw some analogies from such other fields. Some of the most basic differences must,
however, be kept in mind while making such analogies. The compressional pressures used in “powder metallurgy” are on the average much greater than those required for tabletting. Moreover, metals are generally harder and more elastic than the tablet materials which are comparatively softer and liable to decomposition and plastic deformation.

(1) Theoretical considerations on the process of compressing powders:

Discussing the mechanism of compressing powders in “Powder metallurgy,” Seelig (4) subdivides it as follows:

(a) Packing: During this preliminary stage of compression, friction between the particles absorbs most of the compressional energy applied. This leads to a closer packing of the particles and voids in the substances are greatly reduced.

(b) Elastic and plastic deformation: During this stage, particle deformation and die-wall friction are the main energy consumers. Whereas the tablet materials may be considered as undergoing mainly a plastic deformation (no recovery on release of pressure), the metallic surfaces of the die may suffer some elastic deformation. The latter depends particularly on the magnitude of the pressure and the nature of the metal surface of the die.

(c) Cold working with or without fragmentation: In this final stage of compression, the tablet materials suffer fragmentation, which increases with increase in pressure. This fragmentation is accompanied by a corresponding increase in total surface area and reaches a maximum at a particular pressure which is an important characteristic of the different materials (5). There is no further increase in surface area beyond this point which may be followed by increasing and stronger bond formation.

A gross increase in surface to surface contact areas may also result in the increase of adhesive forces during this pressing action. A considerable degree of attrition
takes place between adjacent particle surfaces at this stage. It may involve pulverisation of protruding projections, thus obliterating the microscopic irregularities of the surface of the particles.

Goetzel (6) refers in a detailed review of the various concepts of the mechanism of bonding between particles when subjected to pressure, to a theory of "mechanical interlocking." Since smaller pressures are used in the tablet compression, the theory may also provide a good explanation of the bonding of average tablettng materials. Sintering of the particles of materials having a low melting point may occur if the pressure is too high during pressing. Such cases are, however, comparatively rare and such materials are seldom pressed without addition of auxiliaries since sintered compacts show very bad disintegration characteristics.

According to this theory of "mechanical interlocking," the pressure results in a shearing off of projecting points of the particles. The particles tend to move in the direction of the applied pressure thus involving the movement of some particles towards or past others and causing a slippage. This slippage is, of course, considerably affected by the interparticle friction, which, in turn is a function of the surface and contours of the particles. Thus more symmetrical particles will slip more easily than rougher ones, whilst the latter provide stronger interlocking and also produce a higher mechanical strength in the compacts. Kügi (7) had observed that tablets compressed from "pressed-granules"—which have more rugged surfaces—show comparatively greater mechanical strength, than those prepared from the more symmetrical "shaken-granules."

We carried out an experiment consisting of compressing a mixture of "pressed-granules" of phenacetine and sucrose prepared by granulating them separately with an aqueous, alcoholic mixture. Tablets thus compressed were kept in contact with water at ordinary temperature without movement for 24 hours. Most of the sucrose dissolved in the water during this time, leaving behind undisturbed the compressed skeleton
of the Phenacetine granules. A microscopical study of the nature of this deformation, also exhibited in the Photograph no. 1 to 4, showed that the individual granules form a great number of projecting tentacles. The photographs no. 1 and 2 show the granules of phenacetine and sucrose, before and after compression respectively. The photographs 3 and 4 show the typical deformation of the granules after compression into a tablet, and the projecting tentacles formed. These points have a great tendency to hook into each other to provide junctions for the bonding of the particles into a compact. This phenomenon of mechanical interlocking is also represented in a schematic diagram 1.

![Diagram 1. Packing scheme of the particles on compression.](image)

(2) The difficulties experienced during tablet making:

Some difficulties are occasionally experienced in the process of tabletting certain materials which give rise to broken or, in other cases, disfigured tablets. In extreme cases, it may become very difficult to compress some materials because of persistent binding or sticking in the tablet machine. The various causes and their remedies as given in the tablet literature are summarised in the following review. A systematic consideration of the individual factors involved in the
PHOTOGRAPH 1

Granules before compression (1×15 times enlarged)

PHOTOGRAPH 2

Granules after compression (1×15 times enlarged)
The skeleton of a tablet of the Phenacetine and Sucrose granules remaining after dissolving its Sucrose portion in water.
same then follows. The most important difficulties encountered in tabletting are "STICKING" and "CAPPING".

(A) STICKING (Binding ; Picking)

"Sticking" is a term employed if the granules adhere to the faces of the punches and the die. In certain cases the adherence may occur only in the die wall. This phenomenon is also commonly known as "binding". On the other hand, this adherence may occur mostly on the punch faces, and create a very rough surface of the tablets produced. This phenomenon is referred to as "picking". However, these different conditions can be included in the general term "sticking" since the various causes for all of them are essentially the same. The occurrence of "sticking" may be due to:

(a) the presence of too much moisture in the granules which in turn may be due to
   —insufficient drying;
   —absorption of moisture due to the hygroscopic nature of the material and to the presence of too much moisture in the atmosphere;
   —moisture released from the centre of a large granule when it is broken into smaller pieces.
(b) scratched or badly polished metal surfaces of the die and punches.
(c) too much die clearance with a very loose fitting lower punch, permitting large amounts of fine powder to fall through the aperture and cause high friction. In extreme cases, it may be accompanied by production of much noise typically termed "crying of the machine".

(B) CAPPING (Splitting ; Chipping ; Fissuring)

"Capping" is a term employed if one surface or the other (more commonly the upper one) splits off during or after ejection of the tablet from the die-cavity. Cracks or crevices may also be developed around the tablet without completely
splitting the tablet surfaces. This is known as "chipping" or "fissuring" etc. These can, however, also be included in the general term "CAPPING". It may be due to any of the following causes:

(a) too high a compressional pressure.
(b) an excessive amount of air or other gases adsorbed by the particles. With certain substances (aerophilic subst.) there is a great tendency towards air adsorption. The air is entrapped during the high speed compression process and expands suddenly on removal of the pressure to cause "capping".
(c) the presence of excess of fines (though the presence of a certain amount of fines i.e. about 20% maximum, is rather useful in filling up the voids and the irregularities of bigger particles).
(d) too soft granulation—which may be due to the use of insufficient binding agent or to excessive drying. The necessary coherent strength is then not imparted to the compressed tablets which cannot resist the action of friction during ejection.
(e) too dry granulation—which, as stated above, renders the binder less effective by converting it into a dried gel.
(f) certain crystalline forms of particular substances appear to cause persistent "capping" and they should be finely powdered before granulation.
(g) worn or badly polished metal surfaces of the die and punches. After continuous use, dies sometimes exhibit a "ring" due to wear at the point of compression. The tablet is then distorted when it is ejected through a comparatively narrow upper neck thus leading to "capping". Similarly, damage to the punch faces can cause the edges to be turned into hooks which pull off the top of the tablets after compression.
(h) the speed of compression. If this speed is too high, the punch has a stamping rather than a squeezing action and increases the probability of entrapment of air. It is better to compress aerophilic substances at comparatively low speeds.

Moe and Würzen (7) have reviewed the various concepts advanced to explain the phenomenon of “capping” occurring in tablet compression. Summarising, it may be considered as due to the following different causes:

(a) too dry a granulation which weakens binding properties.
(b) expansion of entrapped air on release of pressure.
(c) too high pressure leading to compression beyond the limit of elasticity and causing a slight expansion of the tablets after pressure release.
(d) a theory put forward by K. Pind (8) that the increased pressure, whilst increasing the density of the particles also leads to increased inter-particle friction which is responsible for a non-uniform distribution of pressure inside the tablet. This may lead to the formation of weak “pressure-pyramids” in the diagonal direction for a tablet of rectangular shape. The tablets formed tend to break along these weak points.

It is interesting to note that in the field of “powder-metallurgy” similar difficulties are also observed occasionally, and are known as “splitting” or “crack-formation”. It is quite useful at this stage to review the pertinent literature briefly. Seelig (9) and Goetzel (10) state in a detailed discussion of these problems that “crack-formation” which mostly occurs at an angle of about 45° to the die-wall, is caused by unfavourable pressing conditions. The various mechanical failures and their suggested causes are:

(a) a 45° shear failure which generally occurs on slow pressing of hard powders at moderate or high pressures and of soft powders at very high pressures. This failure may be eliminated by the use of a lubricant.
(b) another type of 45° failure appears at the edge of the compact and proceeds inwards in the form of lamination. It occurs primarily during very rapid pressing and is usually overcome by reducing the speed.

(c) an uneven filling of the die also creates shear stresses in addition to straight compression stresses and thus leads to laminar fractures.

(d) the high compression of air entrapped in many cavities within and between the particles results in expansion and lateral distortion on release of pressure.

(e) due to elastic expansion of the compact while leaving the die on ejection, the top sometimes becomes free to expand while the bottom is still retained in the die. If the compact is not strong enough to withstand this abrupt change in stress distribution, failures appear in the form of lamination in the top surface plane of the compact. To overcome this type of failure, it may be advisable to maintain the compact under pressure from the two opposite sides during ejection (as provided for in some of the Rotary type machines).

(f) An additional factor is the magnitude of the die-wall friction which offers high resistance to the coherent strength of the compact. Any local lack of uniformity in the density of the compact will exaggerate the effect of this factor. Such failures can be eliminated by the use of highly polished die-wall surfaces.

The above review of the various difficulties experienced during tablet compression shows that the main factors influencing them are either of a physical or of a mechanical nature and that they may be classified as follows:

**PHYSICAL FACTORS**:

(A) **Particle characteristics**
   (aa) Aerophilic or Hydrophilic nature
   (bb) Particle size distribution
   (cc) Crystal structure of substances
The binding properties of the particles

(B) Tablet size and shape

(C) The magnitude of compressional pressure

(D) The amount of moisture in the particles

(E) The atmospheric conditions

MECHANICAL FACTORS:

(A) The method and direction of pressing (type of machine)

(B) The speed of compression

(C) The die and punches

(aa) Degree of polishing of the surface

(bb) Materials of construction

(cc) Size and shape of the die and punches

(3) The influence of the various physical factors:

The various factors mentioned above and their possible influence can be considered individually as follows:

(A) Particle characteristics:

(aa) Aerophilic or Hydrophilic nature:

Finholt (11) in a discussion of the tabletting methods classifies the various tablet materials as hydrophilic or water-loving substances (such as starch, lactose, ferrotartrate, etc.) and aerophilic or air-loving substances (such as acetanilide, phenacetine, etc.). It is commonly observed that relatively speaking the aerophilic substances are more difficult to compress. This is possibly due to the fact that it is difficult to moisten such substances with aqueous solutions which facilitate application of a coating of binding agent to the individual particles. This difficulty may be overcome by imparting a hydrophilic nature to such substances by treatment with emulsifiers such as cetyl alcohol, tweens, etc., (12) or by mixture with hydrophilic substances such as starch, etc. They can also be moistened with a small volume of ether after treatment with binders such as gelatine solution, etc. The ether vapours help to displace the adsorbed airfilm, which hinders contact
between binder solution and the particle surface. An acidified, alcoholic solution of gelatine may be used with equal advantage as wetting agent.

(bb) Particle size distribution:

It is often found easier to compress granules of rather uniform size although various amounts of fines can be tolerated and are sometimes necessary for proper compression of the tablets. Busse and Uhl (13) remark that harder granules will tolerate greater amounts of fines than softer ones. Silver and Clarkson (14) recommend an amount of 10-20% fines as being quite satisfactory for general purposes, although particular cases may require individual consideration.

(cc) Crystal structure of substances:

It is known that certain crystalline substances such as sodium chloride and other alkali halides are very easy to compress even directly. Others exhibit particular crystal forms which are consistently difficult to compress. For successful tableting, they should be obtained in some other crystal form. Typical examples are aspirine, calcium lactate, ferrous sulph. excitated, dry ext. of sagrada, etc. (15). Kregiel (16) has made some interesting observations in this connection, "that substances belonging to the cubic crystal system present no difficulty on direct compression whilst those of the monoclinic crystal system usually stick to the punches. In addition, crystal system of the elements of practically every group of the periodic table is common to all the elements of the same group." In "powder metallurgy" also, Goetzel (17) states that susceptibility of metals to plastic deformation depends largely on their crystal structure. Most metals with a face centered cubic lattice are more easily deformable than those with a body centered cubic lattice which require comparatively much higher compacting pressures. It is interesting to note that the lubricant action of some of the most important solid lubricants, such as graphite and talc etc., is attributed to their lamellar crystal structure, which permits uniform splitting and easy gliding of one part over the other. Higuchi and coworkers (18) claim establishment of tentative correla-
tions between ionic structure, melting point, and hardness of sub-
stances and their compressional behaviour. Sufficient work has
not yet been done in this direction. Further investigations are
required to establish generalisations of such fundamental nature.

(dd) The binding properties of the particles:

Some substances, for example, the sugars, possess very
good natural binding properties. Some additional binding
agent must be added to others, however, to impart such
properties, which help in forming a compact with sufficient
coherent strength even when comparatively lower pressures
are used. A certain percentage of moisture must also be present
in such granules during compression to ensure a more efficient
action of the binding agents; these agents form dried gels
when excessively dried.

(B) Tablet size and shape:

The size, particularly the ratio of height to the diameter
of the tablets, and the particular shape of the tablets can
also influence the ease of compression and needs proper
selection. It is often noted that deeply biconvex tablets show
much greater tendency to "capping". The distribution of
pressure and accordingly the density distribution within the
tablets possibly play an important part.

(C) The magnitude of the compressional pressure:

The application of different pressures during tabletting
plays a very important role. The correct pressure must be
applied in order to avoid unnecessary complications. During
recent years, a number of investigations have been made,
showing the effect of varying pressures on the general
properties of the tablets. Studies to determine the effect of
different compressing pressures on the ease of compression
or "compactability" of different materials do not seem to
have been made. Compactability is a term indicating capa-
bility of formation of a well shaped, coherent compact which
can be properly compressed as well as ejected out of the
die-cavity. It is generally found, however, that application
of more than "optimum-pressure" during tabletting is an
important factor causing "capping". Hence it is necessary to work with the minimum pressure, imparting sufficient mechanical strength to the tablets. This is dependant on the ultimate use of the tablets. Thus, "lozenges" or similar tablets, which should dissolve slowly in the mouth, must be more strongly compressed than other average tablets for internal administration. Another important effect of higher pressures is an increase in friction, which obviously necessitates the use of greater amounts of lubricants.

(D) The amount of moisture in the particles:

Another important factor which varies from one manufacturer to another and for the same manufacturer from one batch of the same tablet granulation to another, is the amount of moisture present in the particles. The variations are primarily due to different humidity conditions in different places and at different seasons and also to the method of drying the granules. Apart from a few larger manufacturers who control the moisture content of their granules before tabletting, this content is very seldom standardised in general practice. Empirical knowledge indicates, however, that too dry granules sometimes cause "capping", whilst overmoist granules are mainly responsible for "sticking". Wiirtzen (19) in his pioneer work on the subject showed that phenacetine could only be tabletted satisfactorily at a moisture content of 2.23-2.54%. Below or above that amount there was tendency to "capping" or "sticking", respectively.

(E) Atmospheric conditions:

Frequent changes in atmospheric humidity and temperature during the day and the night as well as in different weathers and different places may affect the moisture content of the granules and the compressing temperature of the tablet machine in different ways. It is common practice for larger manufacturers to work under conditions of humidity and temperature strictly controlled by use of air-conditioning installations. Ferrand (20) states in an interesting review on tablet preparation that many tablet materials normally difficult
to compress, can be tabletted much more easily on compression at 10% humidity. He further suggests investigations on the influence of tabletting under reduced pressure.

(4) The influence of various mechanical factors:

(A) Method and direction of pressing:

Two types of machines, namely the rotary and the eccentric type, are commonly used in the preparation of tablets. These types differ both in the manner of application of pressure and in construction. The eccentric machines apply pressure only from the upper side. Rotary machines, on the other hand, press from both the upper and the lower sides simultaneously. Some of the rotary machines are so constructed that the upper punch remains on the pressed tablet for a short time during which the lower punch ejects the tablet from the die-cavity. The latter method of application of pressure has the advantage compared with the former method that it gradually squeezes out air entrapped in the material. This helps in avoiding the "capping" tendencies of certain materials. Moreover, the use of rotary machines ensures uniform pressure and density distribution throughout the tablet.

(B) Speed of compression:

It is a general tendency to run the tablet machines at the highest possible speed so as to obtain the maximum possible output. It is often observed that certain substances, particularly of less deformable and aerophilic nature, are very susceptible to difficulties such as "capping." High speed, like high pressures, releases frictional, thermal, and electrical energy which may lead to a softening of certain substances with lower melting points and thus cause "sticking" tendencies. Many such difficulties can be overcome by running the machines at lower speeds.

(C) The die and Punches:

(aa) Surface polish and materials of construction:

The presence of slight scratches or insufficient polishing of the surfaces of the die and punches can also cause "sticking" and "capping." Use of better polished and stronger metallic
surfaces of the die and punches permits reduction of the amount of "lubricant." Little and Mitchell (21) discuss the compression of substances for which the use of lubricants is not permitted and suggest the use of dies and punches made of non-ferrous metals, such as phospho-bronze, etc. Burlinson (22) refers to the abrasive nature of certain vegetable drugs, for example, powdered digitalis leaf, which exert an extremely harmful effect on the surfaces of ordinary steel dies and punches and also cause "capping." In such cases, he recommends the use of dies and punches made of tungsten carbide, one of the hardest alloys known. It can withstand the action of even the most abrasive substances without suffering damage to its mirror-like surface.

Janson (23) has written a comprehensive review on the manufacture of different tablet implements (dies and punches etc.). He states that only special steels containing chromium, manganese, vanadium, tungsten, etc., as constituents should be used even for average dies and punches. In no case should ordinary carbon steel be used. He further stresses the necessity of ensuring the highest possible surface finish on the die and punch linings. For ordinary purposes the punch and die surfaces are usually polished and buffed with abrasive powders such as tin oxide, emery, etc., on fine brushes running at high speeds. Janson, however, refers to the complicated machinery and techniques used by the bigger manufacturers of such implements to ensure an absolutely smooth surface without the slightest scratch. Referring to the hard chromium linings sometimes used for covering ordinary steel die and punch surfaces, Janson stresses that hard chromium plating must be differentiated from chrome polishing. The difference in these two processes, he states, lies in the fact that only hard chromium plating exerts a useful action in reducing friction.

Goetzel (24) has discussed in great detail the problems connected with the construction and use of dies and punches for "powder metallurgy." He states, with reference to general wear and tear and strength of the dies used: "expressed in
terms of the life of the die or the number of operations before it is worn out beyond the highest tolerance permissible, it can be said that tungsten carbide is at least ten times superior to hard chrome plated tool steels, which in turn are about five to ten times superior to high chrome/high carbon tool steel. Among the different steels, water hardened medium carbon steel has the lowest resistance."

It is usual to employ linings of the above-mentioned strong alloys on a relatively cheap steel base because of the cost of such alloys. Goetzell gives the following order of such linings based on their comparative strength:


Ferrand (24) suggests the use of siliconised die and punches to reduce friction during tablet compression.

(bb) Size and shape of die and punches:

Besides the nature of the materials of construction, it is also important to have a proper clearance between the die and the punches. Smith (25) suggests that the maximum clearance between die and punches for diameters ranging from 3 mm to 12.5 mm should be not more than 3% of the standard measurements. The degree of curvature of concave punches and the ratio of the thickness at the edges to that at the central crown must also be taken into consideration. Smith further suggests that the punches used for the preparation of convex-faced tablets of 10 mm diameter should have a radius of curvature of 15 mm for uncoated tablets and 7.5 mm for tablets which are subsequently to be coated. Thus, tablets for coating should have a greater convexity and much thinner edges.

