Chapter I

General background

1. Introduction

The compressed tablets have been manufactured for more than 100 years and are today the single most widely used dosage form for the administration of drugs. It is already known that absorption of a drug into the bloodstream from an intact solid dosage form follows a fairly well defined sequence of events in Figure 1(1). Most drugs used in acute therapy must be available for action in a very short period of time following oral administration, for such agents, the dissolved drug must be presented to the absorption site as rapidly as possible. A tablet will be medicinally useless unless the active ingredients are made available for absorption from the gastrointestinal tract (2).

It is the function of a tablet disintegrant to facilitate the breakdown of the tablet into small particles, the greatly increased surface area of these particles results in a higher rate of dissolution in the gastrointestinal fluids. The rate of absorption and physiological availability of many drugs that are administered orally in tablet form is a function of their rate of dissolution (3,4). Such that the disintegration of a compressed tablet into granules or individual particles is a rate limiting step for the

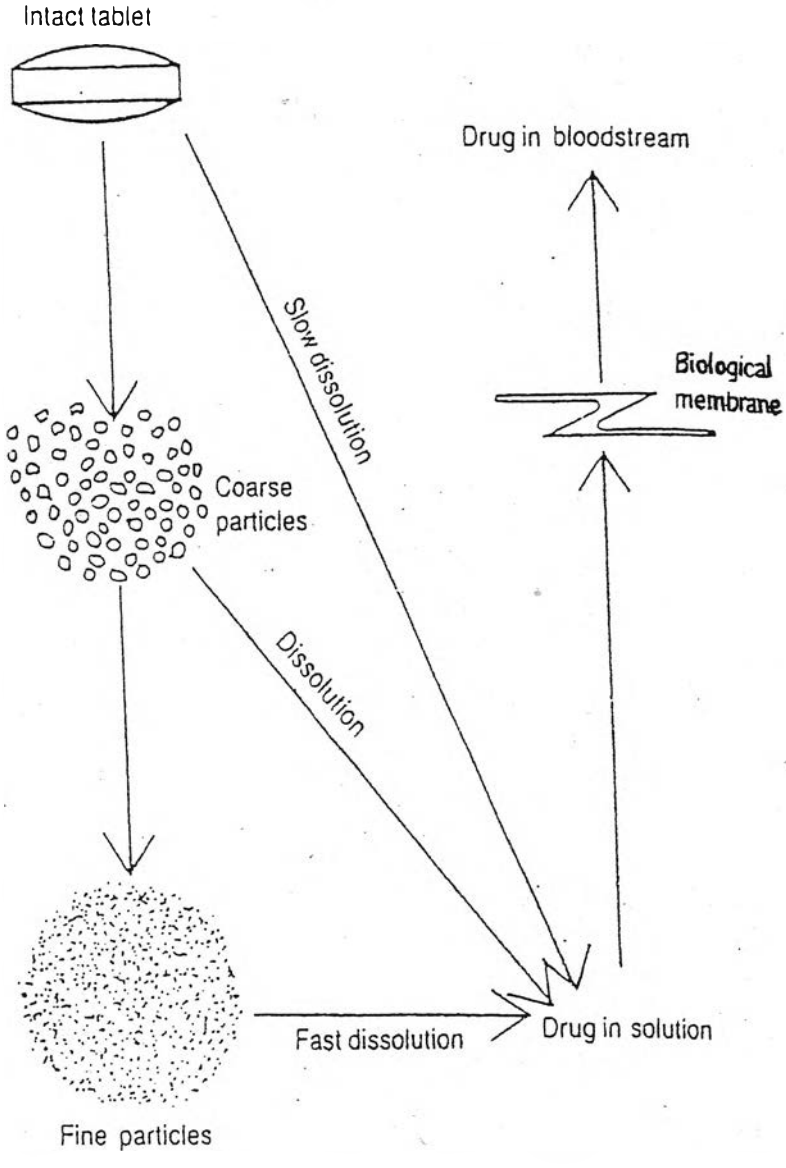


Figure 1 The absorption of a drug into the bloodstream from an intact solid dosage form

dissolution of drugs. Therefore a rapid disintegration process is the prerequisite for a good bioavailability (5).