The dies are sometimes modified mechanically to ease ejection of the tablets, if the addition of lubricants is not permitted. Quite often, the end of the opening of the die-cavity is
slightly tapered. The beneficial action of such tapering is limited to a very small angle beyond which it shows very little improvement. The purpose of such tapering is to relieve the stress imposed on the compact by the elastically over-expanded die and may be achieved by a minute enlargement of the die-cavity in the direction of ejection. Alternatively, some method of internal lubrication of the inner die-wall may also be used. This can be done by making an undercut on the lower punch and wrapping a piece of worsted soaked in liquid paraffin on this cut. It may also be achieved by some special lubricating device (26) fitted on the lower punch; the lubricant is forced along a special track drilled in the lower punch with outlets about half-way up the punch stem. The lubricant thus distributes itself around the inner wall of the die. In some cases, the lubricant can be injected through the die.

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"The Evaluation of Starches as Tablet Lubricants"

1. INTRODUCTION

In a study of the lubricants used in tablet making, Münzel and Kägi (1) have differentiated and classified these auxiliary substances as follows:

(1) "Gleitmittel" or "Glidants" : substances which improve the flowing or gliding properties of the tablet materials. They are generally powdery substances which deform only slightly when subjected to the compressing pressures.

(2) "Antiadhesives" or "Lubricants" : substances which facilitate smooth ejection of the compressed tablets from the die and also prevent their sticking to the metallic surfaces of the die and punches. They are mostly deformable under pressure and do not always improve the flow of the tablet materials under normal conditions.

The use of different terminologies in different languages to define these substances has led to a slight confusion. In German and the Scandinavian languages, the term "Gleitmittel" denotes the function of improving the gliding properties of the materials. Hence most of the workers in this field using such nomenclature based their methods of evaluation of such substances mainly on their property of increasing the flow rate of different materials. Quite recently Hansen (2), in a study of magnesium stearate as a "Gleitmittel", investigated mainly its effect in improving the flow rate of different materials and the related accuracy of dosage of the tablets produced. On the other hand, the term "lubricant" is generally used in the English language for substances which show antisticking properties and reduce friction between bodies subjected to pressures. Most of the investigations undertaken by people using this terminology, were based until recently (3) on evaluation of
anti-sticking properties or facilitation of the ejection of compressed tablets. In order to clarify this situation, we propose a term "QLIDANT" corresponding to the German word "Gleitmittel". It must, however, be emphasised that there really exists a genuine need to differentiate these two classes of substances, based on their somewhat different functions. On the one hand there exist substances, such as paraffin oil and stearic acid, which show anti-sticking properties but hinder the flow of the tablet materials under normal conditions. Thus they are only "lubricants" (Schmiermittel; Anti-adhesives; Gegenklebmittel). On the other hand, other substances, such as natural starch, have excellent flow improvement properties, as shown by our present investigations, but they have almost no action in facilitating ejection of compressed tablets. These substances may therefore be termed "glidants" (Gleitmittel). There also exist a few substances, such as talc, which may be included in either of these groups. While considering the nature of action of the two classes, it must be pointed out that "glidants" have to act only under normal gravity and the weight of the granules in the feed container. "Lubricants" must rather smooth out the flow or ejection of a completely deformed and densely compressed mass.

2. Theoretical considerations on the mode of action of "glidants"

As stated above, "glidants" are added to the tablet materials to improve their flow properties. The flow rate denotes the speed at which the materials flow over an inclined surface of the hopper or the feeder shoe. The flow of the material is produced by a kind of shear stress. When the material is moved by gravity alone, this stress is proportional to the loading weight of the tablet granules in the container, provided the cross-section of the flowing stream remains unchanged. The resistance to flow among different particles is primarily indicated by the amount of inter-particle friction. This resistance depends also on the distance within which one particle interferes with the free movement of
other particles either by direct or indirect contact. The particles may be prevented from moving separately by temporary adherence or interlocking with one another. Thus clusters are formed which may occupy a considerable space. The phenomenon of cluster formation depends on the morphological characteristics of the material and varies markedly with the size, shape and structure of the particles. If all the particles were truly spherical, they would generally roll more readily. It has been observed by Kägi (4) that "shaken-granules" prepared by shaking the moist mass on a sieve, show better flow than "pressed-granules" prepared by pressing the mass through the sieve. This is mainly due to the more symmetrical form of the former type of granules.

Thus the "flow" of materials is dependent upon the following factors:

(a) the coefficient of interparticle friction

(b) particle size distribution: a certain percentage of fines is useful in filling up the voids of the bigger particles, but a very large amount of fines may lead to poor flow.

(c) particle shape: "pressed granules" with a long, irregular shape flow relatively badly compared with the more symmetrical "shaken granules."

(d) the amount of adsorbed moisture in the particles: moist materials do not flow as well as dry substances.

The manner in which "glidants" act in improving flow of tablet materials has been explained by Münzel and Kägi (5). They decrease adhesion between the granules themselves on the one hand and between the granules and the wall of the container on the other hand. The symmetrical, smooth shape and surface of these additives help to fill up the irregularities of the original particles and thus lead to a more rapid and more uniform flow.

3. Starches as "glidants" or "lubricants"

The use of starch as an auxiliary in tablet making has been
recognised for a very long time. So much so that Kägi (6) refers to starch as "universal auxiliary agent" for tablet making. Simultaneously he refers to a few other functions of starches which have not yet been clarified and which need further investigation. This remark applies more particularly to their use as lubricant in tablet making. So far controversial opinions based merely on empirical experience have been expressed on this matter. Another important question that needs clarification is the comparative efficiency of different varieties of starch and their derivatives. It is often found that certain varieties of starch are recommended in preference to the others.

Kerr (7) suggests that the following factors may be considered as mainly responsible for the lack of mobility of certain starch samples:

(a) high percentage of ether extractives.
(b) high percentage of water extractives which cause tackiness on exposure to humid atmospheres.
(c) electrostatic charges.
(d) prolonged heating in a dry state.
(e) high moisture content.
(f) the shape and size of starch grains or aggregates.

Most of these differences can be avoided by selecting a starch of pharmocopoea quality. The important variables still remaining are moisture content, shape, and grain size of the different varieties of starch. The average moisture content of air dried starch lies between 10-13% but is slightly higher in potato starch at about 15%. Discussing the relative mobility of different starches, Kerr suggests that careful drying to 5% moisture content might produce a greater mobility. This possibly represents complete removal of all the surface moisture and the residual 5% moisture may be considered as bound water. If, however, drying is carried to completion by the use of higher temperatures and longer periods irreversible changes may be produced in the properties of the
starch. It develops a lack of mobility which is characteristic of some dextrines.

The shape and size of the grains of different starches may be summarised as follows:

**TABLE I**

<table>
<thead>
<tr>
<th>Variety of starch</th>
<th>Shape and size of component granules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylum solani</td>
<td>mostly simple granules, ovoid or spherical often somewhat flattened; ovoid gran, 30-100μ and sub-spherical gran, 10-35μ in diameter.</td>
</tr>
<tr>
<td>Amylum maydis</td>
<td>polyhedral or rounded gran, about 10-30μ in diameter.</td>
</tr>
<tr>
<td>Amylum oryzae</td>
<td>simple and compound gran, single gran, about 2-12μ in diameter; compound gran, ovoid, usually 12-30μ long and 7-12μ wide and contain from 2-150 components.</td>
</tr>
<tr>
<td>Amylum tritici</td>
<td>mostly simple gran, with a circular or oval form; smaller gran, 5-10μ and larger gran, 20-25 or up to 50μ in greatest diameter.</td>
</tr>
<tr>
<td>Amylum marantae</td>
<td>mostly simple gran, of oval shape, ranging in length from 15-70μ with a fairly average size of 25-50μ in length.</td>
</tr>
</tbody>
</table>

For further details, refer B. P. 1953, p.514

Starch derivatives which are claimed to help in compressing various tablet materials are sometimes offered (8). Some non-swelling starch derivatives** (9) are also often suggested as substitutes for talc as "lubricant" for surgeon's gloves during surgical operations. These derivatives are mostly etherified starches which lose most of their swelling properties by chemical treatment. For our investigations, we selected, in addition

* no literature available, but only an indication of the manufacturing firms,
to acid-hydrolysed soluble starch, a commercial sample of non-mucillagenous starch A.N.M. Puder (9b) as well as two other varieties of non-swelling ether starches which we prepared ourselves. The following list includes all the different varieties of starch and starch-derivatives used in our present investigations:

1. Amylum solani (Potato starch)
2. Amylum maydis (Corn starch)
3. Amylum oryzae (Rice starch)
4. Amylum tritici (Wheat starch)
5. Amylum maranta (Arrowroot starch)
6. Amylum solani dried
7. Amylum solubile Pharm. Danica IX (Soluble starch)
8. A.N.M. Puder (9)
9. A.N.M. Puder + 2% Magnesium oxide
10. Ether starch sample A (Seth)
11. Ether starch sample A + 2% Magnesium oxide
12. Ether starch sample B (Flury)
13. Ether starch sample B + 2% Magnesium oxide

The flow properties of pure lactose granules, as altered by the above-mentioned starches, were compared with the alterations produced by adding similar amounts of talc. Münzel and Kägi (10) had shown it to be an effective method for comparing the "glidant" properties of the different substances.

Some of the above mentioned starches were tested also for the "lubricant" action. The method of evaluation was based on the property of a lubricant to decrease the force of ejection required to eject the tablets out of the die, after compression. The following starches were selected for this test:

- Amylum maydis (Corn starch)
- Ether starch sample A (Seth)
- Ether starch sample A + 2% Magnesium oxide
- Ether starch sample B (Flury)
- Ether starch sample B + 2% Magnesium oxide

These starches were added in amounts of 10% of the weight of the granules and were thoroughly mixed together before
compression. Their "lubricant" property was compared with that of talc, which was also added to the granules in similar proportions.

4. Experimental

Preparation of dried Amylum solani:

Accurately weighed amounts of 1, 3, 5, 10, 15, 20% of Amylum solani were placed in separate china dishes and spread out in thin layers. They were kept in a hot air oven at a temperature of 40°C for a period of 24 hours. Each of these portions of dried starch was taken out of the oven just before mixing with the granules. The moisture analysis of the starches was made with Karl Fischer Reagent which showed a moisture content of 13.3% in ordinary undried starch and 3.5% in dried starch.

Preparation of ether starch derivatives (11):

700 gm of Amylum maydis were gradually moistened with a filtered solution of potassium hydroxide (35 gm dissolved in 140 gm of absolute alcohol) and the whole mass thoroughly mixed. 35 gm of epichlorhydrine dissolved in 70 gm absolute alcohol was added to the moist mass and the whole again mixed very thoroughly. After keeping for a period of half an hour, the powder was spread out in thin layers and dried in an oven at a temperature of 40°C for 3 hours. The dried powder was passed through sieve IV Ph. Helv. V (225 meshes per cm²). The whole treatment was repeated on the dried powder and finally the starch derivative thus obtained was repeatedly washed with distilled water until the washings gave no further coloration with phenolphthaline solution. The product was dried completely in an air oven at 40°C and sieved again. The starch derivative thus prepared was tested for loss in swelling properties (12). A certain percentage of magnesium oxide is added to some trade samples of such starch derivatives and is said to improve their mobility. We therefore investigated the pure samples as well as others to which 2% of magnesium oxide had been added for comparison.
PHOTOGRAPH 5

Brinell Press
Quantitative evaluation of the "flow" of the granules and comparison of the efficiency of different "glidants" was effected by the method of Münzel and Kägi (10).

We used in our experiments pure lactose (Sacharum lactis Ph. Helv. V) granulated with 30 gm of a solution of soluble starch (Amylum solubile Ph. Danica IX) for every 100 gm of lactose. The granules were pressed through sieve III Ph.Helv. V (16 mesh per cm²) and dried overnight at room temperature (20°) followed by drying for 3 hours in a hot air oven at 40°C. The dried granules were separated from fines by passage through sieve IV Ph. Helv. V (225 mesh per cm²). The "glidants" in powder form were sieved through sieve IVa Ph. Helv. V (400 meshes per cm²) and finely spread over the granules. The granules were placed in a glass bottle and rotated for five minutes to ensure thorough mixing with the glidant. Exactly 150 gm of granules were taken each time and the "glidants" added in increasing amounts of 1, 3, 5, 10, 15, 20 per cent of the weight of granules. The mixed granules were allowed to flow through the "dispensing funnel" for 10 seconds every time.

The measurement of the force of ejection of the compressed tablets, with the Brinell Press

The Brinell press has already been referred by Kägi (13) and is also shown in the photograph no. 5. It is a hydraulic press used more commonly for the metal hardness testing. It enables the application of known amounts of pressure which can be read in kg on the attached dial. The pressure is applied by raising of a platform of a metallic flask by continuous flow of oil on opening a valve. This platform forms the bottom of the pressing system and presses the object against an upper stationary metal head. Pressure can be applied by the use of two different flasks. The outer, larger metal flask can apply up to maximum total pressures of 5000 kg whereas, under similar conditions the smaller flask applies one-tenth of this pressure. Hence to read off the pressure applied by the smaller flask, the pressures indicated on the dial scale should be reduced to one-tenth, since it is calibrated for the larger flask.
In our experiments, the larger flask was used to apply the compressional force, whilst the smaller flask was used for ejection. After compressing the tablet, the upper punch was removed and the die was inverted so that the lower punch now faced the stationary metal head. In absence of any bottom support for the tablet in the die now, it is ejected out when the smaller metal flask rises and pushes the punch from above. The speed of elevation of the flask was maintained at a minimum and remained constant throughout the experiment. The force applied, on raising the metal flask, was indicated by a corresponding movement of an indicating needle along the calibrated scale of the dial.

The granules were accurately weighed into amounts of 100 mg and carefully transferred into the die-cavity whose bottom was supported by the lower punch. After inserting the upper punch at the top, the whole set was placed in the Brinell press for compression. A die of 6 mm diameter and flat faced circular punches were used for the compression. The compressing pressures were maintained to constant total force of 500 kg (equivalent to 1770 kg/cm²) throughout these experiments.

5. Results

The results of the above mentioned experiments are presented in the following tables (2-4) and diagrams 2 and 3:
### TABLE 2

The "GLIDANT" action of different varieties of starch

<table>
<thead>
<tr>
<th>S. No.</th>
<th>GLIDANT</th>
<th>Amount %</th>
<th>Average wt. gm. X</th>
<th>Standard deviation S. rel.</th>
<th>Flow-factor f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Lactose</td>
<td>—</td>
<td>105.89</td>
<td>1.89</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>1 Talc</td>
<td>1</td>
<td>107.07</td>
<td>1.05</td>
<td>1.011</td>
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<tr>
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<td>120.58</td>
<td>2.07</td>
<td>1.138</td>
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</tr>
<tr>
<td></td>
<td>15</td>
<td>123.25</td>
<td>1.30</td>
<td>1.164</td>
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<td>2 Amyl. solani</td>
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<td>120.61</td>
<td>0.99</td>
<td>1.139</td>
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<td>128.08</td>
<td>1.09</td>
<td>1.219</td>
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<tr>
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<td>15</td>
<td>138.61</td>
<td>1.45</td>
<td>1.309</td>
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<td>20</td>
<td>151.21</td>
<td>1.66</td>
<td>1.423</td>
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<tr>
<td>3 Amyl. Solani (dried)</td>
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<td>110.97</td>
<td>1.49</td>
<td>1.048</td>
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<td>2.26</td>
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<td>151.21</td>
<td>1.25</td>
<td>1.423</td>
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<td>6 Amyl. tritici</td>
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<td>139.03</td>
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</tr>
</tbody>
</table>
Diagram 2.—The influence of different varieties of Starch added as "glidants" on the increase of flow rate of pure lactose granules.
**TABLE 3**

The "GLIDANT" action of various derivatives of starch

<table>
<thead>
<tr>
<th>S. No.</th>
<th>GLIDANT</th>
<th>Amount in gm.</th>
<th>Average wt. X</th>
<th>Standard deviation S. rel.</th>
<th>Flow-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pure Lactose</td>
<td>—</td>
<td>105.89</td>
<td>1.89</td>
<td>1.000</td>
</tr>
<tr>
<td>1</td>
<td>Amyl. solubile</td>
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<td>113.07</td>
<td>1.24</td>
<td>1.068</td>
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<td>1.28</td>
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<td>115.42</td>
<td>3.07</td>
<td>1.090</td>
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<tr>
<td></td>
<td>+ 2% Mag. Oxide</td>
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<td>119.65</td>
<td>1.50</td>
<td>1.130</td>
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<td></td>
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<td>124.42</td>
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<td>148.14</td>
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<td>Ether starch (sample A)</td>
<td>1</td>
<td>108.74</td>
<td>1.50</td>
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<tr>
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<td>115.20</td>
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<td>115.52</td>
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<td>121.24</td>
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<td>1.145</td>
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<td>128.86</td>
<td>1.73</td>
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<td>20</td>
<td>131.51</td>
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<td>1.242</td>
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<td>Ether starch (A)</td>
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<td>2.89</td>
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<td></td>
<td>+ 2% Mag. Oxide</td>
<td>3</td>
<td>115.73</td>
<td>2.19</td>
<td>1.093</td>
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<td>5</td>
<td>123.78</td>
<td>2.05</td>
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<td>10</td>
<td>128.33</td>
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<td>15</td>
<td>137.65</td>
<td>3.02</td>
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<td>144.32</td>
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<td>113.40</td>
<td>1.57</td>
<td>1.071</td>
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<td>119.02</td>
<td>1.16</td>
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<td>5</td>
<td>119.97</td>
<td>1.62</td>
<td>1.133</td>
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<td>10</td>
<td>123.89</td>
<td>1.94</td>
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<td>15</td>
<td>138.18</td>
<td>1.11</td>
<td>1.305</td>
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<td></td>
<td>20</td>
<td>138.71</td>
<td>1.94</td>
<td>1.310</td>
</tr>
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<td>7</td>
<td>Ether starch (B)</td>
<td>1</td>
<td>110.44</td>
<td>1.57</td>
<td>1.043</td>
</tr>
<tr>
<td></td>
<td>+ 2% Mag. Oxide</td>
<td>3</td>
<td>116.79</td>
<td>1.99</td>
<td>1.103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>122.40</td>
<td>3.05</td>
<td>1.156</td>
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<td></td>
<td>10</td>
<td>128.76</td>
<td>1.46</td>
<td>1.216</td>
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<td></td>
<td></td>
<td>15</td>
<td>133.95</td>
<td>2.31</td>
<td>1.265</td>
</tr>
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<td></td>
<td></td>
<td>20</td>
<td>139.45</td>
<td>2.08</td>
<td>1.317</td>
</tr>
</tbody>
</table>
Diagram 3.—The influence of various derivatives of starch added as "glidants" on the increase of flow rate of pure lactose granules.
**TABLE 4**

The force of ejection in kg to eject the tablet out of the die, after compression in the Brinell press with force of 500 kg per tablet (equivalent to 1770 kg/cm²).

<table>
<thead>
<tr>
<th>Tablet material</th>
<th>Average force of ejection in kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Lactose granules</td>
<td>72.0</td>
</tr>
<tr>
<td>&quot; &quot; + Talc 10%</td>
<td>17.6</td>
</tr>
<tr>
<td>&quot; &quot; + Amylum maydis 10%</td>
<td>52.0</td>
</tr>
<tr>
<td>&quot; &quot; + Ether starch A 10%</td>
<td>57.0</td>
</tr>
<tr>
<td>&quot; &quot; + &quot; and 2% Mag. oxide 10%</td>
<td>64.2</td>
</tr>
<tr>
<td>&quot; &quot; + Ether starch B 10%</td>
<td>58.8</td>
</tr>
<tr>
<td>&quot; &quot; + &quot; and 2% Mag. oxide 10%</td>
<td>75.2</td>
</tr>
</tbody>
</table>

6. Discussion

(1) "Glidant" action of different varieties of starch:

It is quite evident from the results in the Table and Diagram 2 that all the varieties of natural starch possess very good "glidant" properties. On addition to pure lactose granules they improve the flow of the latter to a considerable extent. The investigations made by Kägi (13) showed that talc and carbowax 6000 possessed the best "glidant" properties. Our present study proves that starches can have as much as twice the effect of talc in increasing flow at the same proportion of 20% by weight of the granules.