Over the years other materials have been proposed as tablet disintegrants and have become commercially available. Starches are the most widely used tablet disintegrants. In addition to starches, a large variety of materials have been used and reported to be effective as tablet disintegrants. Such substances include veegum HV, agar, bentonite, cellulose product, natural sponge, cation-exchange resin, alginic acid, guar gum (6-12), and more modern disintegrants such as cyclodextrin polymer, soya polysaccharides, cross-linked casein, etc (13-15). Most investigators show that an increase in concentration of disintegrant causes a decrease in disintegration time. But it can be seen that a critical concentration of disintegrant is pointed out when increasing the amount of disintegrant in a given formulation of tablets. At this critical concentration, disintegration time, often dramatically decreases. Above this critical concentration, disintegration time, may continue to decrease slowly or remain constant at its lowest value (16). The mechanism of tablet disintegration has been widely studied. Several theories have been put forward :water sorption, swelling, heat of wetting, capillary action, annihilation of cohesion forces between particles in presence of water, follow by particle-particle repulsion . Several mechanisms are perhaps

involved in the disintegration process. There is no doubt that water uptake is the first step in any process of disintegration. The rate of water absorption has been implicated as an important mechanism (17).

In this study two new substances which may be used as tablet disintegrants, are also investigated. The substances to be tested are the material from the marine resources. These materials are chitin and chitosan. Chitinis a natural carbohydrate polymer that occurs primarily as a structural constituent in the shells of crustacean and insect, and to a lesser extent in other plant and animal forms. From crustaceans, chitin is available for current and potential uses in various fields. Chitin is an acetylated polyamine, which is biodegradable and non-toxic. It is the most abundant natural polymer, after cellulose. And it is a close chemical relative of cellulose, and like cellulose,can be modified both chemically and physically to produce materials with a wide variety of potentially useful properties. It can also be produced in a deacetylated form known as chitosan. A variety of applications of chitin and chitosan have been proposed. Both chitin and chitosan can be produced and cast into tablets, films, gels, beads and so on. Over the years there have been a number of references to the use of chitin and chitosan derivatives as pharmaceutical excipients in formulation (18,19).

2. The purpose of this study

In this study, paracetamol is chosen as a model drug, since it is a sparingly water-soluble drug and used in high dose administration, 500 mg per tablet. Therefore the results of tablet disintegrant are clearly observed. The objectives of this study are :

a) To investigate the optimum concentration of chitin and chitosan in order to use as tablet disintegrants.

b) To investigate the physical properties of chitin and chitosan, and to compare these with other disintegrants, such as corn starch, sodium starch glycolate, microcrystalline cellulose, and cross-linked sodium carboxymethylcellulose (croscarmellose sodium).

c) To evaluate and compare the physical properties of tablets containing various disintegrants.

d) To elucidate the stability of paracetamol tablets with various disintegrants after exposure to high temperature and humidity.

e) To identify the mechanism by which chitin and chitosan function as tablet disintegrating agents.

3. Literature review

3.1 General

The rapid absorption of drugs from tablets requires effective disintegration and dissolution. Disintegration is the first step, and it may also be the limiting one, in the dissolution of active principles from solid dosage forms (20). During the course of this evolutionary process, incorporation of efficient disintegrant prior to tabletting provides pharmaceutical formulations with the means of quantitatively controlling the disintegration of solid dosage form. It is generally recognized, however, that rapid tablet disintegration is a positive factor in the formulation of immediate-release solid dosage forms because it can accelerate dissolution expectially in the case of slightly soluble drugs (21,22).

Disintegrant is the term applied to various agents added to tablet granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in an aqueous environment (23). Basically, the disintegrant's major function is to oppose the efficiency of the tablet binder and the physicial forces that act under compression to form the tablet. Ideally, it should cause the tablet to disrupt, not only into the granules from which it is compressed, but also into the powder particles from which the granulation is prepared (24-27).

Disintegrants constitute a group of materials that, on contact with water, swell, hydrate, change in volume, or react chemically to produce a disruptive change in the tablet. This group includes various forms of starches, celluloses, algins, vegetable gums, clays, ion-exchange resins, and acid-base combination. A list of commonly used tablet disintegrants are given in Table 1(28). The following categories are used as tablet disintegrant described in this study.

3.1.1 Starch and modified starch

Starch

Starch is commonly used throughout the pharmaceutical industry in dry powder form as a tablet disintegrant. Natural starch must be presented in concentration from about 3-15%. It does not compress well, however, and tends to increase tablet friability and capping if used in high concentrations (29). In granulated formulas, about half the total starch content is included in the granulation mixture, and the balance as part of the final blend with the dried granulation. But it is well known that wetted starch grains (intragranular starch in wet granulations) are not as effective a disintegrant as dry starch (30).