Efforts have long been made to find a therapeutically indifferent substitute for talc, which is equally effective in "glidant" properties. Starches have not merely similar but much better "glidant" action. In addition to being indifferent, they also possess the advantage of functioning as "disintegrants" of the compressed tablets. It must, however, also be emphasised that our further investigations showed that unlike talc (which also possesses good lubricant properties), starches only have "glidant" properties without any lubricant effect. When, however, substances difficult to compress have...
to be tabletted, the "glidant" action of starches must be supplemented by the addition of some lubricant or other means of lubrication.

Our investigations show that there does not exist a very significant difference in the efficiency of different varieties of starch. Our results permit classification of the different types of starch in the following order of "glidant" efficiency:

**TABLE 5**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>GLIDANT</th>
<th>1%</th>
<th>3%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amyl. solani</td>
<td>1,055</td>
<td>1,110</td>
<td>1,139</td>
<td>1,219</td>
<td>1,309</td>
<td>1,428</td>
</tr>
<tr>
<td>2</td>
<td>&quot; dried</td>
<td>1,048</td>
<td>1,076</td>
<td>1,100</td>
<td>1,193</td>
<td>1,311</td>
<td>1,428</td>
</tr>
<tr>
<td>3</td>
<td>Amyl. maranta</td>
<td>1,104</td>
<td>1,143</td>
<td>1,172</td>
<td>1,267</td>
<td>1,311</td>
<td>1,383</td>
</tr>
<tr>
<td>4</td>
<td>Amyl. maydis</td>
<td>1,042</td>
<td>1,089</td>
<td>1,117</td>
<td>1,194</td>
<td>1,281</td>
<td>1,346</td>
</tr>
<tr>
<td>5</td>
<td>Amyl. tritici</td>
<td>1,093</td>
<td>1,129</td>
<td>1,155</td>
<td>1,212</td>
<td>1,272</td>
<td>1,324</td>
</tr>
<tr>
<td>6</td>
<td>Amyl. oryzae</td>
<td>1,052</td>
<td>1,080</td>
<td>1,127</td>
<td>1,192</td>
<td>1,244</td>
<td>1,267</td>
</tr>
<tr>
<td>7</td>
<td>Talc</td>
<td>1,011</td>
<td>1,065</td>
<td>1,102</td>
<td>1,138</td>
<td>1,164</td>
<td>1,184</td>
</tr>
</tbody>
</table>

It is interesting to note from the above Table that the most commonly used Amylum solani (Potato starch) has the best "glidant" action. Moreover, "dried" starch did not show any difference in action compared with the "undried" sample. On the other hand, Amylum oryzae (Rice starch) possessed less glidant effect than the other varieties of starch. This may possibly be due to the fact that, though the granules of this variety of starch are the smallest, they have a great tendency to form clusters containing as many as 150 individual grains. Kerr (14) states, in a discussion of the relative mobility of starches that the reasons for one starch being more mobile than another are not clearly understood. A satisfactory explanation for all phases of mobility can probably not yet be given.

(2) "Glidant" action of different "DERIVATIVES" of starch:

The data presented in the Table and Diagram 3 show that the various derivatives of starch tested possess just as good "glidant" properties as pure starches. The investigations bring out another important point, that these derivatives show much
better "glidant" properties than talc, but are not more efficient than natural starches. It is therefore preferable to use pure natural starches as "glidants" particularly in view of their lower price, if use of the derivatives is not justified by a special reason. Another interesting observation to be drawn from this data is that the addition of small amounts of magnesium oxide to the pure starch derivatives increased their "glidant" action to some extent. Of all the derivatives tested, Amylum solubile, showed the poorest "glidant" action.

(3) "Glidant action of different amounts of starch or its derivatives:

It is interesting to note that the "flow-rate" of the granules increases with the addition of increasing amounts of starch or its derivatives. The increase may be considered linear within limits. Whereas 5% of talc increases flow by about 10%, starches show in general an increase of about 14%. This increase is much more appreciable when starches are used in still higher proportions. Some of the starches (Amylum solani) show almost double the increase in flow produced by talc, when used in amounts of 20%. In actual practice, starches are frequently used in amounts of 10-15% as disintegrators. They are added to the dried granules, just before compression. In such circumstances, this addition of starch can combine both the functions of a "disintegrator" and of a "glidant". The addition of 10% of starch increased the flow of the pure lactose granules by an average of 20% of the original flow. The final question of using different amounts of these starches as "glidants" should also be considered from the point of view of their influence on the mechanical properties, moisture content, rate of disintegration and relative effect on the stability of different substances.

(4) Influence on the uniformity of flow:

A calculation of the standard deviation of the individual values from the average value, as indicated by the term S rel. in Tables 2 and 3, indicates that a small improvement in the uniformity of flow is produced by the addition of these different starches and their derivatives. This may possibly be due to the fact that the original, pure lactose granules were separated from
all the powder finer than Sieve IV Ph. Helv. V. The original granules themselves possessed a fairly uniform flow.

(5) "Lubricant" action of starch and its derivatives:

The results in the table 4 show that pure starch as well as its derivatives like ether starch show very little "lubricating" property. Whereas the addition of talc showed a very marked decrease in the ejection force as compared to that required for tablets compressed from pure lactose granules, the addition of similar amounts of starch or its derivative showed almost negligible improvement. This shows that although starch possesses extraordinary property of improving the flow of lactose granules (glidant property) it has hardly any effect in decreasing the ejection force required to eject its compressed tablets (lubricating property).

7. Summary

The important conclusions based on these investigations are summarised as follows:

(1) Natural starches possess very good "glidant" properties in increasing the flow of tablet materials. The starches produced as much as twice the flow produced by talc, which is a very efficient substance in this respect.

(2) The various starch derivatives tested are as effective "glidants" as natural starch and better than talc. They do not show, however, any advantage over natural starches as far as "glidant" properties are concerned.

(3) The different varieties of starch do not show any very significant differences in relative efficiency as "glidants". Our experiments showed that the sample of Amylum solani (Potato starch) tested possessed the best "glidant" properties.

(4) Starch and its derivatives do not show any "lubricating" action and do not decrease appreciably the amount of force required to eject the compressed tablet of pure lactose.
8. References

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(8) Firma FARICO, Kaatstraat 6, Utrecht (Holland)
   "Poudres a Comprimes"
(9) a. "A.N.M. Puder" Firma Neckar Chemi GMBH, Oberndorf/Neckar (W. Germany)
   b. "Biosorb Powder" (Starch powder 108) Ethicon Laboratories, U.S.A.
(11) Anderson and Würtzen, Dansk Tiddskr. Farmaci, 27, 25 (1953)
(12) New and Non-official Remedies 665/666 (1950)
(13) Kägi, Thesis. E.T.H. 1953, p. 188
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Chapter III

"The influence of different compressional pressures and tablet heights on the friction produced during tablet making"

1. INTRODUCTION

In the process of tablet making, a densification of the tablet mass is brought about by the application of pressure. The pressure converts the substances into definite shapes and imparts them a definite mechanical strength. It has been shown by some workers (1) (2) that the magnitude of compressing pressures has a great influence on the properties of the tablets. The use of higher pressures results in greater mechanical strength and also increases the time of disintegration of the tablets.

The application of force during tabletting is found to be necessary in the following two stages:

(a) during the compression of the tablet-mass into dense tablets

(b) during the ejection of the compressed tablet out of the die-cavity.

During the compression stage certain pressures are necessary to produce the desired transformation in the physical state and impart the necessary properties to the tablets. The pressure selected should be such that it produces a balance between the properties of minimum disintegration time and maximum mechanical strength. In the ejection stage, however, the force used is dependent on the amount of friction between the compressed tablet surface and the surrounding die-wall. It is generally considered desirable to reduce the force required to eject the tablet to a minimum. Hence, varying amounts of substances called "lubricants" or anti-adhesives are added to the tablet mass to achieve this purpose. It is known from empirical experience that higher pressures necessitate the use of corres-
pondingly higher amounts of lubricants. Patel (3) in an evaluation of tablet lubricants, states that increase in compressing pressure requires an increased force to eject the tablets. Until now very few investigations have been made to ascertain the nature of the friction produced and the mechanism of action of the lubricants added during tablet making. Wolf, Dekay and Jenkins (4) assumed that certain characteristic properties of the substances under compression may influence the nature of the electric charge produced by the generation of frictional heat. They suggest that the lubricants may function in some manner to conduct readily the excess of such electric charges. The results of their investigations however hardly lead to any definite conclusion in this respect. Nelson and coworkers (5) in an evaluation of tablet lubricants report that the compressional force lost to the die-wall and the force necessary to eject the tablets, are linearly dependent on the area of the tablet in contact with the die-wall. These factors are obviously interdependent and represent the frictional resistance produced during the compressional process.

There are two important laws of friction, known also as "Amonton's Laws", which are stated as follows:

1. The frictional resistance is proportional to the load, and
2. the frictional resistance is independant of the area of the sliding surfaces.

These laws are generally applicable to elastic bodies such as metals. Some of the non-metals like glass and plastics also show similar frictional properties. This behaviour of metals is said to be due to their ability to flow plastically and weld together under load (6). Such welded junctions have to be broken during the sliding process. With most of the non-metals, particularly those having markedly crystalline structures, it is difficult to envisage a flow and subsequent welding like metals. Nevertheless many non-metals, even of a crystalline nature, show similar frictional properties and it is possible that another mechanism analogous to such a welding process is responsible for their frictional behaviour. In tablet compression
frictional resistance develops between a metallic surface (die-wall) and a non-metallic surface (compressed tablet). Bowden and Tabor (12) remark that Amonton's laws of friction hold only when the area of intimate contact increases with the load.

In our subsequent experiments, we have investigated the validity of these laws of friction in the particular system of surfaces involved during tablet compression. An attempt is also made to explain the nature of the friction produced and the mechanism of action of the lubricants used in tablet making.

2. Experimental

(A) The influence of increasing pressure on the corresponding force required for the ejection of the compressed tablets.

A granulation was prepared from pure lactose by granulating with water and pressing through sieve no. III, Pharm. Helv. V (16 mesh per cm²). The granules were dried first at room temperature overnight and, after removing any clusters of the granules, were further dried in a hot air oven at 40°C for 3 hours. The dried granules were mixed with 5% of talc and tumbled in a glass bottle for 10 minutes to ensure thorough mixing.

The granules were accurately weighed into amounts of 100 mg and carefully transferred into the die-cavity whose bottom was formed by the lower punch. After inserting the upper punch at the top, the whole set was put in the BRINELL PRESS for compression. A die of 6 mm diameter and flat faced, circular punches were used for the compression.

Total compressing force ranging from 500 kg to 5000 kg was applied during the tests. At each range of compressing pressure, five tablets were compressed and the force for their ejection was measured. The results were expressed as their average value.

(B) The influence of increasing surface area of contact of the tablets with the die-wall on the corresponding ejection force.

The granulation of pure lactose containing 5% talc was compressed with the same die and punches of 6 mm diameter.
in the BRINELL PRESS in the manner already described. A constant total compressing force of 500 kg was applied throughout these experiments. Varying amounts of granules ranging from 75 mg to 150 mg were compressed in order to obtain corresponding variations in the thickness and surface area of contact of the tablets with the die wall. The force necessary to eject five tablets compressed at each weight level was measured and average values were calculated.

3. Results

The results of the experiments described above are presented in the following tables no. 6 and 7 and also in the diagrams no. 4 and 5.

TABLE 6

The relation between the applied compressional force and the corresponding ejection force necessary to eject the tablet out of the die cavity.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Total force* of compression in kg</th>
<th>Average force* of ejection in kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500</td>
<td>38,12</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
<td>66,52</td>
</tr>
<tr>
<td>3</td>
<td>1500</td>
<td>93,14</td>
</tr>
<tr>
<td>4</td>
<td>2000</td>
<td>112,60</td>
</tr>
<tr>
<td>5</td>
<td>2500</td>
<td>119,80</td>
</tr>
<tr>
<td>6</td>
<td>3000</td>
<td>156,80</td>
</tr>
<tr>
<td>7</td>
<td>3500</td>
<td>190,80</td>
</tr>
<tr>
<td>8</td>
<td>4000</td>
<td>225,80</td>
</tr>
<tr>
<td>9</td>
<td>4500</td>
<td>255,50</td>
</tr>
<tr>
<td>10</td>
<td>5000</td>
<td>273,80</td>
</tr>
</tbody>
</table>

*The above stated force is the total force for the particular 6 mm diameter size tablets and corresponds to a pressure of (1770 kg/cm²) for 500 kg total force.
TABLE 7

The influence of different surface areas of contact of the tablet with the die-wall on the corresponding ejection force when compressed with a constant force of 500 kg.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Wt. of grans. mg.</th>
<th>Ejection force kg</th>
<th>Height of tablets mm</th>
<th>Surface area of contact with the die cm²</th>
<th>Ejection force per cm² kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>30,74</td>
<td>1,72</td>
<td>0,325</td>
<td>94,5</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>37,62</td>
<td>1,95</td>
<td>0,368</td>
<td>102,2</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>40,36</td>
<td>2,33</td>
<td>0,440</td>
<td>91,7</td>
</tr>
<tr>
<td>4</td>
<td>115</td>
<td>46,72</td>
<td>2,63</td>
<td>0,497</td>
<td>94,0</td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>56,16</td>
<td>2,91</td>
<td>0,550</td>
<td>102,1</td>
</tr>
<tr>
<td>6</td>
<td>135</td>
<td>57,82</td>
<td>3,10</td>
<td>0,586</td>
<td>98,4</td>
</tr>
<tr>
<td>7</td>
<td>150</td>
<td>66,52</td>
<td>3,53</td>
<td>0,667</td>
<td>99,7</td>
</tr>
</tbody>
</table>

4. Discussion

(A) The results of table 6 and diagram 4 show that if the amount of material under compression be kept constant, any increase in the force of compression results in a corresponding increase of the force required for ejection of the tablets. Bowden and Tabor (7) state that even the best polished metal surfaces contain microscopic irregularities, which they call “hills and valleys” and which are larger than the molecular dimensions. If two solids are placed in contact with each other, then the surfaces would be supported on the summits of the irregularities and large areas would be separated by a distance which is greater than the molecular range of action. The application of a load to the metallic bodies leads to their elastic deformation (8) and releases a larger area of the contact surface. In the earlier stages of pressure application the deformation produced is elastic and recoverable. Thus the surfaces return to their original condition when the load is removed. As the load is increased, however, the mean pressure at the points of contact also increases until it reaches a certain critical point at which the elastic limit is exceeded and any further pressure leads to a
Diagram 4.—The relation between different compressional force and the corresponding ejection force during the compression of a constant weight of tablet granules.

Diagram showing the relationship between compressing force in kgms and ejection force in kgms.
Diagram 5.—The influence of different surface areas of contact of the tablet with the die-wall on the corresponding ejection force.
plastic, non-recoverable deformation. Once plastic flow commences, the effective pressures increase somewhat more slowly and full plasticity occurs at a load between 50 and 100 times that at which plastic flow commences. The elastic limit of various metal surfaces is different and the point at which the onset of plasticity occurs is also correspondingly different and depends on the relative hardness of the different metals. Bowden and Tabor (9) describe the different loads necessary to reach such a stage for different metals and show that tool steels require loads nearly three times larger than those for ordinary mild steels.

During tablet compression no direct loads are applied to the metallic die-wall. But according to the compression mechanism postulated by Seelig (10) as already discussed in the first chapter, a certain portion of the applied pressure is transmitted to the die-wall during the stage of tablet mass deformation. Such transmitted pressures depend on several factors, most important of which are: (1) the relative hardness and deformation characteristics of the tablet mass; (2) the co-efficient of inter-particle friction and (3) the magnitude of compressional pressures. If a well lubricated granulation or a material with low co-efficient of friction be compressed, a major part of the compressional pressure is consumed by deformation and densification of the tablet mass and comparatively small forces are absorbed by inter-particle friction and also transmitted to the die-wall. The studies of Nelson and coworkers (11) show that proper lubrication of the granules or the die-wall can very appreciably reduce the force lost to the die-wall and results in a greater force reaching the lower punch. It may hence be assumed that the average range of the forces acting on the metallic die-walls is comparatively smaller and often remains within the limit of elasticity of the average metals used for tablet dies and punches.

If however the composition and amount of the material under compression be maintained constant, any increase in the total applied pressure will also lead to a corresponding increased
transmission of pressure to the metallic die-wall. Evidently it would lead to an increasing deformation of the metal surface and release more surface asperities which come into contact with the tablet surface. It results in an increase in the strength as well as the number of contact points of friction or adhesion. The increase in the total adhesion is reflected by a corresponding increase in the force required for the ejection of the tablet. The force of ejection is necessarily the force required to break all the points of adhesion between the tablet and the metallic die surface. This explains also the direct and linear relationship found between the force of ejection and the compressional force lost to the die-wall, as found by Nelson and coworkers (12).

Within the precision of the instrument we used and considering the fact that measurements spread over a couple of weeks involve atmospheric and such other variations, it can be remarked that the ejection force tended to be directly proportional to the compressional force used. This is in accordance with Amonton's Law which states "that the frictional resistance is proportional to the load applied."

(B) The results in the table 7 and diagram 5 show that by employing a constant force of compression, any variation in the surface area of the tablets formed leads to a corresponding variation in the amount of friction produced. The amount of such friction can be measured from the force required to eject the tablet out of the die. It can also be observed that, whilst the total force of ejection changed with any variation of the tablet surface area, such force remained constant when calculated per unit area of the surfaces involved.

When a compressional force is applied to a metal surface, it leads to a suppression of the minute superficial asperities of the metal and releases a certain area of the metal surface for immediate contact with the other surface. The extent to which such an area of contact is released, is dependent on the magnitude of the compressing pressure as well as on the hardness of the metal surface. Thus for a particular metal surface it will vary directly with the pressure applied. If the
compressing force be maintained constant for a particular die, the area of contact of the metal die surface will obviously remain constant. If however different lengths of tablets are compressed under constant pressure, the apparent change in the amount of friction produced corresponds to that of the tablet surface area of contact. Since the area of the metallic die surface remains constant, the strength of the friction junctions or the adhesion between the two surfaces also remains constant, while such junctions may increase in number when the tablet surface area of contact is increased. It is hence found that whilst the apparent amount of friction or the ejection force varies with the tablet surface area, it remains constant, per unit area of this surface. Thus it is seen that the frictional resistance, which is essentially a measure of the strength as well as the number of contact points of the two surfaces, is dependent on the compressing pressure and remains independent of apparent surface areas. It can be said from these results, that the statement of Amonton's law, "that the frictional resistance is independent of the area of the sliding surfaces and depends on the applied load" is supported for the types of surfaces involved during tablet compression.

Our results are further in agreement with those of Nelson and coworkers (12) who reported similar findings in experiments with un lubricated sulthathiazole granules on an instrumented tablet machine (13) based on a similar method of ejection force measurements.

A consideration of the nature of the friction produced and the mechanism of action of "LUBRICANTS" in tablet compression:

When two surfaces in contact are made to move over one another an opposing force is experienced which resists this movement and is known as the "force of friction." The amount of this frictional resistance is said to be dependent on the nature of the two sliding surfaces. The smoother the surfaces, the lesser is the frictional resistance. Evidently friction is a function of certain characteristics of the surfaces which are in contact with one another.
The friction produced during tablet compression, may be subdivided as follows depending on the types of surfaces which enter into contact with one another:

(a) the inter-particle friction among the particles of the tablet mass during the compressional stage.

(b) the friction between the metallic surface of the die-wall and the particles of the tablet mass during compression.

(c) the friction between the surfaces of the compressed tablet and the surface of the die-wall, during ejection of the tablet.

(a) Inter-particle friction:

The friction is here represented by the co-efficient of friction of the particular material under compression. In view of the continuous fragmentation of the particles during this stage, the crystal structure and particularly the ease of their cleavage and hardness govern its range to an appreciable extent. Bowden and Tabor (14) discussing the friction of non-metals state that the majority of non-metallic crystalline substances are anisotropic (non-uniform) in their strength properties as compared to polycrystalline, isotropic metallic specimens. Some studies made on the crystals of sod. nitrate, pot. nitrate and ammon-chloride showed that with regard to sliding over themselves, their co-efficient of friction was very low ($\mu=0.5$) and in the presence of surface films of longchain polar compounds, the friction was reduced to about ($\mu=0.12$). Further that, for such substances, Amonton's Law holds over an appreciable range of loads and sliding is accompanied by considerable surface damage and fragmentation of the solids.

(b) Friction between tablet particles and the die-wall during compression:

The nature of the friction here is largely dependent on the surface condition and the relative hardness of the metallic die-wall and on the compressional force applied. A highly
polished, smooth, and hard metallic surface would show a comparatively lesser friction even at rather high pressures. During this stage an increasing number of contact points are formed, on the one hand by the fragmentation of the particles and on the other by elastic deformation of the metal surface, which releases more asperities on application of greater pressures.

(c) Friction between the surfaces of the compressed tablet and the die-wall during ejection:

The friction experienced during ejection is a net result of the friction of the above two stages. The ejection force is in large measure the force required to break and shear the junctional points where the two surfaces adhere to one another. When both the surfaces in contact are metals, the nature of these metallic junctions is explained as being due to their tendency to flow plastically under pressure, leading to a strong adhesion and ultimate welding at the points of contact. While it is difficult to postulate a similar welding of the relatively softer tablet materials, strong adhesion due to a localised softening or melting at the contact points may occur. McFarlan and Tabor (15) discussed the relations between friction and adhesion and pointed out that whereas adhesion is a measure of the tensile strength of these junctions, friction is a measure of their shear strength.

During ejection, the relative strength of these junctions and the coherent strength of the tablet compact play a very important role in determining the nature of the wear occurring during shearing. Bowden and Tabor (16) state that the magnitude of the frictional force and the extent and type of surface damage caused by sliding are determined primarily by the relative physical properties of the two sliding surfaces. Their behaviour is dependent in particular on the relative hardness of the two surfaces. If the sliding speeds are high, it also depends on their relative softening or melting points. Bowden and Tabor (17) considered the various possibilities which may occur and state that:

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(1) if the junction is weaker than the two surfaces themselves, shearing may occur at the actual interface where the junction is formed. Consequently the material removed from either of the surfaces will be very small even though the friction may be relatively high;

(2) if the junction is stronger than one of the bodies, shearing will often occur within the bulk of the weaker body and fragments of the weaker body will be left adhering to the harder surface. This type of wear gradually builds up a film of the softer material over the harder surface, resulting in increasing friction, surface damage and wear.

The most important function of the various "lubricant" additions is, however, to provide a thin film between the rubbing surfaces. This forms very weak junctions which can easily be torn away by the application of comparatively small ejection forces. On the other hand if such a lubricant film be absent or if the adhesion be so strong (as with more abrasive substances) and the coherent strength of the formed tablet insufficient, typical tearing of the body of the tablet occurs. It leads to a gradual build up of a thin film of tablet mass on the comparatively stronger metallic surface, and is commonly known as "binding" or "sticking" in the tablet terminology. The force of ejection acts in a tangential direction to the circular surfaces of the tablet and is distributed at an angle of 45° within the body of the tablet. This leads to the more commonly observed breakage of the tablet in this direction, particularly when the coherent strength of the tablet is insufficient. This explains the phenomenon known as "capping."

Mechanism of action of "lubricant":

While discussing the mechanism of boundary lubrication Kirk and Othmer (18) state that earlier it was assumed that under boundary conditions, a film of lubricant of molecular dimensions was present and that friction was a result of intramolecular attractive forces. It is now considered that earlier conclusions were oversimplified and that surfaces are not effecti-
vely separated by a lubricant film, even of multilayers. Such surface films are easily penetrated by the protruding asperities even under relatively mild conditions. The films attached to the surfaces by physical forces alone, like those of paraffin oil, are held relatively weakly and thus result in poor boundary lubrication. On the other hand, films attached to the surfaces chemically are more tenacious and provide more protection. Such films can be formed by organic molecules such as long-chain fatty acids and are more effective if their molecules are also capable of undergoing condensation or polymerisation (19). It has been observed that the effective friction-reducing film resulting from the use of long-chain fatty acids is a solid metal soap film. On many metals the formation of the soap may occur through the reaction of the acid with an oxide layer. It has been demonstrated by the fact that if an oxide film is eliminated, none of the common metals can be effectively lubricated by a fatty acid solution such as stearic or oleic acid. Furthermore it was found that, in some cases, if an oxide film was formed in the absence of water, the fatty acids were ineffective. Thus the combined action of water and atmospheric oxygen produces a surface film on the reactive metals which is capable of combining with acids to form an effective lubricating layer of soap. This explains also the function of the so far best known and commonly used tablet lubricants namely metal soaps such as calcium and magnesium stearates.

Besides the above mentioned oil or soap lubricants, solid lubricants such as talc or graphite are also widely used. Their lubricating action is attributed to their crystalline layer lattice structure (20). Their plate like structure can withstand a pressure normal to these layers but readily shear away parallel to the layer lines, when a tangential force is applied. Savage (21) has shown that water adsorbed between some of the layers may act as "internal lubricant" permitting the relative motion of these layers. In absence of this adsorbed water, as in high vacuum, graphite proved entirely unable to lubricate.
5. Summary

(1) The increase in the compressional pressures of the tablets leads to a directly proportionate increase in the force required for the ejection of the tablets. The force required for the ejection of the tablets represents the frictional resistance between the tablet and the die-wall surface.

(2) The increase in the total surface area of the tablet coming into contact with the die-wall during compression leads to a corresponding increase in the ejection force, if the total compressional load is kept constant. This force of ejection or the frictional resistance, remains constant, however, per unit area of both the surfaces of contact.

6. References

(1) Higuchi and coworkers, J. Am. Ph. Ass. (Sc.ed.) 42, 194 (1953)
(2) Kagi, Thesis E. T. H., 1953, p. 197
(3) Patel and Guth, Drug Standards, 23, 41 (1955)
(6) Bowden and Tabor, "The Friction and Lubrication of Solids" Oxford 1950, p. 80
(7) Bowden and Tabor, ibid., p. 6
(8) ibid., p. 10
(9) ibid., p. 14
(10) Seelig, "The Physics of Powder Metallurgy" by Kingston p. 344
(11) Nelson and coworkers, loc. cit., p. 599
(12) ibid., p. 601

(14) Bowden and Tabor, loc. cit., p. 161


(16) Bowden and Tabor, loc. cit., p. 78

(17) ibid., p. 285

(18) Kirk and Othmer, "Encyclopedia of Chemical Technology" (1952) vol. 8, p. 501

(19) ibid., p. 502

(20) ibid., p. 531

(21) Savage, Journ. Applied Physics, 19, 1, (1948)
CHAPTER IV

"The influence of varying pressure and moisture content of the granules on tablet compression."

1. INTRODUCTION

As already discussed in the first chapter, a varying amount of moisture present in the granules can also be responsible for some difficulties encountered in the process of tablet making. Wiirtzen (1) has shown that an optimum amount of 2.23-2.54% is essential for the successful tabletting of phenacetine according to his formulation. Not much work on this particular aspect of tabletting seems to exist. Bandeline (2) and other workers, however, emphasised the need for further investigations in this field.

Addition of moisture to the tablet mass is an important step during the preparation of granules by the wet method of granulation. The moistening agent serves as an aggregating agent and as medium in which the various binding agents can be brought more effectively into contact with the tablet mass. After dispersing the moist mass by passing it through a sieve, the granules thus obtained are dried to remove the added moisture. Different methods, temperatures, and lengths of time are employed for this drying operation. The empirical judgment of the tablet maker is usually relied upon to decide whether or not the granules are dry enough for successful tabletting. Sometimes when certain materials show a tendency to "capping", they are considered to have been dried too thoroughly. A small quantity of water, in the form of a fine spray, is added to the granules and thoroughly admixed before compression. Aerophilic substances frequently tend to excessive drying. The Pharmacopoea Danica IX includes certain amounts of hygroscopic agents, such as glycerine, in these tablet formulations to prevent excessive drying.
Hygroscopic substances, on the contrary, are liable to absorb moisture from the atmosphere. If the atmosphere is rather humid, even prolonged drying in an ordinary air oven may not be sufficient to remove all the moisture from the granules. In such cases, the mass sticks to the die or punch surfaces. A very similar condition may arise if high pressure is used and eutectic mixtures are formed resulting in considerable lowering of the melting point. Such melting or softening also leads to "sticking."

In the following investigations, we studied the influence of different amounts of moisture in the granules. These were compressed at different pressures in the Brinell press. The compactability of tablets prepared was carefully observed by examining the surfaces of the tablets as well as those of die and punches in order to see if the former showed any tendency to "capping" or "sticking". Further, the strength of the tablets was tested and compared by using the "Monsanto hardness tester."

2. Experimental

Two different granulations were prepared from the following compositions:

<table>
<thead>
<tr>
<th>GRANULATUM SIMPLEX</th>
<th>PHENACETINE GRANULES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylum solani 700 gm</td>
<td>Phenacetine 500 gm</td>
</tr>
<tr>
<td>Sacchar. Lactis 300 gm</td>
<td>Amylum solani 75 gm</td>
</tr>
<tr>
<td>Mucilage gelatine 4% Q.S.</td>
<td>Mucilage gelatine 4% Q.S.</td>
</tr>
</tbody>
</table>

The granules were pressed through sieve no. IV, Pharm. Helv. V (15 mesh cm²) after moistening with the necessary amount of mucilage gelatine (Pharm. Helv. V), and were completely dried in the hot air oven at 35°C.

(a) Preparation of granules with different amounts of moisture; Compression in the Brinell Press:

50 gm portions of each type of granules were taken in five separate broad glass dishes. Four of these portions were stored in four different desiccators, each of which con-
tained a different constant relative humidity solution* (3). The following substances were employed at a temperature of 20°C:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative Humidity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>100</td>
</tr>
<tr>
<td>ZnSO₄. 7H₂O</td>
<td>90</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>79</td>
</tr>
<tr>
<td>NaBr</td>
<td>58</td>
</tr>
</tbody>
</table>

Air was completely removed from the desiccators, containing the granules and the various constant humidity solutions, by means of a vacuum pump. The desiccators were closed and then contained only the vapours of the corresponding humidity solution. The granules were stored for 48 hours in this condition. The fifth portion of granules was placed in an air oven and kept at a temperature of 40°C for 48 hours also. After this time, samples were taken from each of the portions and analysed for moisture content with Karl-Fischer-Reagent as described below. Amounts equivalent to 100 mg of dry granules calculated on the results of the moisture analyses were weighed out from each portion. The aliquots were carefully compressed in the Brinell-press using a circular die of 6 mm diameter and flat faced punches.

(b) Estimation of the moisture-content of the granules:

The various methods used for the moisture determination of drugs may be classified as follows:

(a) Drying method: An accurately weighed sample is dried in a hot air oven or by infra-red lamp to constant weight. The percentage loss of weight represents the moisture content. Semi-automatic apparatus† using this principal and which does not necessitate periodic withdrawal of the sample from the oven, is available.

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* A constant humidity solution is formed by a saturated aqueous solution of the substances mentioned, in contact with excess of the solute, and maintained in a closed space at a given temp.

† The semi-automatic moisture content tester manufactured by the BRA-BENDER CORPORATION, Rochelle Park, New Jersey (USA).
(b) Distillation method: This involves the distillation of the moisture from the sample, with an immiscible organic liquid, e.g., toluene, in a special distillation apparatus. The method is officially accepted in certain formularies (4).

(c) Conductimetric method: The method described briefly by Ferrand (5) depends on the fact that the electric constant of water is greater than that of the other tablet constituents. The constant measured is directly proportional to the moisture content of the granules. The electric constant or specific inductive force is measured from the corresponding changes in a condenser when the sample under test is placed between two metallic plates.

(d) Karl Fischer Reagent method: This method is simple, quick, and accurate and is being recognised in the newer issues of many Pharmacopoeas. Karl Fischer Reagent (K.F.R.) is a deep brown solution containing iodine, pyridine, SO\textsubscript{2} and methanol. Its colour changes to yellow on reaction with water. The end point may be determined visually or potentiometrically.

For our investigations we used the K.F.R. method as described below in detail:

Due to the rapid loss in the activity of K.F.R. solution ready for use, it is more convenient to store it as two separate, stable solutions. Solution 1 contains pyridine and SO\textsubscript{2} and solution 2 contains iodine and methanol. These solutions are mixed together in the necessary proportions just before use. Mixing of these two solutions is an exothermic reaction and care must be taken to cool both the individual solutions and the mixture thoroughly. The reagent was stored in an automatic burette, from which it was pumped with hand bellows. All the openings of the burette were carefully sealed with exciccator tubes to exclude the effect of outside moisture. The end point
was determined visually. The following procedure was adopted, as described by Sager (6).

"Take as many Erlenmeyer flasks of 50 c.c. capacity as there are samples to be simultaneously tested and three additional flasks. Wash thoroughly and dry completely in a hot air oven. The flasks should then be kept in a desiccator for about half an hour to let them cool down slowly. Designate the three additional flasks as A, B, C and the remaining as 1, 2, 3, etc. Accurately weigh into the additional flasks B, C a small amount of water (about one drop = c mg) and into the flasks 1, 2, 3 etc., the samples to be tested (about 0.1 gm = e mg.). From a burette, measure out accurately 10 c.c. of methyl alcohol (anhydrous) into each of these flasks and keep for about ten minutes during which time the samples are dissolved by gentle rotation of the flasks. The liquids are titrated in the sequence A, B, 1, 2, 3...C with K.F.R. from an automatic burette. The titration should be carried out as quickly as possible, the end-point is reached when the colour of the solution changes from yellow to reddish brown.

The activity factor (W) for the K.F.R. is calculated from:

\[ W = \frac{c}{b-a} \]

where \( a = \) the no. of cm\(^3\) of K.F.R. used for A.
\( b = \) the no. of cm\(^3\) of K.F.R. used for B and C

(since the value of the activity is calculated twice, at the beginning and at the end of the titrations, the value of W for further calculations should be taken as the average of both these values).

The water content of the test samples 1, 2, 3 etc. may be calculated as:

\[ \frac{(d-a)}{e} \cdot \frac{S}{100} = \% \text{ water} \]

where \( d = \) the no. of cm\(^3\) of K.F.R. used for titration of the liquids of flasks 1, 2, 3 etc.
\( e = \) weight of the substance.
Photograph 6

Monsanto Hardness Tester
It is important to note that all the flasks should be given practically identical treatment as far as drying time and temperature is concerned. They should then be stored in a desiccator for the same length of time etc. The activity factor of the K.F.R. should be freshly determined before every experimental series and the titrations always carried out in the sequence described above."

(c) "Monsanto Hardness Testing" :

The relative strength of the prepared tablets was tested with the "Monsanto Hardness Tester"* also mentioned by Bandelin (2) and Smith (7) and shown in the photograph 6. It is a small and handy pressure test instrument which measures the resistance of the tablets to crushing. It is a chromium plated instrument about 20 cm long and weighing about $\frac{1}{2}$ kg. It consists essentially of a cylindrical barrel containing a strong spring and an indicator which moves over a graduated scale when pressure is applied by turning a screw knob at the top. Tablets up to a maximum size of 12,0 mm diameter can be placed edgewise between a stationary anvil and a movable spindle. The tablet should be carefully centred so as to be perpendicular to the pressing surfaces and just sufficient pressure applied to hold it in position. The initial zero reading is read off the scale. Pressure is then applied uniformly till the tablet breaks to give the final reading on the scale. The difference between the two readings represents the pressure in kilograms necessary to break the tablet. Particular care should be taken to clean the crushing surfaces thoroughly before every test and to place the tablet correctly. Pressure should be applied in a slow and progressive manner. Only just sufficient pressure should be applied to keep the tablet in position, since this pressure determines the zero reading of the measurements. An average value of the measurements for ten tablets was taken and called "Monsanto hardness" in kg and used for the comparison of the different tablets.

* Made by the Monsanto Chemical Company Ltd., St. Louis (USA).
3. Results

The results of the above mentioned experiments are presented in the tables 8 and 9 and diagrams 6 and 7:

**TABLE 8**

The Influence of varying Pressures and Moisture in the Phenacetine Granules

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Hygrostat Solution</th>
<th>Relative Humidity %</th>
<th>Granule Moisture %</th>
<th>1 (250 kg)</th>
<th>2 (500 kg)</th>
<th>3 (1000 kg)</th>
<th>4 (4000 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mon. Hard* kg</td>
<td>Compactability</td>
<td>Mon. Hard kg</td>
<td>Compactability</td>
</tr>
<tr>
<td>1</td>
<td>Water</td>
<td>100</td>
<td>7.55</td>
<td>1.52</td>
<td>+</td>
<td>2.02</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>ZnSO&lt;sub&gt;4&lt;/sub&gt; 7H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>90</td>
<td>3.72</td>
<td>1.90</td>
<td>+</td>
<td>4.42</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>NH&lt;sub&gt;4&lt;/sub&gt;Cl</td>
<td>79</td>
<td>3.52</td>
<td>1.46</td>
<td>+</td>
<td>3.30</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>NaBr</td>
<td>58</td>
<td>3.08</td>
<td>1.50</td>
<td>+</td>
<td>3.08</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Oven drying at 40°C</td>
<td>-</td>
<td>0.94</td>
<td>1.00</td>
<td>+</td>
<td>2.42</td>
<td>+</td>
</tr>
</tbody>
</table>

* Monsanto Hardness  + = Compactability satisfactory  - = Compactability unsatisfactory
Diagram 6.—The influence of varying pressure and moisture on the compactibility of Phenacetine granules.
### TABLE 9

The Influence of varying Pressures and Moisture in the Granulatum Simplex

**Total Compressing Pressures**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Hygrosol solution</th>
<th>Relative Humidity %</th>
<th>Granule Moisture %</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250 kg</td>
<td>500 kg</td>
<td>1000 kg</td>
<td>4000 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mon. Hard kg</td>
<td>Compact-ability</td>
<td>Mon. Hard kg</td>
<td>Compact-ability</td>
</tr>
<tr>
<td>1</td>
<td>Water</td>
<td>100</td>
<td>27.20</td>
<td>Heavy-Sticking</td>
<td>0.3</td>
<td>Sticking</td>
<td>Sticking</td>
</tr>
<tr>
<td>2</td>
<td>ZnSO₄ 7H₂O</td>
<td>90</td>
<td>21.35</td>
<td>3.70 +</td>
<td>4.0</td>
<td>Sticking</td>
<td>4.90 +</td>
</tr>
<tr>
<td>3</td>
<td>NH₄Cl</td>
<td>79</td>
<td>12.86</td>
<td>2.00 +</td>
<td>5.3 +</td>
<td>5.64 +</td>
<td>6.0 +</td>
</tr>
<tr>
<td>4</td>
<td>NaBr</td>
<td>58</td>
<td>10.46</td>
<td>1.89 +</td>
<td>4.8 +</td>
<td>4.40 +</td>
<td>5.27 +</td>
</tr>
<tr>
<td>5</td>
<td>drying at 40°C</td>
<td>-</td>
<td>2.75</td>
<td>0.50 too weak</td>
<td>0.65 capping</td>
<td>1.47 capping</td>
<td>3.00 capping</td>
</tr>
</tbody>
</table>

Note: Mon. = Monolithic; Compact-ability = Compressibility; Sticking = Sticking; Heavy-Sticking = Heavy-Sticking.
Diagram 7.—The influence of varying pressure and moisture on the compactibility of “Granulatum Simplex.”