Natural starch consists of two different polymers of glucose, amylose and amylopectin, as shown in Figure 2. The amylose molecule is a long linear

Table 1 Common disintegrants usually used in tablets

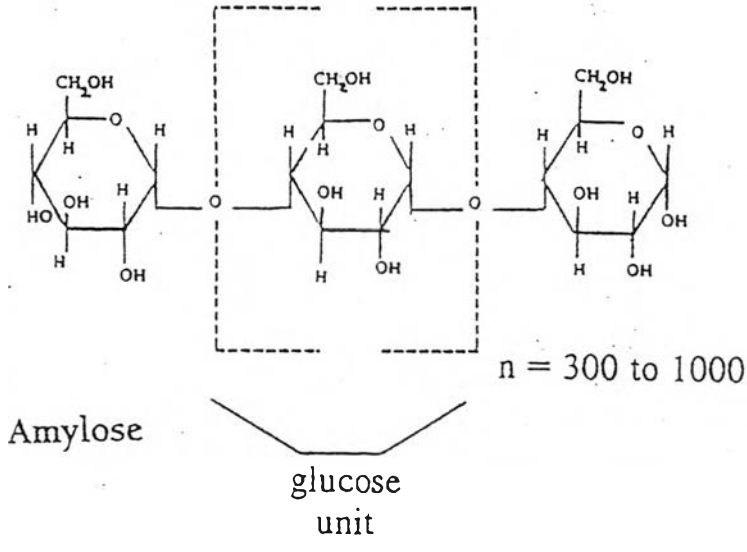
STARCHES AND DERIVATIVES		
MATERIAL	NATURE OF THE DISINTEGRANT	SUPPLIER
Corn starch		Roquette
Standard maize starch		Roquette
Waxy maize starch	starch without amylose (hybrid plant)	Roquette
Potato starch		Roquette
Rice starch		Prolabo
PRIMOJEL Standard	carboxymethylstarch	Doittau
PRIMOJEL LV	carboxymethylstarch with low viscosity	Doittau
EXPLOTAB	carboxymethylstarch	Ed. Mendell
STARX 1500	maize starch milled and agglomerated with water	Staley
CELLULOSES AND DERIVATIVES		
ELCEMA P 050	cellulose particle size from 1 to 50 µm	Degussa
ELCEMA P 100	cellulose particle size 1 to 100 µm	Degussa
ELCEMA F 150	cellulose, fibers from 1 to 250 µm	Degussa

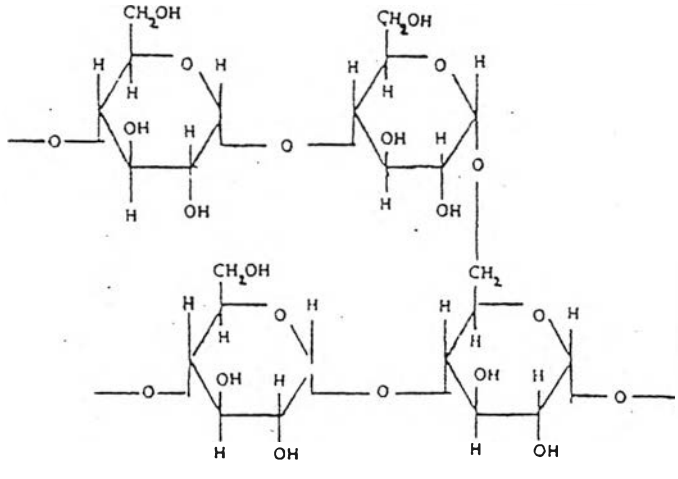
Table 1 (continue)

CELLULOSES AND DERIVATIVES		
MATERIAL	NATURE OF THE DISINTEGRANT	SUPPLIER
ELCEMA g 250	cellulose granulated from 90 to 250 µm	Degussa
AVICEL PH 101	cellulose microcrystalline	F.M.C.
AVICEL PH 102	cellulose microcrystalline granulated	F.M.C.
METHOCEL 50 cps	methylcellulose	Dow chemical
Sodium carboxymethylcellulose	CMC low substituted	Prolabo
NYMCEL ZSB 10	CMC-degree of substitution from 0.20 to 0.26	Nyma
NYMCEL ZSB 16	CMC-degree of substitution from 0.34 to 0.40	Nyma
AC-DI-SOL	cross-linked CMC	F.M.C.
L-HPC	hydroxypropylcellulose low substitued	Shin Etsu
AVICEL RC 591	mixture of microcrystalline cellulose (89%) and of CMCNa (11%)	F.M.C.