Moisture levels: 12.86%, 21.35%, 10.46%, 27.2%.
4. Discussion

(a) Influence of the composition of the granules:

Pure phenacetine and Sacharratum lactis, when compressed alone, are known to give rise to difficulties during tabletting. Starch is generally added to the tablet formulations as a disintegrator as well as a filler. Our experiments show that it can also act as an excellent "water-regulator" when kept in contact with atmospheres containing different amounts of humidities. Since phenacetine and Sacharratum lactis are both non-hygroscopic substances, it was possible to obtain different moisture contents in their granulations by addition of different amounts of starch.

(b) Influence of different moisture contents of granules:

Our results show that both a very low and a very high moisture content affects adversely the compactability of some granules. Besides showing "capping" and "sticking" to the die and punches, the tablets thus made exhibited very low relative strength as measured by the "Monsanto hardness tester."

By compressing phenacetine granules at a total pressure of 500 and 1000 kg/per tablet (of 6 mm diameter), it was observed that the tablets prepared were weakest at a high moisture content of 7.55% and also at a low moisture content of 0.94%. The optimum range of moisture from 3.08-3.72% offered the best compactability of the granules. Their relative strength increased with increasing moisture content within this range.

A similar observation is made on applying a similar force of 500 and 1000 kg/per tablet to compress the "Granulatum simplex." The weakest tablets were produced at the highest moisture content of 27.2% and also showed heavy "sticking" on slight increase of compressing pressure. Similarly, the tablets prepared from granules at the lowest moisture content of 2.75% were the next weakest and tend to "capping" with a slight increase in pressure. The optimum range of moisture content for this granulation lies between 10.46—12.86%. Once again, increasing the pressure within this range increases the strength.
of the tablets. On increasing the moisture content to 21.35%, however, it was observed that the hardness of the tablets prepared was lower than that of tablets with 12.86% moisture at pressures above 500 kg.

These observations show that it is important to compress many granules within their optimum range of moisture content. The amount of moisture in the granules can become a very important factor responsible for the "capping" or "sticking" shown by many substances. The relationship may be represented schematically as follows:

Diagram 8.—The influence of increasing moisture content in the granules, on the compactability and relative strength of the tablets.

(c) Influence of varying pressures in presence of different amounts of moisture in the granules:

It is interesting to note that, with increasing moisture in the granules, the same pressures produce comparatively stron-
ger tablets of the same material. In the compression of "Granulatum simplex," the strength of the tablets prepared continued to increase with increasing pressure. In the case of phenacetine granules, a maximum strength was reached at a pressure of 1000 kg. The strength of the tablets showed a decline at greater pressures of 4000 kg.

This may be due to the fact that a water film may act as a weak lubricant, (= Schmiermittel, Antiklebmittel) when present in increasing amounts it decreases friction to an increasing extent. The moisture present may at the same time improve functioning of the binding agents used. They are otherwise present in the less effective form of dry gels, to which they have been converted during drying of the granules.

In the case of phenacetine granules, an increase of pressure above 1000 kg decreases the strength of all tablets with different moisture contents. In the case of "Granulatum simplex," however, the strength always increased at higher compressing pressures. This greater tolerance of high compressing pressures and resulting increased friction in the case of "Granulatum simplex" may be due to the higher amounts of starch (75%) present in the granules as compared with phenacetine granules with smaller amounts of starch (15%). The presence of slightly moist starch imparts greater elasticity and binding strength. The starch also absorbs more moisture. All these factors lead to a better resistance of the tablet to the frictional forces acting on it.

5. Summary

(1) Starch present in the tablet granules acts as an excellent "water-regulator" depending on the amount present and the humidity of the surrounding atmosphere.

(2) The moisture content of the granules can be an important factor in causing "capping" if the moisture content is too low, and "sticking" if the moisture content is too high.

(3) At certain optimum moisture contents, certain tablet materials can be compressed to comparatively stronger...
tablets even at relatively lower pressures. Hence it is very important to standardise and control the moisture contents of uniform formulations to achieve better mechanical properties of the tablets.

(4) The presence of moisture within a certain range acts as a weak lubricant in the compression of the tablet materials.

(5) The addition of greater amounts of starch as a "filler" at certain limited moisture content, increases the elasticity and also the strength of the tablets.

6. References

(1) Wurtzen, Archiv. Pharm og Chemi, 43,217 (1936)
(2) Bandelin, Amer. J. Pharm., 1945, April, p. 124
(3) Merck Index, 1952, p. 1134
(4) National Formulary U.S.A. (1950)
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(7) Smith, Pharm. Journ., 109,227, (1949)
Chapter V

"The influence of varying moisture contents and storage conditions on the physical properties of the tablets".

1. INTRODUCTION

It has been widely observed that several types of tablets show a considerable change in physical properties when stored over a long period. Although most such tablets comply when freshly made with the necessary requirements for such properties as disintegration and hardness, they may show a marked change in the course of time. There have been cases where legal proceedings were instituted against some pharmacists (1) (2) who were not aware of the altered properties of such types of tablets, which they had in stock. Many workers (3) (4) (5) (6) (7) have confirmed the occurrence of such a phenomenon. Ewe (3) found that, while some types of tablets showed increased times of disintegration after long storage, others had this time shortened. Smith and Stephenson (5) investigated several batches of phenacetine tablets from different manufacturers for time of disintegration and hardness and found that in the majority of the cases, these properties had worsened after storage. They remarked, however, that in their opinion the increased hardness did not explain for the loss of property of disintegration. Burlinson and Pickering (6) studied the influence of the various physical factors such as the granulation methods, moisture content, and compressing pressures, on the change of important physical properties after a storage period of 4 years.

Higuchi and coworkers (8) observed that the granules produced from a given formulation at different times may exhibit different disintegrating characteristics. From our earlier investigations described in the previous chapter, it was found
that certain physical factors such as different compressing pressures and moisture content play an important role in the satisfactory manufacture of tablets. The presence of certain optimum amounts of moisture was found to be necessary for proper compression of certain tablet granulations studied. In our subsequent experiments, a study has been made of the influence of different moisture contents present in the granules on their disintegration and hardness properties. The tablets were compressed with a constant force and were stored at two different temperatures for a period of four weeks. Afterwards their properties and the moisture content were re-analysed, to observe any change which may have taken place.

2. Experimental

The granulations of "Granulatum simplex" and the phenacetine granules were adjusted to different moisture contents by storing under atmospheres of different "constant humidity solutions" as described in the previous chapter. The granules were analysed for moisture content with Karl Fischer Reagent, by the method already described.

Accurately weighed amounts, equivalent to 100 mg. of dry granules, were compressed in the Brinell press using a die of 6 mm diameter and flat faced punches. A total constant force of 500 kgm. was used for the compression of all the tablets. The compressed tablets were immediately analysed for moisture content and the properties of disintegration and hardness. The "Monsanto hardness tester" was used to test hardness according to the method already described. The disintegration time was tested by the "Erweka" apparatus described below.

Further batches of 30 more tablets were prepared from each of the granulations containing different moisture content and were packed in ordinary cardboard pill boxes. They were stored for a period of four weeks at temperatures of 35°C in an electric heated air-oven working at the normal atmospheric humidity and 4°C in a refrigerator working at the normal atmospheric humidity at this temperature.
The disintegration test with the “Erweka” apparatus:

The “Erweka” apparatus as shown in the diagram 9 and photograph 7, consists of an iron platform A supporting a cylindrical metal jacket B which is filled with water at a temperature of 37°C. In the jacket B is contained a glass beaker filled with the “disintegration fluid” used in the experiment. The platform A can be electrically heated to warm the “disintegration fluid” by means of the water contained in the jacket B. The “disintegrating fluid” is maintained at a constant temperature by the thermostat K dipping
Photograph 7

Erweka Apparatus
into it. A mechanical assembly which may be called a "disintegration boat" D hangs from the head of the apparatus. Its bottom consists of the sieve E, on which the tablet F can be placed and covered by a plastic lid G. A metallic rod runs from the centre of the lid G towards the top of the apparatus and makes a contact with the metallic hand which controls the working of the apparatus. When the thermostat K and the "disintegration boat", are brought into contact with the "disintegration fluid", the apparatus is set in motion. The "disintegration boat" makes six light backward and forward movements followed by a stronger jerk during one minute. Three watches L fitted at the head of the apparatus are synchronised with the apparatus. These watches show the time in seconds, minutes, and hours individually. As the disintegrated parts of the tablets pass through the sieve, the plastic lid G comes into contact with the sieve E. There occurs a slight lowering of the metallic head H resulting in contact with the projecting metallic hand of the apparatus. This movement is indicated by the simultaneous lighting of a red, signal lamp I, and the whole apparatus comes to a stop automatically. The time taken for the disintegration of the tablet is recorded in the watches L.

It is important, however, to place the tablet exactly in the middle of the sieve to avoid a slight tilting of the covering plastic lid G. Such a tilting of the plastic lid may cause contact with the sieve at some point and result in stopping the apparatus, although the tablet is still undisintegrated on the sieve. A similar situation can also arise, if the tablet contains ingredients liable to form a sticky paste. In such cases, the lid sticks in the paste and is drawn prematurely towards the sieve to make contact. In order to avoid such difficulties, the apparatus was used without the plastic lid and the end point controlled visually.

3. Results

The results of the experiments are presented in the following tables:
TABLE 10

The influence of varying moisture content and the storage conditions on the physical properties of the "Granulatum simplex" tablets

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Sat. Hygros-</th>
<th>Relative Humidity %</th>
<th>Granule Moisture %</th>
<th>Immediately after compression</th>
<th>After storage for one month at 35°C</th>
<th>After storage for one month at 4°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>100</td>
<td>27,20%</td>
<td>14,5%</td>
<td>22-1200</td>
<td>0,3**</td>
</tr>
<tr>
<td>2</td>
<td>ZnSO₄</td>
<td>90</td>
<td>21,35%</td>
<td>13,19%</td>
<td>28-191</td>
<td>4,0</td>
</tr>
<tr>
<td>3</td>
<td>NH₄Cl</td>
<td>80</td>
<td>12,86%</td>
<td>10,69%</td>
<td>114</td>
<td>5,30</td>
</tr>
<tr>
<td>4</td>
<td>NaBr</td>
<td>58</td>
<td>10,46%</td>
<td>10,15%</td>
<td>127</td>
<td>4,80</td>
</tr>
<tr>
<td>5</td>
<td>Oven dried at 40°C</td>
<td>—</td>
<td>2,75%</td>
<td>3,96%</td>
<td>41-1800</td>
<td>0,65***</td>
</tr>
</tbody>
</table>

* Monsanto Hardness
** sticking
*** capping
**** clusters of granules formed after disintegration and float on the water surface
***** granules do not pass through sieve after 2 hours
oo more than one hour
### TABLE 11

The influence of varying moisture content and the storage conditions on the physical properties of 'Phenacetine' tablets.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Sat. Hygrostat solution</th>
<th>Relative Humidity %</th>
<th>Granule Moisture %</th>
<th>Immediately after compression</th>
<th>After storage for one month at 35°C</th>
<th>After storage for one month at 4°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>100</td>
<td>7.55</td>
<td>4.8</td>
<td>117</td>
<td>2.02**</td>
</tr>
<tr>
<td>2</td>
<td>ZnSo₄</td>
<td>90</td>
<td>3.72</td>
<td>3.4</td>
<td>140</td>
<td>4.42</td>
</tr>
<tr>
<td>3</td>
<td>NH₄cl</td>
<td>80</td>
<td>3.52</td>
<td>2.5</td>
<td>73</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>NaBr</td>
<td>58</td>
<td>3.08</td>
<td>2.5</td>
<td>60</td>
<td>3.08</td>
</tr>
<tr>
<td>5</td>
<td>Oven dried at 40°C</td>
<td>—</td>
<td>0.94</td>
<td>0.93</td>
<td>323</td>
<td>2.42***</td>
</tr>
</tbody>
</table>

* Monsanto Hardness
** Sticking
*** Capping
4. Discussion

(a) The influence of different moisture contents on the properties of tablets, tested immediately after their compression.

The granules of the "Granulatum simplex" which contained a very high amount of moisture, showed that on compression much of the water was squeezed out and flowed along the lower punch. The tablets showed a marked tendency to "sticking" to the punches. Almost all its granulations containing different amounts of moisture, also showed a decrease in moisture content after compression. The completely dried granules which had very little initial moisture content, showed a tendency to "capping" and absorbed some moisture after compression. The results of disintegration and the hardness testing of the tablets showed that the presence of an optimum moisture content of 10-11% in the granules produced tablets with comparatively the best properties. They had a minimum disintegration time and a maximum hardness in comparison to those prepared from granules with other moisture contents.

A similar behaviour was noticed with the "phenacetine granules" which also showed a slight decrease in moisture content of the different granules on compression. The completely dried granules, however, remained quite unchanged. In the phenacetine granules also, the presence of an optimum moisture content in the range of 2.5—3.4% produced tablets which were better with regard to disintegration and hardness properties.

In view of the non-hygroscopic nature of both lactose and phenacetine, the different amounts of absorbed moisture may be assumed to be taken up by the other constituent present, namely starch. It is possible that different amounts of moisture may lead to a swelling of the starch grains to different extents. This may be considered to be the factor responsible for the difference observed in the behaviour of the same granules. The tablets prepared from granules containing very high amounts of moisture showed on disintegration that individual
disintegrated granules tended to form clusters of granules which would not pass through the sieve, even after a long time. Similar behaviour was also observed with the tablets from the completely dried granules. In such cases their disintegration time is given by two limits first when the individual granules separated from one another, and the second when they all passed through the sieve. In general it can be said that certain optimum moisture contents are necessary for certain granules. They are necessary not only for proper compression (as shown by the results of previous experiments), but also to impart the best physical properties to the compressed tablets.

The moisture analysis of the tablets, immediately after their compression shows that in almost all the cases, the compression of granules was accompanied by certain loss in their moisture content. Nelson and coworkers (9) in their study on the energy expenditure in the tablet compression process, found that there is always a certain rise in temperature of the tablets during compression. This rise depends however on the magnitude of the compressing pressure or the energy applied and further on the thermal capacity of the tablet material. The loss of moisture in the tablets on compression may hence be traced to this development of the heat and thus the moisture present may increase the thermal capacity of the tablet granulation.

(b) The influence of different storage temperatures on the loss of moisture and the properties of the tablets.

The tablets prepared were stored at two different temperatures of 35°C and 4°C for a period of four weeks. It was observed that all the tablets—though containing different amounts of moisture before storage—fell to an approximate constant moisture content which depended on the temperature of storage.

In the case of “Granulatum simplex” the moisture content of all the tablets, fell to 4.5% after storage at 35°C and to 10% when stored at 4°C. It is somewhat interesting to note that
all the tablets when freshly prepared from granules containing initial moisture between 10-11% had shown comparatively better properties of disintegration and hardness. These properties remained unchanged on storage at a temperature of 35°C while there was an improvement in the property on storage at a temperature of 4°C. The disintegration time showed a reduction to nearly one-third compared with the original tablets. The change in this property of the tablets prepared from granules containing higher or lower initial moisture than the optimum range, was greater when stored at a higher temperature than at a lower temperature. The hardness of the tablets also showed a similar tendency. They were relatively weaker after storage at 35°C than on storage at 4°C. Evidently these decreases in the properties of the tablets are also related to the greater loss in moisture on storage at higher temperatures.

The change in the properties of phenacetine tablets stored at the two different temperatures showed a similar trend. Their moisture contents approached an average of 1.5% on storage at 35°C and of 2.7% on storing at 4°C. Disintegration tests show that this property was very badly effected on storage at 35°C. The disintegration time of all the tablets, containing different initial moisture contents was very appreciably increased, though the tablets prepared at an optimum moisture content of 2.5% still showed relatively small disintegration times than all the others. On storage at 4°C, however, the disintegration time was very slightly increased in all the tablets. This increase in the time of disintegration occurred in almost the same order as in the initial tablets. The hardness measurements showed a general increase in hardness of all the tablets on storage at 35°C whereas storage at 4°C led to a general decrease of hardness compared to the tablets tested immediately after compression. Our results are in agreement with the observations made by Gross and Becker (10) while testing the properties of the several disintegrating agents in the tablets after storage for 500 hours at various temperatures. They also found that whereas cold had little effect, the properties of tablets were markedly affected by heat.
5. Conclusions

From our previous experiments, it was observed that the presence of an optimum moisture content was helpful in the successful compression of certain granulations. Our present investigations show that this optimum moisture content was also necessary to impart relatively better physical properties to the tablets. It was also found necessary to control the loss of such moisture by careful storage conditions. Storage at lower temperature showed a relatively smaller alteration in such physical properties than storage at higher temperatures.

6. Summary

1. Compression of the tablets generally leads to a certain loss of the initial moisture of the tablet granules.

2. The presence of optimum moisture contents in the tablet granules studied helps in producing tablets with comparatively better physical properties of disintegration and hardness.

3. The different initial moisture contents of the tablets are almost equalized by storing under similar conditions of temperature and atmospheric moisture.

4. Storage of tablets at lower temperatures leads to a smaller change in physical properties and moisture content than on storage at higher temperatures. The tablets prepared from "Granulatum simplex" showed a smaller time of disintegration and phenacetine tablets showed hardly any marked change in disintegration property when stored at 4°C for a period of four weeks.

7. References

(1) Pharm. Journ., 113, 245 (1951)
(2) ibid., 118, 485 (1954)
(3) Ewe G.E., J. Am. Ph. Ass., 22, 1205 (1934)
(4) Oxe M., Dansk Tid. Farm., p. 321, (1934)
(5) Smith and Stephenson, Pharm. Journ., 110, 439, (1950)
(6) Burlinson and Pickering, J. Pharm. Pharmacol, 2, 630, (1950)
(7) Mazurek, Die Pharmazie, p. 41, (1954)
(8) Higuchi et. al., J. Am. Ph. Ass. (Sc. ed.) 42, 192, (1953)
(9) Nelson et. al., ibid, 44, 225, (1955)
(10) Gross and Becker, J. Am. Ph. Ass. (Sc.ed.), 41, 157 (1952)
"A study on the compression of pure lactose tablets"

1. INTRODUCTION

Pure lactose tablets are very commonly used by homeopathic pharmacists as a basis for the administration of various homeopathic tinctures. Such tablets commonly weigh up to 100 mg and are used mostly in sizes of 6 to 9 mm diameter. An examination of commercial tablets shows that they are mostly deformed and often have their "caps" separated. The following investigations were undertaken to examine the possibility of producing well shaped and ethically presentable tablets.

The homeopathic specifications require such tablets to dissolve in the shortest possible time and produce an absolutely clear solution. It is further specified that such tablets should not contain any therapeutically active auxiliary substance. Lactose is well known to show several difficulties when compressed alone, this being probably due to the relatively hard and abrasive nature of its crystals. Its compression is facilitated by addition of certain amounts of "lubricant" or "anti-adherent" substances (1), which reduce friction with the metallic die-wall. Unfortunately most of the well known "lubricants" are relatively insoluble in water. In view of the homeopathic specifications, it is not possible to make use of such substances. Hence it was necessary to examine the various newly suggested water soluble "lubricants" and also consider the various physical and mechanical factors which influence compression.

Sperandio (2) has suggested that a 2% solution of pure liquid glucose is the most convenient granulating agent for soluble lactose tablets and an optimum 20-mesh size of the granules is most suitable for the preparation of tablets weighing 1 grain or less. Ray (3) had shown that Carbowax 6000 in the form of fine powder (100 mesh) and in amounts of 2% helps in the compres-
sion of pure lactose. Kügi (4) had, however, observed that in spite of very good flow-increasing properties, Carbowax 6000 has little effect in decreasing "binding" and "sticking" in the compression of "Granulatum simplex" Pharm. Danica IX. In view of such controversial observations, we decided to investigate the use of this agent in greater detail.

2. Experimental

It was found in the course of our preliminary experiments that liquid glucose, as suggested by Sperandio (2) could very well be substituted by pure anhydrous glucose in the granulating agent on account of its more convenient handling properties. Pure lactose was granulated with a 2% solution of anhydrous glucose in distilled water in an amount of 20% (100 cm³ of solution for 500 gm lactose). The moistened mass was pressed through sieve IV Pharm. Helv. V (225 meshes per cm²). The granules were dried overnight at room temperature (20°C) followed by a 2 hour drying in a hot air oven at 35°C. The granules were sieved through sieve V Pharm. Helv. V (729 meshes per cm²) and all the finer portion which passed through it was separated.

The granules were compressed on an eccentric machine (Comprex) and average flat faced circular punches were used with a die of 9 mm diameter. The weight of the tablets was adjusted to 100 mg. An attempt was first made to compress these granules alone, without any other auxiliary addition. This was however found to be extremely difficult since all the tablets produced showed "capping" and on many occasions showed a vertical cleavage. On examination of the die and punch surfaces a hard crust-like deposit was noticed. A careful study was made of the compression mechanism and the movement of the punches was closely followed. It was noticed that at the very beginning of ejection, a sharp cracking sound was produced and was accompanied by cleavage of the tablet surface while it was still in the die. Such a noise is often termed "crying of the machine" in tablet terminology. It indicates an extreme degree
of friction between the die and the tablet material. Further the lower punch was very difficult to move to its downward position after ejection of the tablet. It was often pushed down with a loud noise by the lever arm controlling its vertical movements. This indicated a serious "binding" condition which was evidently due to the great friction being produced.

It was decided to study the effect of addition of Carbowax 6000 as "lubricant". It was added in the form of a fine powder (120 mesh) in proportions of 1, 2, 3, and 5% separately to equal amounts of lactose granules and mixed thoroughly by tumbling in a glass bottle for 10 minutes. The comparative flow rate of these granules containing different amounts of Carbowax was tested according to the method of Münzel and Kägi (1). The results are presented in the following table:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Lubricant</th>
<th>Flow-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose granules</td>
<td></td>
<td>1,000</td>
</tr>
<tr>
<td>Lactose granules + Carbowax</td>
<td>1%</td>
<td>1,010</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>1,074</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>1,038</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>1,062</td>
</tr>
</tbody>
</table>

The above results show that Carbowax 6000 improved "gilding" of the lactose granules when added in amounts of 2%. The above granules containing different amounts of Carbowax were further tested for compressional behaviour and the following observations were made:

(a) the addition of Carbowax 6000 resulted in an appreciable improvement in keeping the tablet well bound together, during and after compression in the die.

(b) on being ejected from the die, the formed tablet now did not show the cleavage of its surface which was very
characteristic in compression of lactose granules without any addition of Carbowax.

(c) though the tablets were well formed in other respects they still showed an appreciable amount of "sticking" on the faces of both the punches resulting in a coarse appearance of the produced tablets. During a continuous run, it was found necessary to clean the punch surfaces after compression of every 20 tablets, if further good tablets were to be obtained.

(d) the addition of Carbowax 6000 in amounts of 2—5% had almost a similar effect on the compression of lactose.

The average disintegration time of these tablets was found to be 1 minute 16 seconds.

To study the effect of Carbowax 6000 in a 20% solution it was dissolved in warm 95% alcohol at a temperature of 35°—40°C and sprayed in amounts of 2% Carbowax on to the granules. These granules were dried at room temperature for ten minutes and mixed thoroughly before compression. A further improvement was noticed resulting in compression of about 50 tablets in a continuous run before it was necessary to clean the punches. The average disintegration time of these tablets was found to be slightly higher, being 1 minute 54 seconds.

It was decided to observe the influence of varying moisture content on the compressional behaviour of lactose granules. The moisture determination of lactose granules before and after adding 2% Carbowax 6000 in powder and also in solution form was made with Karl Fischer Reagent. The granules after completely drying possessed a moisture content between 4.32—4.80%. All these granules showed the above-mentioned difficulties of "binding" and "sticking".

A fresh granulation of lactose was prepared by the previously described method except that 2% of glycerine was added to the granulating solution to act as a hygroscopic agent and achieve a higher moisture content in the granules. The granules were dried at room temperature (20°C) for 36 hours, The moisture
analysis of the granules showed very little increase in the moisture content of the granules; moreover similar difficulties were experienced during compression.

With a view to avoid the adherence of the tablet crust to the faces of punches, a cleansing mixture was thoroughly rubbed in and the punch faces were washed with alcohol. A slight improvement was noticed but was still far from being satisfactory. It was therefore decided to repolish the set of die and punches completely first by mechanical milling and then nickeling. These newly polished punches were later used for the compression of lactose granules containing 2% Carbowax powder. It was observed in the course of quite long runs that perfectly good tablets were obtained without intermittent cleaning of the punch faces.

3. Discussion

Pure lactose produces a very great amount of friction when compressed alone under the pressure of the tablet machine. The high friction produced results in a corresponding strong adhesion of the surface of the compressed tablet to the metallic die wall. Due to the strong adhesion, the force required to break these points of adhesion and eject the tablet out of the die is correspondingly very high. This high force of ejection results in tearing or breaking of the body of the tablet which is weaker than its adhesion to the die wall. This is clearly shown by the typical cleavage and "capping" of the compressed tablets during ejection, even while they are in the die cavity. While the tablet is torn from its main body, it leaves a certain amount of its material still adhering to the die wall, more particularly at the points of adhesion. The amount of such material increased during a continuous run and offers increasing amount of friction and rubbing to the punches which is also accompanied by much sound.

Carbowax 6000 is found to possess weak lubricating properties and when added alone it does not offer sufficient lubrication to produce satisfactory lactose tablets. The important function
of a "lubricant" is to provide a surface film between the rubbing bodies and to weaken points of adhesion so that relatively much less force is required to break them and lead to the ejection of the tablet. Nelson and coworkers (5) had shown that Carbowax is comparatively less efficient in decreasing the force of ejection than the more preferable lubricants such as metallic stearates. Little and Mitchell (6) suggest the use of very highly polished surfaces of the dies and punches or use of non-ferrous metals for their construction, particularly for use in cases where lubricant substances may not be used. Burlinson (7) suggests the use of hard metals such as tungsten carbide for construction of die and punches for compression of very abrasive substances.

The results of our investigations show that if the weak lubricating effect of Carbowax 6000 be supplemented by use of well polished surfaces of punches and dies, it is possible to compress lactose into well shaped tablets. Such tablets also fulfill the other requirements of solubility, etc., according to homeopathic specifications.

4. Summary

(1) Pure lactose produces a high friction when compressed alone in a tablet machine. The friction produced leads to a strong "binding", "sticking", and "capping" of the lactose tablets with the metallic surfaces of die and punches. It is hence extremely difficult to prepare satisfactory lactose tablets without the addition of "lubricant" substances to decrease the friction produced.

(2) Among the water soluble lubricants, Carbowax 6000 decreases friction and the force required for the ejection of the tablets. It increases very much the flow of the lactose granules.

(3) The lubrication provided by Carbowax 6000 alone is insufficient to produce satisfactory lactose tablets with the ordinary die and punches used in tableting. Such tablets may still tend to stick to the punch surfaces.
(4) The use of extremely well polished and smoothed metal surfaces of the dies and punches decreases considerably the friction produced during tabletting.

(5) It is possible to produce satisfactory tablets of lactose by the use of very well polished die and punches and an addition of 2% of Carbowax 6000 powder. Such tablets meet the requirements of homeopathic specifications.

5. References

(2) Sperandio and Dekay, J. Am. Ph. Ass. (Sc. ed.), 41, 245, (1952)
(7) Burlinson, J. Pharm. Pharmacol., 6, 1062, (1954)
Chapter VII

"A comparative study of the properties of tablets compressed with eccentric and rotary types of tablet machines."

1. INTRODUCTION

There are two types of machines generally used for the preparation of tablets:

(a) Eccentric type
(b) Rotary type

The eccentric machines can only be operated with one die and one to four punches at a time. The rotary machines are however operated with a much greater number of dies and punches which may vary from fifteen to as many as forty sets used simultaneously. Evidently the latter type of machine is used where a very great output of tablets is required. The important differences in the construction and operation of both types of machines are briefly described below:

(a) Eccentric type:

In this type of machine, the die-seat remains stationary and the feeding device for the material is moved. The feeding device consists of a stationary hopper and a moving feeder shoe which may work in either of the following ways:

—by a backward and forward movement.
—by a semi-circular rotation around one fixed point

The movement of the feeding shoe, fills the material into the die cavity.

Pressure is applied by means of an eccentric which transmits the pressure to a plunger carrying the upper punch. By means of a suitable device, the length of the plunger can be adjusted so that the total pressure applied can be regulated. The lower punch forms a stationary base, whilst the upper punch penetrates into the die cavity and presses the material.
The important features in the operation of this type of machine have been discussed by Kägi (1).

(b) Rotary type:

In this type of machine, the feeding device remains stationary and the movement is effected by three distinct elements:

1. A circular "turret" which contains a number of dies along its rim.
2. A set of upper punches,
3. A set of lower punches.

A frame-shaped feeding device remains stationary and spreads the material over a number of dies which pass under it with the revolving "turret". The dies are filled when the lower punches are at their lowest position. As the moving dies and the punches reach the end of the feeder frame, the lower punches are slightly raised to a predetermined height, by an adjustable "dosing-cam" at the bottom. Thus a small amount of the material is expelled and leaves behind in the die, an amount equal to the weight of the finished tablet. Such a filling action ensures better and more uniform filling of the die, more especially because an excess of material is always first added.

Pressure is applied in this machine by passing both upper and lower punches between two adjustable rollers. The applied compressing pressure can be varied by adjusting the height of these rollers. The compression of the material takes place by simultaneous pressing from both the upper and the lower side.

The working principle of such a type of machine is shown in the diagram 10 and is briefly described as follows:

The "die-turret" a is revolved horizontally around its axis by a gear. The upper punches d and the lower punches e are guided into the dies and moved up and down by the stationary upper punch grooved channel g and the lower punch railing k.

The lower punch e moves along the lower platform i up to the feeder shoe p where the empty space of the die f is filled up with the material. On further movement of the "die-turret" a, the lower punch e is slightly raised by an adjustable "dosing-
Diagram 10—"The working principle of a Rotary machine."

Diagram 10: "The working principle of a Rotary machine."

Diagram labels:
- a: die-turret (rotating)
- b: upper pressure roller
- c: lower pressure roller
- d: upper punch
- e: lower punch
- f: die
- g: upper punch grooved channel
- h: pre-compression channel
- i: lower platform
- j: lower punch railing
- k: lower punch railing
- l: dosing-cam
- m: lifting-channel
- n: tablet scraper
- o: tablet
- p: filling shoe
- q: feeding-hopper
- a: die-turret

Diagram description:

The expels a small amount of material from the die $f$. The expelled material is diverted towards the centre of the turret and is carried round till it reaches the feeder frame again. The lower punch $e$ is again drawn downwards so that the material lies slightly below the top of the die during compression. As the lower punch $e$ passes under the lower pressure roller $c$, it is raised up again. The upper punch $d$ is elevated while passing over the filler shoe $p$, but is afterwards lowered by the upper grooved channel $g$. The upper punch descends down further.
and enters the die \( f \) while passing through the pre-compression channel \( h \). Immediately afterwards follows pressing due to the upper pressure roller \( b \) and coincides exactly with pressing by the lower punch \( e \) exercised by passage over the lower pressure roller \( c \). This simultaneous pressing from both the ends results in the compression of tablet \( O \).

The upper punch \( d \) is raised up again by the grooved channel \( g \) and is completely lifted away from the pressed tablet \( O \). As the lower punch \( e \) passes along the lifting channel \( m \), it is pushed up and takes with it the finished tablet \( O \). The ejected tablet is scraped off by the scraper \( u \) and directed towards the outlet channel built along the turret.

As the upper punch \( d \) reaches the filler shoe \( p \), it is raised to its highest position by the grooved channel \( g \). Simultaneously, the lower punch \( e \) is drawn downwards by the lower punch railings \( k \) and remains at its lowest position while passing under the feeder shoe \( p \).

In certain models of the Rotary machine, the tablet is formed by "double compression" of the material. Pressure is applied by comparatively small pressure rollers during the first compression cycle. Air is thus squeezed out of the material without subsequent ejection of the compact. A greater pressure is applied during the second compression cycle by passage of the punches under relatively bigger pressure rollers which compress the final tablet and eject it. Such a compression mechanism is generally recommended for materials showing greater tendency for air adsorption.

So far no systematic scientific investigations appear to have been conducted to determine any difference which may exist in the properties of tablets compressed by these two different types of machines. We have undertaken this investigation in our present study. The same granules were compressed to the same density in an eccentric and a rotary machine at the same time. The important properties of both batches of tablets were determined to ascertain any differences which might exist between them. A micro-hardness test was made to compare the relative
strength of the upper and the lower surfaces of the same tablet and also the strength of similar surfaces of tablets from the two machines. The results were subjected to statistical "analysis of variance" to judge the significance of variations.

2. Experimental

Two portions of the same granulation batch of Gantrisin* "Roche" (3,4—dimethyl-5-sulphanilamido-isoxazol) were compressed simultaneously in a single punch eccentric machine and in a rotary machine. The dies and punches used in both the machines were exactly of similar shapes and diameters. Since it was impossible to measure accurately the pressure applied by the machines, the tablets were compressed to the same density by carefully controlling the weight and the thickness of the tablets made from both the machines. The apparent density of the compressed tablets has been stated to be a highly sensitive function of the compressional pressures (2). The upper and the lower surfaces of the tablets from both the machines were also marked differently by using definite stamping marks engraved on the punches used for compression. It was thus possible to identify the upper and the lower sides of the tablets during testing of their surface hardness.

The tablets prepared were subjected to the following tests:

(a) Time of disintegration, using the "Erweka" apparatus.
(b) Mechanical strength:
   (1) Tensile strength measurement with the "Dynstat" apparatus described by Kägi (3).
   (2) "Monsanto hardness" measurement according to the previously described method.
   (3) "Loss on rolling" in the "Turbula" apparatus described by Kägi (3).
(c) "Surface hardness", with the "CEJ-Microhardness tester" according to the method described below.

(*) I take this opportunity of expressing my thanks to F. Hoffmann-La Roche & Co. AG., Basle for providing me with the above material.
Ten tablets of each type were used to test the time of disintegration of the tablets and average value calculated from the disintegration times of the individual tablets. The standard deviation \( s \) of the \( N \) individual measurements \( X_i \) and the mean value \( \bar{X} \) was calculated from the formula:

\[
s = \sqrt{\frac{(X_i - \bar{X})^2}{N-1}}
\]

An upper and lower limit of confidence of the average mean value \( \bar{X} \) was calculated from the standard deviation \( s \) as follows:

\[
\bar{X} \pm \left( t_{0.05} \cdot s \right) = \text{upper limits of confidence} - \text{lower limits of confidence}
\]

where, \( \bar{X} \) = average disintegration time

\( t_{0.05} \) is the \( t \) value for 9 degrees of freedom

\( s \) = the standard deviation

The upper and lower limits of confidence signify that, if an infinite number of samples of the same batch of tablets be tested for D. time, the average value of 95% such repetitions (with \( t_{0.05} \)) will lie between these two limits.

The test for "Surface hardness" with "CEJ-Microhardness Tester":

Spengler and Kaelin (4) were the first to refer to a method of comparing the surface hardness of different tablets. They used an instrument which is commonly used in metallurgy for similar purposes. In this method, a small diameter steel ball is allowed to penetrate the sample surface under a certain load applied for a known period. They used a ball of 1, 2 mm diameter under a load of 200 gm applied for 10 seconds and 1500 gm applied for 20 seconds. They compared the depth of penetration of the metal ball into the surfaces of different tablets. The greater the depth of penetration, the weaker is the tablet. Smith (5) also referred to similar method. He used a sharp edged diamond pyramid as the penetrating head, in place of the steel ball used by the earlier workers. He measured the area of the indentation produced by applying
a load of 1 kg for a known period. From the area of indentation, the hardness in Vickers Pyramidal Numerals (V.P.N.) could be calculated. The V.P.N. are among the recognised units for expressing the hardness of metallurgic samples.

The tablet surfaces are generally much softer than the metallic bodies. Hence, there is great possibility that, using such indenting pressures as above, the very fine penetrating heads may easily reach the bottom of the tablet samples. Besides the fragile and soft nature of most of the tablet constituents, it is very seldom possible to get a sharp edged indentation such as is necessary for an accurate measurement of the surface area. In view of such difficulties, none of the above mentioned methods could be used effectively, if the strengths of different surfaces of the same tablet are to be compared.

We used the instrument known as "micro hardness tester"* in our investigations. Such instruments are used in metallurgy for measuring the hardness of very soft metallic surfaces such as aluminium, etc. They permit the measurement of the hardness of different surfaces without affecting the deeper layers of the body of the tablet.

The test sample must be held firmly in position because of the extreme sensitivity of the instrument. Even a slight change in the position of the test sample during pressing can lead to significant differences in the results. Hence, we used specially made steel moulds, of exactly the size and shape of the tablets to seat and hold them firmly during the test. The steel moulds were further held in position by clips on the platform of the apparatus.

The "CEJ-Microhardness tester" used in our investigations and also shown in the photograph 8 consists of the following important parts:

(a) a platform to seat and hold the test samples firmly during the tests. It can be raised or lowered by a screw adjustment provided at the bottom.

* The "CEJ-Microhardness tester" mentioned is made by Aktiebolaget C. E. Johansson, Eskilstuna (Sweden).
"CEJ—Microhardness Tester"
(b) a "mikrokator" dial which contains a calibrated scale with divisions of 0.002 mm and an indicator needle which moves over this scale to indicate the depth to which the pressing head sinks into the sample.

(c) a mechanism for application of load in which different weights can be easily replaced. The load assembly can be geared to act on the sample body by the movement of a lever arm. This pressure assembly can be disconnected from the test-sample by raising the lever arm.

(d) a "microscope" to read the area of indentation. For our investigations this was not used at all.

The pressing head consisted of a metal ball of 2.5 mm diameter and was used under a load of 25 gm applied for 10 seconds. The depth of penetration of this metal ball in the tablet surface was read on the scale. In order to suppress the superficial unevenness of the surface at different points, an initial load of 3 gm was applied in all measurements and taken as zero-point, before applying a further load of 25 gm. A number of points were marked on each tablet surface, in identical positions, where the hardness was to be tested. The tablet along with the mould was carefully seated on the platform and the pressing head was placed exactly on the marked point of the tablet surface. By lowering of "pressing assembly", the ball was brought to a distance of 1 mm above the tablet surface. Adjustment of a screw provided at the bottom, raised the whole platform and the tablet slowly so that the tablet surface touched the steel ball and the indicating needle at the dial reached the zero point. The "pressing assembly" was then geared into action by slowly lowering the lever arm. The pressure was applied for exactly ten seconds and the corresponding depth of penetration was read off the scale of the dial. After this period, the "pressing assembly" was disconnected by raising the lever arm. A greater depth of penetration indicated a comparatively weaker surface.

Eight different points were selected on each surface and five tablets were tested from each batch. The difference in depth of penetration at different points of the surfaces were
non-uniform and very slight. The results were therefore subjected to statistical "analysis of variance" to establish the significance of such differences.