Table 1 (continue)

MACROMOLECULES AND FINELY DIVIDIED SOLIDS		
MATERIAL	NATURE OF THE DISINTEGRANT	SUPPLIER
Alginic Acid		Prolabo
VIDOGUM KL 175	guar gum	Unipectine
ESMA SPRENG	casein formaldehyde	Edelfettwerke
PECTIN BRUN PHAL	citrus pectin high esterified	Unipectine
PECTIN BRUN NF	orange pectin high esterified	Unipectine
AMBERLITE IRP 88	cation exchange resin (potassium)	Rohm and Haas
POLYPLASDONE XL	cross-linked poly-vinylpyrrolidone	G.A.F.
VEEGUM F	mixture of magnesium and aluminium silicon dioxide	Degussa





Segment of Amylopectin Molecule

Figure 2 Structure formula of starch

chain of anhydroglucose units having a low molecular weight, a high intrinsic viscosity, and a low solution stability in water at ordinary concentrations. It is insoluble in cold water but absorbs a large amount of water and swells. The amylopectin molecule is a larger complex branched chain of tree-like structures with many branches, with a high molecular weight, a fairly high solution stability, and about the same intrinsic viscosity. The relative content of amylose and amylopectin in natural starches varies, depending on the source of the starch. Tapioca starch contains from 17-21% amylose, potato starch contains from 22-25%, and corn starch contains from 22-30% (31). Amylose most likely accounts for the disintegrant properties of starch, and isolated amylose is as effective a tablet disintegrant as intact starch grains (32). Amylopectin, on the other hand, is a good binder but inhibits tablet disintegration and the dissolution of the active ingredient (33). The effectiveness of amylose as a tablet disintegrant indicates that it is not necessary to have an intact starch grain to achieve disintegration.

There are many classical theories that attempt to explain the mode of action of starches. It is once assumed that the function of starch depended on concept relates to the swelling of starch grains on exposure to water, a phenomenon that physically ruptures that particle-particle bonding in the tablet matrix (34).

Although starch grains swell in water, the rate and extent of swelling is still debated (35,36). Furthermore, no investigator has successfully measured starch grain swelling in the dymamic state of tablet disintegration. It can be concluded that the amount of swelling that instantaneously occurs when starch grains are placed in body fluids at body temperature is variable and appears to be minimal. Another theory is that the disintegrant forms pathways throughout the tablet matrix that enable water to be drawn into the structure by capillary action, thus leading to disruption of the tablet (34). Neither of these mechanisms explains the dramatic explosion that often takes place when tablets containing starch are exposed to water. Hess (37) seem to suggest that on compression there is a significant distortion of the starch grains. On exposure to water, these grains attempt to recover their original shape, and in so doing release a certain amount of stress which, in effect, is responsible for the destruction of inter-particulate hydrogen bonds and causes the tablet to be literally blown apart. Starch thus functions as the classical disintegrant.

Sodium carboxymethyl starch (Sodium starch glycolate)

Sodium carboxymethyl starch is a low-substituted derivative of potato starch whose structure closely resembles that of carboxymethyl cellulose. The

glucopyranose units in starch are connected to each other by α- glucosidic linkage, as shown in Figure 3, where as in cellulose the linkages are of the β-glucosidic type. Approximately 25 carboxymethyl groups have been introduced for every 100 glucose units (20). Addition of carboxymethyl groups makes starch grains more hydrophilic but not completely water soluble. The substance's water solubility depends on the degree of substitution. When exposed to water, these modified starch grains swell but maintain their integrity, causing tablet disintegration without releasing the soluble components inside each grain that might increase the viscosity of the surrounding environment and delay further water penetration. However, some sodium carboxymethyl starch grains appear to split open when compressed, a process that releases their contents (30). In wet granulation formulations, sodium carboxymethyl starch is found to be equally effective as a disintegrating agent regardless of the method of addition, i.e., intragranular, extragranular, or as a granulating agent.

Sodium carboxymethyl starch is commercially available as a white to off-white, odorless, tasteless, free-flowing powder. The shape of granules are oval or spherical, 30-100 μm in diameter. It appears to be most effective at levels between 4 and 8 %. It exhibits excellent disintegrant properties at a 5% level. At levels above 8%

generally result in increase disintegration times (29,30). The mechanism takes place involves accelerated absorption of water leading to an enormous increase in volume of granules. This results in rapid and uniform tablet disintegration (38).

3.1.2 Cellulose and modified cellulose

Microcrystalline cellulose

Microcrystalline cellulose is widely used in the pharmaceutical industry. It is used not only as binding agent but also as disintegrating agent in tablets (39). It is manufactured by the controlled hydrolysis of x-cellulose. The structure of micro-crystalline cellulose is shown in Figure 4.

Microcrystalline cellulose is available as a white, odorless, tasteless, crystalline powder composed of porous particles. Addition of microcrystalline cellulose causes rapid disintegration of tablet. The disintegration rate increases with increasing concentration. The optimum concentration is between 4-15% of microcrystalline cellulose. The ability to act as a disintegrant has been found to be worse than that of starch (40) or better than starch (9). Some studies found that a mixture of starch and microcrystalline cellulose is more effective than either of the components singly (9).

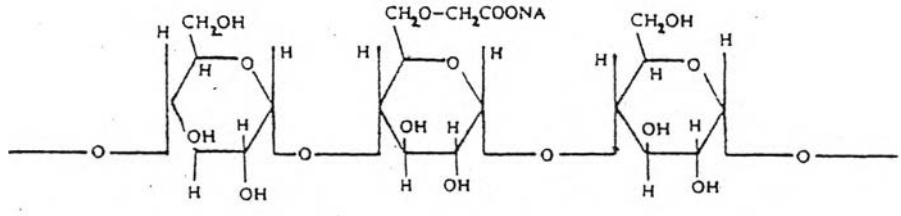


Figure 3 Structure formula of sodium starch glycolate

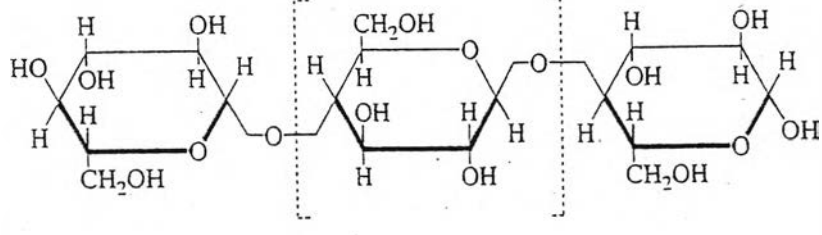


Figure 4 Structure formula of cellulose

Disintegration of microcrystalline cellulose tablet is related to an increase entrance of water into the tablet matrix by the means of capillaries and the subsequent breaking of the hydrogen bonding between adjacent bundles of cellulose microcrystals (41). One drawback to its use is its tendency to develop static charges with increased moisture content, sometimes causing striation or separation in the granulation. This can be partially overcome by drying the cellulose to remove the moisture (23). When wet-granulated, dried and compressed, it does not disintegrate as readily as when unwetted.

Cross-linked sodium carboxymethyl cellulose

(Croscarmellose sodium)

Although several types of sodium carboxymethyl cellulose, a water-soluble cellulose ether, have been used in pharmaceuticals for many years, however, an internally cross-linked sodium carboxymethyl cellulose has evoked interest as a tablet disintegrant. Its structure formula is shown in Figure 5. The cross-linking greatly reduces its water solubility while permitting the material to swell and to absorb many times its weight in water without losing individual-fiber integrity (30). The powder form of this material is widely used as a tablet and capsule disintegrant, usually referred to as a super-disintegrant (42). Croscarmellose sodium is widely regarded as one of most

effective superdisintegrants available. It is effective at quite low concentrations, and normally utilized at levels of 0.5 to 2% (43). Investigators attribute the relatively rapid disintegration to the strong elastic relaxations of cellulose fibers, which may leave large pores in the tablet matrix, facilitating rapid water penetration and the rupture of hydrogen bonds.

3.1.3 Chitin and modified chitin

Chitin

Chitin is a long straight chain polysaccharide constituted of 2-acetamido-2-deoxy-D-glucose whose units are linked by β-(1,4) glycosidic bonds. This natural polymer that can be called poly-N-acetyl-D-glucosamine, can be formally considered a derivative of cellulose in which each C-2 hydroxyl group has been completely replaced by an acetylamino group, ($-NHCOCH_3$), as shown in Figure 6 (18).

Chitin is a grayish to white solid, generally possessing some degree of crystallinity. Differences in the complex structure of the different species and tissues in which it is found may account for differences in chain length, crystallinity and departures from complete acetylation of all the amino groups (44). It is practically insoluble in water, diluted acids, diluted and concentrated alkalies, alcohol and other organic solvents (45). It can be dissolved