5. Results

The results of the various tests are presented in the following table:

**TABLE 13**

<table>
<thead>
<tr>
<th>TESTS</th>
<th>Type of tablet machine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eccentric</td>
</tr>
<tr>
<td><strong>DISINTEGRATION TIME</strong></td>
<td></td>
</tr>
<tr>
<td>Average D. time of 10 tablets, in (seconds)</td>
<td>361,5</td>
</tr>
<tr>
<td>Standard deviations, of individual values from the average in (seconds)</td>
<td>27,00</td>
</tr>
<tr>
<td>Upper and lower limit of confidence in (seconds)</td>
<td>582,3</td>
</tr>
<tr>
<td></td>
<td>140,7</td>
</tr>
<tr>
<td><strong>MECHANICAL STRENGTH</strong></td>
<td></td>
</tr>
<tr>
<td>Monsanto hardness in (kg)</td>
<td>6,825</td>
</tr>
<tr>
<td>Tensile strength with &quot;Dynstat&quot; (relative value)</td>
<td>5,42</td>
</tr>
<tr>
<td>&quot;Loss on rolling&quot; with &quot;Turbula&quot; in (%)</td>
<td>4,32</td>
</tr>
<tr>
<td><strong>SURFACE PENETRATION</strong></td>
<td></td>
</tr>
<tr>
<td>Average depth on upper surface in (µ)</td>
<td>7,06</td>
</tr>
<tr>
<td>Average depth on lower surface in (µ)</td>
<td>5,36</td>
</tr>
</tbody>
</table>
Both the upper and lower surfaces of tablets made with both types of machines were tested for their surface hardness. The variations in the depth of penetration at different points of the surfaces were subjected to statistical "analysis of variance." The results are presented in the following tables:

**TABLE 14**

The "analysis of variance" of surface penetration of tablets made with eccentric machine.

<table>
<thead>
<tr>
<th>Sources of variation</th>
<th>DF</th>
<th>Sum of squares s.s.</th>
<th>Mean Squares M.s.</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper and lower sides</td>
<td>1</td>
<td>57.95</td>
<td>57.95</td>
<td>9.24**</td>
</tr>
<tr>
<td>Individual tablets</td>
<td>4</td>
<td>39.49</td>
<td>9.87</td>
<td>1.57</td>
</tr>
<tr>
<td>Interaction</td>
<td>4</td>
<td>26.38</td>
<td>6.59</td>
<td>1.05</td>
</tr>
<tr>
<td>Error</td>
<td>70</td>
<td>439.16</td>
<td>6.273</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>562.98</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

In addition, the general variations between the both sides and among the five tablets individually were calculated as:

Variation between sides in general \((F) = \frac{\text{M. s. of L. and U. sides}}{\text{M. s. sides . Individual tabs}} = 8.79^{**}\)

Variation among tabs. in general \((F) = \frac{\text{M. s. of individual tabs.}}{\text{M. s. sides . Individual tabs}} F = 1.49\)
TABLE 15

The "analysis of variance" of surface penetration of tablets made with rotary machine.

<table>
<thead>
<tr>
<th>Sources of variation</th>
<th>DF</th>
<th>Sum of squares s.s.</th>
<th>Mean Squares M.s.</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper and lower sides</td>
<td>1</td>
<td>8.3</td>
<td>8.3</td>
<td>2.59</td>
</tr>
<tr>
<td>Individual tablets</td>
<td>4</td>
<td>42.49</td>
<td>10.62</td>
<td>3.32*</td>
</tr>
<tr>
<td>Interaction</td>
<td>4</td>
<td>19.66</td>
<td>4.915</td>
<td>1.53</td>
</tr>
<tr>
<td>Error</td>
<td>70</td>
<td>223.79</td>
<td>3.197</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>294.24</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Variation between sides, in general (F) =

\[
\frac{\text{M. s. of L. and U. sides}}{\text{M. s. of sides \cdot Individual tabs}} = 1.68
\]

Variation among tabs, in general (F) = 2.16

A "combined analysis of variance" was made to compare the surface hardness of upper and lower surfaces of tablets from the two machines. The value for the "least significant difference" was calculated to be 40.00 μ. The difference between the sum of all the measured values of the upper surfaces of tablets from both the machines was 25.60 μ and was less than the "least significant difference" mentioned above. Hence it was insignificant. The difference between the sum of all the measured values of the lower surfaces of the tablets was 68.30 μ and was greater than the value of the "least significant difference" and was hence significant.

The marks (*) on the F ratio represent a significant variation with 5% probability and (**) represent the same with 1% probability.
4. Discussion

The results in Table 13 show that the tablets compressed with the rotary machine were comparatively weaker than those compressed with the eccentric machine.

Higuchi (2) and Kägi (6) had shown that the apparent density of the compressed tablets prepared from a particular granule formulation is a highly sensitive function of the compressional pressures. They also observed that properties such as disintegration time, mechanical strength, and hardness are also related to the density and are all equally sensitive to the applied pressures. Our results show that the manner of pressure application also influences significantly the properties of the prepared tablets. Although the similar apparent density of the tablets indicated the use of probably similar compressional pressures, the testing of the other properties of such tablets did not support this presumption. The tests indicate that “one sided compression” (as in eccentric machines) requires the application of higher pressures to obtain the same “apparent density” of the tablets than those necessary in compression from both sides (as in rotary machines). Consequently, the tablets compressed with the eccentric machine were stronger than those compressed with the rotary machine.

During the compressional process, the densification of the tablet granules is accompanied by a considerable decrease in the amount of adsorbed air. These phenomena are dependent on the following:

- the magnitude of the compressing pressure
- the length of time during which pressure is allowed to act
- the manner in which the pressure is applied i.e. uni- or bilateral

Obviously, all these factors influence jointly the opportunities for escape of the air which is compressed on the application of pressure. The opportunities are much smaller, if the pressure be applied from one side only or if applied too quick. If how-
Diagram 11.—Mechanism of pressure of Eccentric Machine.

1) Punch at the lowest point

2) Punch in the middle

3) Punch at the highest point

Diagram 11a.

Velocity curve:

\[ v = 0 \]  \hspace{1cm} \text{in the middle}  \hspace{1cm} \text{highest point}  \hspace{1cm} \text{in the middle}  \hspace{1cm} \text{lowest point}  

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ever the pressure be applied from both sides and allowed to act comparatively longer, even a relatively lower pressure may achieve the same densification otherwise obtained at higher pressures. Besides the advantage of bilateral compression, the rotary machine allows a somewhat longer period of pressure when the punches pass under the length of the compressing rollers. On the other hand the eccentric machine applies pressure as a sudden stamping stroke acting during a shorter time than in the rotary machine. From a consideration of the actual time of compression for the tablets in both the machines, it was observed that the rotary machine allowed almost double the time in the case of eccentric machine.

For the compression of Gantrisin tablets the rotary machine fitted with 16 sets of die and punches was being run at a speed of 30 rotations of the die-turret per minute. Thus every die was undergoing a complete rotation every 2 seconds. In view of the fact that nearly 2-3 tablets simultaneously remain under pressure of varying degree while passing under the pressure rollers, it may be assumed that they undergo compression individually for a period corresponding to that required for the movement of 1/8 of the die-turret circumference.

Hence the actual time for compression of each tablet in the rotary machine = \( \frac{2}{8} = 0.25 \) seconds.

The eccentric machine was however run at a speed of 60 tablets per minute for preparing the Gantrisin tablets. This represents a time of 1 second for compression of each tablet. During this time, the upper punch travels a complete up and down movement. Hence the time taken for only the downward travel for compression must be half or 0.5 seconds. Such distance was measured to be 3.6 cm. The actual time of compression is however only from the moment the upper punch touches the granules in the die and travels to the maximum depth available for the particular tablet. Such distance in the die was measured to be 0.6 cm. It was further observed with the help of paper models as also represented diagrammatically that to level the upper punch for 0.6 cm an angle of 45° is formed by
the eccenter. Moreover the angular velocity remains constant, in contrary to the punch velocity.

Since time for one full rotation for 360° is 1 second, it would, be half (0.5 second) for 180°, which represents one way up or down travel of the upper punch.

For 45°, it would be \( \frac{0.5 \cdot 45}{180} = 0.125 \) seconds.

Thus it shows that the time of compression for the eccentric machine was half as long as that in the rotary machine (0.125 sec. against 0.250 seconds.) This explains perhaps why the tablets made with eccentric machine required greater pressures than the rotary machine, to achieve the same densification.

It may also be observed that the properties of disintegration and mechanical strength seem to be more sensitive functions of the magnitude of compressing pressures than the "apparent density".

The measurements of surface hardness with the microhardness tester show that they can be used most effectively to evaluate the strength of different tablet surfaces. In view of the small and non-uniform variations in the individual measurements, the significance of the variations should be confirmed by statistical "analysis of variance". The results of these tests may be summarised as follows:

1. The tablets compressed with eccentric machine showed significant differences in the hardness of the upper and lower surfaces of the same tablet.

2. The tablets compressed with the rotary machine are more uniform in the strength of the upper and lower surfaces and showed no significant differences.

3. When similar surfaces of tablets compressed with the two machines were compared with one another, they showed no difference in their upper surfaces while there did exist significant differences in the lower surfaces.

These results suggest that the bilateral compression of the rotary machine leads to a greater uniformity in the strength of different surfaces of the same tablets.
5. Summary

1. The manner of application of pressure, which may be uni- or bilateral, influences the properties of the tablets to a significant extent.

2. Densification of a particular tablet formulation to a tablet of a certain density, requires higher pressure when applied from only one side than on application from both sides.

3. The properties of disintegration, mechanical strength, and hardness are more sensitive to the magnitude of the compressional pressure than the "apparent density".

4. The "apparent density" of the compressed tablets is jointly influenced by the magnitude of the pressure, the length of time and the manner of application of pressure. A relatively smaller pressure can achieve the same "apparent density" of compressed tablet, if applied from both sides and if allowed to act for a longer period.

5. There appears more non-uniformity in the relative strength of the upper and lower surfaces of compressed tablets, when compressed from only one side. A bilateral compression results in a more uniform strength of the different tablet surfaces.

6. References

CHAPTER VIII

"A consideration of different shapes and sizes in tablet making"

1. INTRODUCTION

A great variety of shapes and sizes is available among commercial medicinal tablets. These may differ from one manufacturer to another even for the same type of tablet. The most common shape of the tablets is a circular body with flat or slightly convex sides. There are also offered, however, rectangular, triangular and many other shapes in the case of speciality tablets. In the Scandinavian countries where the Pharmacopeia provides official specification of formula and the method of preparation of the various tablet formulas, the size and shape is also specified officially. These Pharmacopeias specify the size and shape of the die and punches to be used for compression of each tablet formulation. In England, however, great concern has been shown due to this variation and official specifications for the tablets contained in the British Pharmacopeia (1) are being considered.

The preliminary consideration in selection of particular shapes and sizes of the tablets is essentially ethical. These dimensions should be such that the tablets prepared have a pleasing appearance. Similarly, the ultimate use of a tablet is also an important consideration. A tablet meant for making solutions will be required to dissolve as quickly as possible and hence it should be as thin as possible. This will require a larger diameter than average tablets of the same weight. Tablets which are to be dissolved slowly in the mouth, i.e., lozenges, troches etc., should be flat for convenience to the user and thick enough to have a “lasting effect” on which the efficiency of the tablet will depend. Similarly, tablets which have to be coated after compression must have a deep convex shape and be harder.
than other tablets. It is more convenient to have as thin edges as practicable since it is easier to cover a thin edge during the coating process.

In addition to the above considerations, there can also be important technical reasons which may influence the selection of particular dimensions of the tablets. It is often found that the preparation of deep convex tablets is more difficult. The compression of tablets with deep concave punches shows more chances of producing "capping" than that with flat faced punches. Kägi (2) refers to a difficulty experienced in compressing biconvex tablets from Salol crystals, which showed consistent "capping" while it was quite easy to compress them into flat faced tablets. Similarly, the density and compression ratio (the extent to which a powder can be compressed) are also important factors. Thus a lighter and less dense material will need a bigger size die than a similar weight of more dense material.

Quite a number of workers (3) have suggested the various sizes and diameters of the dies and punches which may be used for successful tabletting of different weights, but cases do arise where individual considerations must be given more attention.

Seelig (4) discussed the effect of size on the compact prepared in "powder metallurgy" and remarked that the reduction in height for a given diameter or an increase of diameter for a given height yields higher and more uniform densities. With increase in ratio of die-wall area to the pressing area, the densities drop. From an extensive investigation conducted by Kamm, Steinberg and Wulff (5) on such compacts, they conclude that a density maximum exists at the top edges and the lowest density at the bottom edges of all the compacts prepared by one-sided compression. The density near the cylindrical surfaces of the compact decreases generally with the height from top to bottom and the density near the top centre of the compact is less than the density at the bottom centre. With increasing pressure, the average density increases, but variation in the density throughout the compact also increases. With increased
compact diameters a more uniform density distribution was secured for the same ratio of height to diameter. At the same time, an increase in height caused a less marked increase in density variation than that for smaller diameter compacts. Further, with an increase in the ratio of diameter to height of the compact, the die-wall exerts correspondingly less friction. Goetzel (6) suggests that selection of the optimum height of a compact should be carried out in relation to the ratio between the cross-section area and the perimeter area. Thus the most favourable height of a compact may be expressed in relation to the ratio of volume to the surface as

\[ h = \frac{v}{s} \]

where, \( v = \) volume of the compact \( s = \) surface in contact with die-wall

Since both the volume \( v \) and the surfaces are functions of the height, the expression may also be written as

\[ h = \frac{A}{P} \]

where, \( A = \) cross section area \( P = \) perimeter area

Thus in case of a cylinder, the height is

\[ h = \frac{d^2}{4} \frac{d}{4} = \frac{d}{4} \]

or \( d = 4h = 4 \frac{A}{P} \)

where, \( d = \) diameter of the compact

The compression of curved faced compacts, such as convex tablets, needs more careful consideration than a flat shape. Smith (7) in a detailed review of the suitable dimensions for the various convex tablets, suggests the following:

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Convex tablets not to be coated</th>
<th>Convex tablets for coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>10,0 mm</td>
<td>10,0 mm</td>
</tr>
<tr>
<td>Thickness at crown</td>
<td>5,0 mm</td>
<td>5,0 mm</td>
</tr>
<tr>
<td>Thickness at edge</td>
<td>2,5 mm</td>
<td>1,0 mm</td>
</tr>
<tr>
<td>Convexity or Radius of curvature</td>
<td>15,0 mm</td>
<td>7,5 mm</td>
</tr>
</tbody>
</table>
It can be observed from the dimensions suggested above, that convex tablets must be at least twice or even five times more highly compressed at their edges than that at the centre. This indicates that in such tablet shapes, a non-uniform compression will take place at different points of the compact surface. Evidently such a non-uniformity depends mainly on the radius of curvature of the punches used. It further suggests that in such curved tablets the distribution of pressure will also be different at the various parts of their surfaces. Furthermore, different pressures may be required for the compression of different shapes of the tablets. Janson (8) suggests that the maximum pressures which can safely be applied, without damaging the punches are dependent on the shapes of the punches. In case of deep concave punches, the limit of such pressure is reached at almost half the pressures applicable with flat faced punches.

In our following investigations, we have undertaken a comparative study in the properties of tablets, compressed from "Granulatum simplex" with a same unit area pressure used for compressing three different shapes and sizes of the tablets.

2. EXPERIMENTAL

A series of tablets was compressed using three different sets of dies and punches with different shapes and sizes. All the three dies A, B, C were cylindrical having diameters of (A) 6 mm, (B) 6,5 mm and (C) 7,5 mm respectively. The punches for A were flat faced, whereas those for B and C were concave. The concavity of the punches for B and C was also different. The radius of curvature of the punches of die B was 3,5 mm and of those for die C was 6,0 mm. With each of these sets of die and punches, a similar weight of the granules was compressed on the BRINELL PRESS, using the same unit area pressures. (The unit area pressures kg/cm² being calculated by dividing the total force by cross-sectional area of the pressing surfaces.) This necessitated the use of a different total force of compression for each of the three sizes. The compressing force for the three
being \( A = 500 \text{ kg} \), \( B = 582 \text{ kg} \) and \( C = 777 \text{ kg} \) which were all equivalent to a pressure of \( 1769 \text{ kg/cm}^2 \).

Granulatum simplex (containing Amyl. solani 700 gm, Saccharum lactis 300 gm and granulated with mucilage gelatin 4%) was lubricated by addition of 5% of stearine-talc. For the preparation of all these tablets, accurately weighed amounts of 150 mg of granules were taken. The punches and the dies used were thoroughly cleaned each time before compression.

Afterwards the tablets were subjected to the following tests by the procedures already described in the previous chapters:

1. **Disintegration test**, by using the "Erweka" disintegration apparatus.
2. **Mechanical strength tests**:
   - Monsanto Hardness test
   - "Loss on Rolling" in the "Turbula" apparatus.
3. **Surface Hardness** test by using the "CEJ" Microhardness tester.

### 3. RESULTS

The results of the various tests applied to the three different shapes of the tablets compressed from "Granulatum simplex" are presented in the following table:

<table>
<thead>
<tr>
<th>Die size</th>
<th>Tablet shape</th>
<th>Cross section area cm(^2)</th>
<th>Total force of compression kg*</th>
<th>Disintegration Time seconds</th>
<th>Monsanto hardness kg</th>
<th>Loss on Rolling%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>flat</td>
<td>0.2826</td>
<td>500</td>
<td>200</td>
<td>4.55</td>
<td>2.56</td>
</tr>
<tr>
<td>B</td>
<td>concave</td>
<td>0.329</td>
<td>582</td>
<td>170</td>
<td>3.99</td>
<td>0.57</td>
</tr>
<tr>
<td>C</td>
<td>concave</td>
<td>0.439</td>
<td>777</td>
<td>170</td>
<td>2.90</td>
<td>0.55</td>
</tr>
</tbody>
</table>

* The total force of compression indicated above corresponds to a pressure of \( 1769 \text{ kg/cm}^2 \).
The measurements made with the "Micro-hardness tester" indicated the following depths of penetration (μ) on their surfaces:

- Die A  \( \overline{X}_A \) 3.60
- Die B  \( \overline{X}_B \) 4.20
- Die C  \( \overline{X}_C \) 4.55

In each case, five tablets of one type were selected and five different points were selected and tested on each surface. The average values from all these surfaces (lower and upper together) are represented in the above stated "depth of penetration" (μ) for each type of tablet (\( \overline{X}_A, \overline{X}_B, \overline{X}_C \)).

From the results of statistical "analysis of variance" made to determine if there existed any significant differences among such values of the three different shapes, the following results were obtained:

**TABLE 17**

The "analysis of variance" of the depth of penetration values of the three different shapes of the tablets.

<table>
<thead>
<tr>
<th>Sources of variation</th>
<th>DF</th>
<th>Sum of squares (s.s.)</th>
<th>Mean square (M.s.)</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet shapes</td>
<td>2</td>
<td>21.11</td>
<td>10.55</td>
<td>6.34</td>
</tr>
<tr>
<td>Sides of each tablet</td>
<td>1</td>
<td>1.31</td>
<td>1.31</td>
<td>—</td>
</tr>
<tr>
<td>Interaction</td>
<td>2</td>
<td>5.19</td>
<td>2.595</td>
<td>1.66</td>
</tr>
<tr>
<td>Error</td>
<td>132</td>
<td>227.90</td>
<td>1.6635 (s²)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>255.51</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

According to the above statistical analysis, there are significant differences between the different shapes of the tablets even when considering 1% probability (\( F_{0.01} = 4.786 \)).