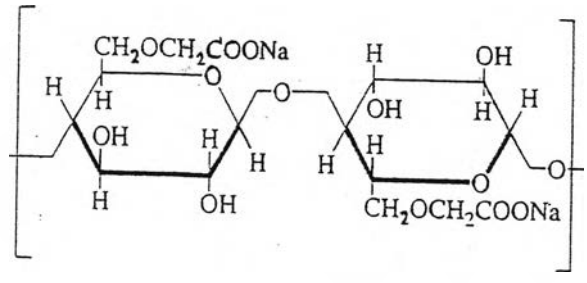


Figure 5 Structure formula of croscarmellose sodium

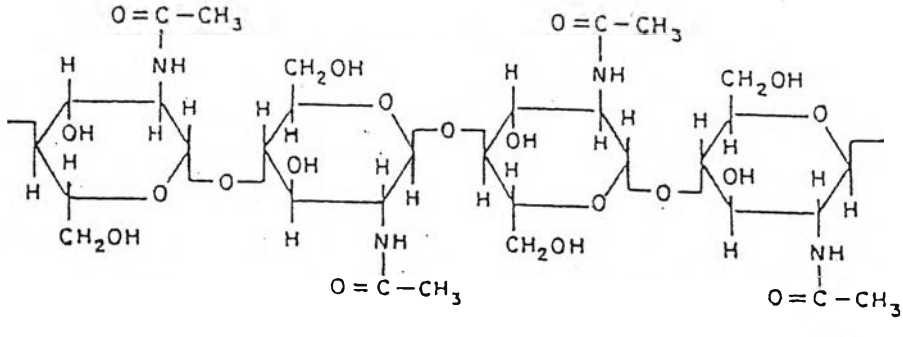


Figure 6 Structure formula of chitin

with difficulty in liquid ammonia. Chitin is sometimes reported to dissolve in hydrochloric acid or sulfuric acid, but in practice it undergoes hydrolysis under limiting conditions (46). Therefore, under normal conditions in diluted acids chitin is not appreciably soluble in a short contact time. In some acids such as 50% nitric acid, 85% phosphoric acid and anhydrous formic acid are used to perform chitin dissolution, therefore, the term dissolution is inappropriate because hydrolysis, molecular weight degradation, deaceutylation and chemical modification (sulfation, nitration etc.) take place under the said conditions and yield dissolved species which are no longer chitin. There are substantial variations in solubility among chitins of different origins and prepared by different methods. Chitin has a hygroscopicity and it is thermally stable to about 260 °C, where it decomposes (47).

Chitin is a crystalline polysaccharide. It occurs in three polymorphic forms which differ in the arrangement of the molecular chains within the crystal cell, they so called α-, β- and γ-chitins. α-Chitin is the tightly compacted, most crystalline polymorphic form where the chains are arranged in an antiparallel fashion. β-Chitin is the form where the chains are parallel. Rudall (48) has suggested that in the γ-form the chains are arranged in sets of three with two parallel chains and one antiparallel. By far the most abundant

polymorphic form is α-chitin. β-Chitin exists in a crystalline hydrate which accounts for its lower stability since water can penetrate between the chains of the lattice. Also γ-chitin can be transformed into α-chitin. The three forms of chitin have been found in different parts of the same organism. X-ray diffraction on chitin shows that α-chitin has an orthorhombic unit cell, which contains disaccharide sections of the two chains. The unit cell of β-chitin is monoclinic and contains the disaccharide repeat of one chain. The chain conformation is the same as in α-chitin.

A variety of procedures has been employed for the extraction of chitin from crustacean shells. In general, extraction of chitin entails steps to demineralize and deproteinize. The procedure generally includes treatments in orgainic solvents to remove pigments, etc. The steps to demineralize and deproteinize have been accomplished by successive treatments in diluted mineral acids and diluted alkali, in either order. All of the acid and alkali treatments cite cause some undesired degradation of the product. Acids used for decalcifying also remove a few acetyl groups, and alkalies, especially at elevated temperatures, cause a certain amount of depolymerization.

A typical commercial process sequence for extraction chitin and by-products from crustacean shell

waste is illustrated on Figure 7 (44). Immediately after grinding, and before any chemical processing, bits of flesh and other soft tissues are separated from the shell and recovered from a water slurry. Further processing consists of removal of the calcareous mineral constituents and the protein that is an integral part of the chitinuous shell. Minerals such as calcium carbonate and calcium phosphate can be removed in a weak acid solution that may be recycled until it is nearly exhausted. Protein can be removed by a 1% alkali solution in about 24 hours at room temperature in a stirred vat, or in 1/2 to 1 hour if steam heated. Chitin produced by this method may then be converted to chitosan. The conventional conversion to chitosan is accomplished by prolonged heating in 40-50% caustic soda.

Chitosan

Chitosan is a biopolymer with unique properties which can be utilized in a variety of ways. Because of its unique and versatile properties, chitosan has great industrial potential, but this potential has yet to be exploited. Commercial chitosan is a particularly exciting polysaccharide for three major reasons; abundant potential resources, unique material characteristics, and various functional properties (49).

Chitosan, (1,4)-2-amino-2-deoxy-β-D-glucan is a polymer with a repeating unit of disaccharides

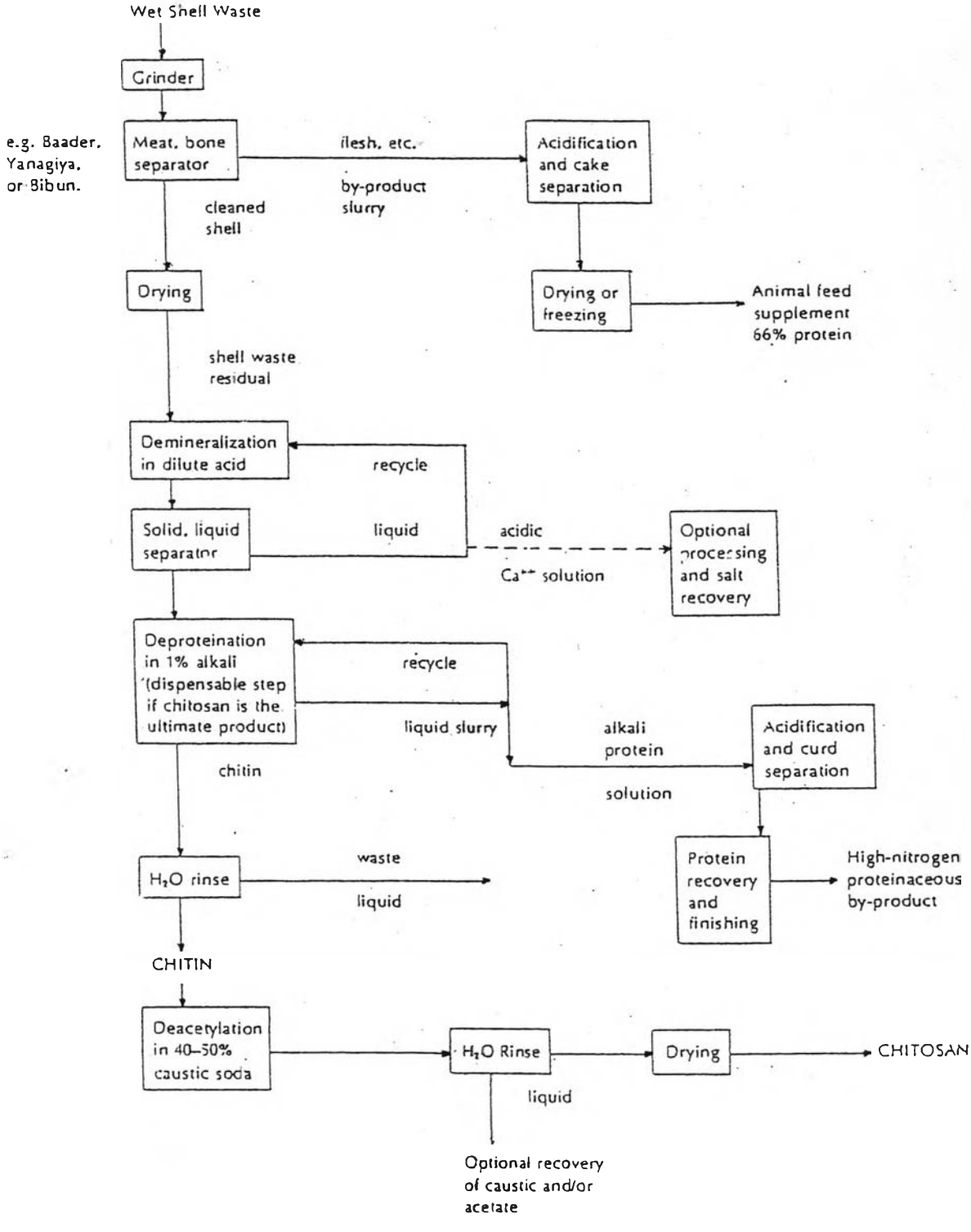


Figure 7 A typical process sequence for extraction chitin and by-products from the crustacean shell waste

also be produced currently by deacetylation of chitin. Chitosan is insoluble in water and organic solvents; it is also insoluble in alkalies and mineral acids except under certain conditions (46). It is soluble in formic acid, acetic acid and 10% citric acid. Inorganic acids can dissolve chitosan at certain pH values after prolonged stirring and warming. Nitric acid can dissolve some chitosan, but sometimes after dissolution one can observe a jelly white precipitate. Hydrochloric acid also requires heating and stirring for hours. Sulfuric acid does not dissolved chitosan because it forms chitosan sulfate which is a white crystalline solid.

The deacetylation of chitin through treatment with strong sodium hydroxide is achieved at an elevated temperature over a controlled period of time, with the material being kept in the solid phase to gain the highest possible yield. Regular chitosan manufactured this way may consequently contain foreign material not solubilized during the process. If a filterable grade is needed, an additional step, including solubilization in an appropriate organic acid, filtration through a specified mesh size filter and spray drying, is added. Unlike the regular grade, chitosan in such a salt form is water soluble. A water soluble grade chitosan is made by dry blending regular chitosan with an appropriate acid. Flow diagram of the chitosan process

is given in Figure 9 (50). The molecular weight of chitosan will depend on the processing conditions, and more grades within the range of 10,000-1,000,000 Dalton will be available. The mole fraction of deacetylated units (glucosamine), defined as the degree of deacetylation, will usually range from 70 to 90 percent. The degree of deacetylation can be varied according to the intended use (19).