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With a view to ascertain where such differences exist among the particular shapes, the following statistical "t" test was applied.

\[
t = \frac{\bar{X}_A - \bar{X}_B}{s} \cdot \sqrt{\frac{N_A \cdot N_B}{N_A + N_B}}
\]

where,

\[
t_{0.05} \text{ (for DF=132)} = 1.9785
\]

\[
s^* = \sqrt{s^2} = \sqrt{1.6635} = 1.29
\]

\[
N_A = 50 \text{ and } X_A = 3.60
\]

\[
N_B = 48 \text{ and } X_B = 4.20
\]

\[
N_C = 40 \text{ and } X_C = 4.55
\]

or

\[
\frac{(t_{0.05} \cdot s)}{\sqrt{\frac{N_A \cdot N_B}{N_A + N_B}}} = (\bar{X}_A - \bar{X}_B)
\]

(*') \( s \) is the standard deviation of all the measurements of the various shapes and sides when taken together.

\[
N = \text{ number of total measurements of lower and upper surfaces of each die size } N_A, N_B, N_C
\]

\[
\frac{2.55}{\sqrt{\frac{50 \cdot 48}{50 + 48}}} = 0.51 \text{ and } X_B - X_A = 0.60
\]

(significant difference)

\[
\frac{2.55}{\sqrt{\frac{50 \cdot 40}{50 + 40}}} = 0.540 \text{ and } X_C - X_A = 0.95
\]

(significant difference)

\[
\frac{2.55}{\sqrt{\frac{48 \cdot 40}{48 + 40}}} = 0.545 \text{ and } X_C - X_B = 0.35
\]

(insignificant difference)

The above test shows that whereas the flat faced tablets showed a significant difference from both the convex tablets (as in the first two cases above), there was no significant difference between the two convex tablets themselves (as in the third case above).
4. DISCUSSION

The results show that in spite of the use of similar unit area pressures for the compression of three different shapes of tablets from the same granulation, there exist appreciable differences in their properties. The tablets compressed from "Granulatum simplex" show that the flat faced tablets were comparatively stronger than both the convex tablets. The former had a comparatively higher "Disintegration Time" and a greater "Monsanto Hardness" than both the convex tablets. An interesting difference was observed in "loss on rolling" in comparison to the convex tablets. This is possibly due to the fact that the convex shape of the tablets offers relatively much fewer points of contact with the rubbing walls of the glass bottle than the cylindrical shapes.

On the other hand, the two convex type of tablets which had different sizes and varying convexities, showed similar "disintegration time" and quite identical "loss on rolling" in the Turbula. Their slightly different hardness shown by the "Monsanto hardness tester" may possibly be due to their different diameters and thickness, since the tablets are placed edgewise while applying the crushing force by the "Monsanto tester."

The results of the surface-hardness measurements with the "Microhardness tester" showed on a statistical analysis of variance of a number of such measurements, that the flat faced tablets were comparatively stronger than the two convex tablets. Whereas the flat faced tablets differed significantly from the two convex shapes, there were no significant differences in the surface hardness of the two convex shapes.

5. SUMMARY

1. The different shapes of the tablets (as flat faced or convex faced etc.) show a variation in physical properties even when compressed with similar unit area pressures.
2. The flat faced tablets show a relatively greater strength than the convex shape tablets.
3. The flat faced tablets, in spite of their relatively greater strength, show a higher "loss on rolling" as compared with slightly weaker convex tablets.

6. REFERENCES

(1) Denston T. C., J. Pharm. Pharmacol., 6, 1068 (1954)
   b. Moe and Würtzen, Farm. Tid 54, 621, (1944)
   c. Little and Mitchell, "Tablet Making" 1949, p. 53
(6) Goetzel, "Powder Metallurgy" vol. 1, p. 294
ZUSAMMENFASSUNG
ZUSAMMENFASSUNG

I
Einleitung


Die Kunst des pharmazeutischen Tablettierens ist weitgehend empirisch. Grundlegende wissenschaftliche Arbeiten darüber existieren nur wenige; zahlreicher sind hingegen die Forschungen auf dem verwandten Gebiete der Pulvermetallurgie.

(1) Theoretische Betrachtungen über die Komprimierung von Pulvern

In der Pulvermetallurgie werden folgende Stadien der Pulverkomprimierung durch Druckanwendung unterschieden:

(a) dichte und hohlraumarme Packung der Pulverpartikel aus Metall

(b) elastische und plastische Deformation der Partikel

(c) Kaltverfestigung mit oder ohne Bruch der Partikel, verbunden mit erhöhter Adhäision der Partikel dank der großen Kontaktroberfläche

Für die Erklärung der Tablettenbildung scheint aber die Annahme der "mechanischen Ineinanderschachtelung oder Verkeilung" der Partikel besser geeignet zu sein als die der Presskörperbildung durch Adhäision.

An Tableten, die zu gleichen Teilen aus einem Phenazetin- und einem Traubenzuckergranulat zusammengesetzt sind, kann deutlich die Verformung der Phenazetingranulatkörner durch den Pressvorgang gezeigt werden. nachdem man durch Einlegen der Tablette in Wasser den Traubenzucker herausgelöst hat (Photographien 1-4).
(2) Die Schwierigkeiten der Tablettenherstellung

Beim Tablettieren können folgende Störungen auftreten:

(A) Kleben

Das Kleben der Tablettenmasse kann entweder nur an der Matrizenwandung oder an den Stempeloberflächen oder an beiden Stellen auftreten. Die Gründe dafür sind:

(a) zu feuchtes Granulat
   —wegen ungenügender Trocknung,
   —wegen zu feuchter Luft oder Hygroskopizität des Materials,
   —aus dem Innern grosser zerbrochener Granulatkörner tritt noch Feuchtigkeit aus.

(b) verkratzte oder schlecht polierte Stempel—oder Matrizenoberflächen

(c) zu viel Spielraum des unteren Stempels in der Matrise, so dass Pulver in den Zwischenraum fällt, wo es das 'Knarren' der Tablettenmaschine verursacht.

(B) Deckeln and Springen

Bei dieser Erscheinung springt entweder beim Ausstossen der Tablette eine deckelartige Schicht ab oder es zeigen sich Risse und Sprünge in der Seitenfläche der Tablette. Die Gründe dafür können sein:

(a) zu grosser Pressdruck,

(b) zu starke Adsorption von Luft durch 'aerophile' Substanzen, die sich nach der Pressung wieder ausdehnt,

(c) Überschuss an feinen Partikeln,

(d) zu weiches, mechanisch zu wenig widerstandsfähiges Granulat,

(e) zu trockenes Granulat,

(f) Substanzen mit ungünstiger Kristallform, die vorher durch Pulverisieren zu zerstören ist,

(g) abgenutzte oder schlecht polierte Metalloberflächen der Stempel und der Matrise,
zu hohe Pressgeschwindigkeit.

Ähnliche Schwierigkeiten treten auch in der Pulvermetallurgie auf.

Aus den Tablettierungsschwierigkeiten lässt sich die folgende Zusammenstellung der Faktoren, die bei der Herstellung von Tabletten eine Rolle spielen, ableiten:

**Physikalische Faktoren:**

(A) Partikel-Eigenschaften
   (a) Aerophilie und Hydrophilie
   (b) Korngrößenverteilung der Partikel
   (c) Kristallstruktur der zu pressenden Substanz
   (d) Bindeigenschaften der Partikel

(B) Tablettengröße und — form

(C) Größe des Pressdruckes

(D) Feuchtigkeitsgehalt der Partikel

(E) die atmosphärischen Bedingungen (relative Feuchtigkeit, Temperatur)

**Mechanische (technische) Faktoren:**

(A) Art und Richtung des Druckes (Rundläufer oder Exzenter-Maschine)

(B) Pressgeschwindigkeit

(C) Matrize und Stempelpaar

   (a) Güte der Politur der Metalloberfläche
   (b) chemische Zusammensetzung des Konstruktionsmaterials
   (c) Größe und Form

Anhand von Beispielen wird die Bedeutung dieser Faktoren erläutert und belegt.

**II**

Die Eignung von Stärken als Tablettengleitmittel

Bei den Gleitmitteln sind 2 Gruppen zu unterscheiden:

(a) **Eigentliche Gleitmittel**, die das Nachrutschen der Tablettenmassen im Fülltrichter und im Gleitschuh (Füllschuh) verbessern, und
(b) Antiadhäsions-oder Gegenklebmittel (Schmiermittel), welche die Adhäsion der gepressten Tablette an den Metalloberflächen der Matrise und der Stempel herabsetzen.

Weder das deutsche Wort 'Gleitmittel' noch das englische 'Lubricants' umschreibt beide Aufgaben dieser Hilfstoffgruppe, so dass eigentlich 2 Ausdrücke gewählt werden müssen (z. B. Gleitmittel und Schmiermittel; Glidants und Lubricants).

Die Prüfung verschiedener Stärken und von mit Epichlorhydrin verätherter Stärke auf ihr Vermögen, die Gleitfähigkeit von Granulaten im 'Klappentrichter' zu erhöhen, ergab, dass sie sogar bis etwa zweimal so wirksam wie Talk sind. Zwischen den Stärkesorten selbst sowie zwischen natürlicher und verätherter Stärke bestehen aber keine signifikanten Unterschiede.

Als Schmiermittel hingegen, welches den Ausstoss der Tabletten aus der Matrise erleichtern soll, sind die Stärken dem Talk deutlich unterlegen. Gemessen wurde dieser Unterschied zwischen Talk und Stärken mit der Brinellpresse, mit deren Hilfe bestimmt wurde, was für eine Kraft aufgewendet werden muss, um die mit einem bestimmten Druck gepresste Tablette aus der Matrise auszustossen.

III

Der Einfluss verschiedener grosser Pressdrucke und der Tablettendicke auf die Reibung beim Tablettieren

Kraft muss während des Tablettierens aufgewendet werden:

(a) beim Komprimieren der Tablettenmasse zu einem Presskörper und
(b) beim Tablettenausstoss.

Der Druck beim Tablettieren darf aber nur so gross sein, dass die Tablette noch in nützlicher Frist zerrällt.

Beim Tablettenausstoss hängt die anzuwendende Kraft von der Reibung der Tablette an der Matrizenwandung ab, die man durch 'Schmiermittelzusatz' möglichst weitgehend herabzusetzen sucht.

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Die Reibungsgesetze (Amonton's Gesetze) lauten:

(1) Die Reibung ist proportional dem Druck;

(2) Die Reibung (pro Flächeneinheit) ist unabhängig von der Grösse der aneinanderreibenden Flächen.

In der Tat kann mit Hilfe der Brinellpresse belegt werden, dass die Ausstosskraft für eine Tablette umso grösser ist, mit je mehr Druck sie gepresst wurde. Wenn hingegen verschieden schwere Granulatmengen mit stets gleichem Druck gepresst werden, so wird wohl ihre Dicke, damit auch ihre Berührungsfläche mit der Matrizenwand und die gesamte aufzuwendende Ausstosskraft grösser, aber die pro cm² zu verwendende Ausstosskraft ist praktisch konstant.

Anschliessend wird vom mehr theoretischen Standpunkt aus diskutiert, wieso und wie Reibung zwischen der Tablettenseitenfläche und der Matrizenwand zustande kommt und wie Schmiermittel diese vermindern können.

IV

Der Einfluss des Druckes und des Feuchtigkeitsgehaltes des Granulates auf die Tablettenherstellung

Der richtige Feuchtigkeitsgehalt der Tablettenmasse ist ein wichtiger Faktor, damit die Tablettenpressung gelingt. Er wird aber in praxie rein empirisch festgestellt. Wenn z. B. 'Deckeln' auftritt, so wird die Tablettenmasse einfach mit Wasser besprüht. Zu aerophilen Substanzen wird als hygroskopischer Hilfsstoff gern Glycerin zugesetzt.

Mit zu feuchten Tablettenmassen tritt 'Kleben' der Tablettenoberflächen an den Metallflächen ein, das oft auch durch beim Pressen entstandene Eutektika bewirkt werden kann.

Die Versuche wurden mit folgenden 2 Granulaten durchgeführt:

—Granulatum simplex (Ph. Dan. IX) aus Kartoffelstärke und Milchzucker;
—Phenazetingranulat aus Phenazetin und Kartoffelstärke.


In beiden Granulaten wirkt Stärke als 'Wasserregulator', wie aus den verschiedenen Feuchtigkeitsgehalten der in den verschiedenen Hygrostaten gelagerten Tabletten hervorgeht.

Beim Pressen des Phenazetingranulates wirkt sich sowohl ein hoher wie ein tiefer Feuchtigkeitsgehalt nachteilig auf die Komprimierbarkeit aus; in beiden Fällen entstehen 'weiche' Tabletten. Das Optimum der Feuchtigkeit in diesem Granulat liegt bei 3-3,7%.

Gleicherweise ergeben beim Granulatum simplex das feuchteste und das trockenste Granulat die 'schwächeren' Tabletten; beim feuchten tritt dazu noch 'Kleben' der Tablettenoberfläche ein; beim trockenen zeigt sich mit Druckerhöhung 'Deckeln'. Der optimale Feuchtigkeitsgehalt lag hier bei ca. 10,5-12,8%.

Werden Granulate von verschiedenem Feuchtigkeitsgehalt mit dem gleichen Druck gepresst so entstehen mit steigendem Feuchtigkeitsgehalt stärkere Tabletten.

Wird ein Granulat von bestimmtem Feuchtigkeitsgehalt mit jeweils größerem Druck gepresst, so nimmt im Falle des Granulatum simplex die Festigkeit der Tabletten zu, im Falle des Phenazetingranulates aber von einem Druck von mehr als 1000 kg/cm² an ab. Dieser Gegensatz wird damit erklärt, dass das Granulatum simplex wegen seines hohen Stärkegehaltes beim Komprimieren grössere Elastizität und Bindeflächen besitzt und ebenso eine grössere Fähigkeit, Wasser festzuhalten, welches, wenn in genügend grosser Menge vorhanden, in Form eines dünnen Films auf der Tablettenoberfläche beim Ausstoss der Tablette als Schmiermittel wirkt.
V

Der Einfluss des Feuchtigkeitsgehaltes und der Aufbewahrungsbedingungen auf die physikalischen Eigenschaften der Tabletten


Beim Pressen der Tablettenmassen tritt ein gewisser Feuchtigkeitsverlust ein, der wahrscheinlich wegen Wärmeentwicklung beim Tablettieren verdunstet. Die Granulate mit dem im vorherigen Kapitel gefundenen optimalen Feuchtigkeitsgehalt zeigten die kleinste Zerfallszeit und dennoch die höchste Härte.

Beim Lagern gleichen mit der Zeit alle Tabletten ihren ursprünglich verschiedenen Feuchtigkeitsgehalt demjenigen der umgebenden Atmosphäre an.

Die Lagerungstemperatur beeinflusst die Änderung der Tablettenegenschaften entscheidend. Bei 4° bleiben die anfänglichen Tablettenegenschaften gut erhalten oder verbessern sich unter Umständen sogar, bei 35° können sie sich aber unter Umständen in ungünstigem Sinne verändern.

VI

Ueber die Komprimierung reiner Milchzuckertabletten

Reiner Milchzucker (wie er als Hilfsstoff für die Herstellung homoeopathischer Tabletten gebraucht wird) ergibt beim Komprimieren hohe Reibung in der Matrize der Tablettenmaschine, was zum 'Kleben' und 'Deckeln' führen kann. Es ist deshalb unmöglich, ohne die Beigabe eines Schmiermittels die Reibung zu
vermindern. Nur muss es (gemäß homoeopathischem Arzneibuch) wasserlöslich sein (was Talk ausschliesst).

Unter den wasserlöslichen Schmiermitteln vermag z.B. Carbowax 6000 die für den Ausstoss der Tablette nötige Kraft zu reduzieren. Ferner zeigt dieser Stoff guten Gleitmitteleffekt für Milchzuckergranulate. Dennoch ist auch Carbowax 6000 ungenügend, wenn nur gewöhnliche und nicht tadellos polierte Matrizen und Stempeloberflächen vorliegen.

Milchzuckertabletten, welche den homoeopathischen Vorschriften genügen, können hergestellt werden durch

—Granulierung des Milchzuckers mit einer 2%igen Glukoseslösung,
—durch Zusatz von Carbowax 6000 in Pulverform als Gleit und Schmiermittel und
—durch Verwendung hochpolierter evtl. gehärteter Metallflächen im Matrizeninnern und an den Pressflächen der Stempel.

VII

Vergleichende Untersuchung der Eigenschaften von Tabletten, die auf einer Exzenter-bzw. einer Rundläufer-Tablettenmaschine gepresst wurden

beim Komprimieren gegeneinander zulaufen, Tabletten mit gleicher Härte der oberen und der unteren Seite erhalten wurden. Bei den Tabletten aus der Exzentermaschine war hingegen die untere Oberfläche, die auf dem unteren, sich nicht bewegenden, sondern ruhenden Stempel lag, signifikant härter. Vergleicht man die Härten der oberen Tablettenflächen zwischen der 'Exzenter' und der 'Rundläufer'-Tablettengruppe, so war kein signifikanter Unterschied festzustellen, beim Vergleich der unteren Oberflächen aber wohl, womit erwiesen ist, dass der Umstand, ob der Stempel während der Pressung ruht oder sich bewegt, die verschiedenen Härten der Tablettenoberflächen bedingt.

Im übrigen waren die Rundläufer-Tabletten durchwegs mechanisch schwächer als die Exzenter-Tabletten und zerfielen demzufolge auch rascher. Die Gründe, wieso trotz Pressung des gleichen Granulates auf gleiche Dicke in den beiden Maschinentypen Tabletten mit verschiedenen Eigenschaften entstehen können, dürften die folgenden sein:

—Druck im einen Falle einseitig nur von oben, im anderen zweiseitig d.h. gleichzeitig von oben und unten.

—verschiedene Dauer des Pressvorganges (Zeit zwischen der Berührung des Granulates in der Matrize durch den oberen Stempel bis zum Rückzug des oberen Stempels von der Oberfläche der fertig gepressten Tablette); im vorliegenden Falle dauerte der Pressvorgang in der Exzentermaschine nur halb so lang als im Rundläufer.

Aus den Ergebnissen muss geschlossen werden, dass trotz gleicher Tablettendicke offenbar der Pressdruck in den beiden Maschinentypen entweder nicht gleich war oder wenn er insgesamt doch gleich war, zeitlich verschieden und mit seinen 'Kraftlinien' anders verlief.

VIII

Eine Betrachtung über den Einfluss verschiedener Tablettenformen und -größen beim Tablettieren

Die Tablettenformen sind ausserordentlich verschieden, meist nur aus aesthetischen oder psychologischen Gründen und
weniger mit wissenschaftlich belegten Absichten. Oft zeigt sich aber, dass eine bestimmte Tablettenmasse nicht in irgendeine, sondern nur in bestimmte Formen gepresst werden kann. Aus der Pulvermetallurgie mit ihren grossen Presskörpern ist bekannt, dass die Dichte des Presskörpers nicht durchweg homogen ist, sondern dass an besonderen, von der Form abhängigen Stellen Dichtemaxima bestehen; vor allem darf die Höhe des Presskörpers nicht beliebig sein.

Curriculum Vitae

of

PYARE LAL SETH, citizen of India

I was born at Amritsar (Punjab), India on July 15, 1928 as son of Ganga Ram Seth. After attending the school at Amritsar for 10 years, I passed the Matriculation examination of the University of Punjab, Lahore, in 1942. After a further study of two years, I passed in 1944 the Intermediate Medical Science Examination of the said University and began the study of Pharmacy. I studied for the next three years at the Department of Pharmacy of King Edward Medical College, Lahore and in July 1947 I passed the final Degree Examination of Bachelor of Pharmacy, of the University of Punjab, Lahore.

After a period of apprenticeship for 1½ year in some manufacturing laboratories, I joined the Pharmaceutical industry and worked as a practising pharmacist in various capacities.

I came to Switzerland in October 1953 and started working at the School of Pharmacy of the Swiss Federal Institute of Technology, Zürich on the research work being submitted herewith.