Reacting chitosan with a controlled amount of a multivalent anion will result in a cross-linking between the chitosan molecules. The network formed has the ability to keep large amounts of water, with some systems holding as much as 95% or more. This cross-linking can be done in acid, neutral or basic environments, depending on the method applied (51,52).

Application of chitin and chitosan

Chitin and chitosan have been reported to have some useful medical applications such as a blood anticoagulant, a wound-healing accelerator, a surgical suture, and an artificial organ membrane (47,51). Recently, the pharmaceutical application of chitin, chitosan, and its derivatives has been attempted. Some applications were :

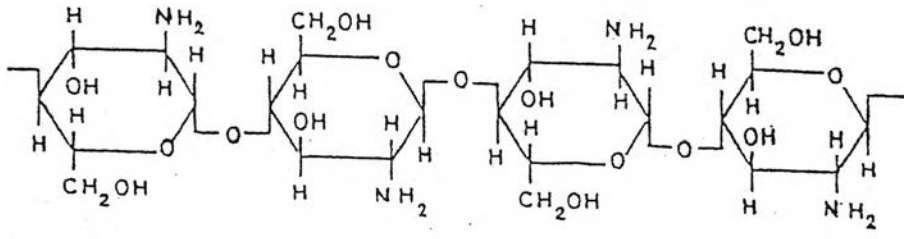


Figure 8 Structure formula of chitosan

CHITIN

1) DEACETYLATION

2) DRYING

CHITOSAN - Sea Cure™ flake

3a) MILLING
- Sea Cure™ powder

4a) BLENDING
- Sea Cure SD™ powder

3b) DISSOLVING (ACID)

4b) FILTERING

5b) SPRAY DRYING
- Sea Cure™
- Protasan™

Figure 9 Chitosan process

a) Directly compression diluents

Sawayanagi and collaborators (53,54) suggest that chitin and chitosan, as well as crystalline cellulose, may be suitable for use as diluents with friction-lowering properties for chewable, sublingal or oral mucosal tablets prepared by direct compression process.

b) Enhancement dissolution of poorly soluble drugs

Chitin and chitosan lower the degree of crystallinity of poorly soluble drugs by co-grinding, and the dissolution rate of such drugs even in tablet form is enhanced (55,56).

c) Controlled release

There are plenty of potential applications, including microgranulation systems, sustained release matrices, erodible matrices, controlled release gel systems and a sustained release vehicle in wet granulation (19). Both chitin and chitosan can be produced and cast into tablets (57-59), films (60,61), gels (62-64), beads (65), granules (66,67) and so on. They can also be used as a digestible supporting material for sustained release drug formulation for oral, intravenous or implant administration (19). Chitosan, with around 70% of deacetylation, is also a biodegradable polymer, which can be employed as a material for the preparation of implantable or injectable dosage forms with sustained release property, being useful for a chemotherapy of cancer and other diseases (68).

d) Intragastric buoyant preparations

Chitosan also has potential in the design of dosage forms that prolong the residence time in the stomach, It has gel-forming properties in the low pH range, that may prevent or weaken drug irritation to the stomach. A compressed tablet of chitosan float immediately and keep buoyant in an acidic medium. An excellent buoyancy is also obtained in tablets with the foamy layer of chitosan, and in preparation based on granules having internal cavities (68). Karlsen and collaborators (19) have been able to produce chitosan-drug containing granules with internal cavities, which will float in the gastric fluid and gradually swell in acidic media pH 1 to 8. When this formulation is tried with prednisolone as a model drug, a sustained release effect is readily obtained. Buoyant preparations show prolonged plasma concentration profiles of prednisolone compared with those of ordinary dosage forms.

3.2 Methods for evaluating the swelling properties of disintegrants

Accordingly the swelling is undoubtedly a universally accepted mechanism of tablet disintegration (1,17). Many properties related to swelling have been used to explain disintegration efficiency. The methods for evaluating the swelling properties of disintegrants can be divided into two basic groups:

3.2.1 methods for the quantitative evaluation of disintegrant swelling (swelling extent)

3.2.2 methods for the qualitative evaluation of disintegrant swelling (swelling efficiency).

3.2.1 Methods for the quantitative evaluation of disintegrant swelling

These methods are well known and presented in Table 2, and may be grouped into :

A. methods for the evaluation of swelling in bulk, that is water uptake capacity of disintegrant powder bed

B. methods for the evaluation of intrinsic swelling, that is individual particle volume increase (69).

The former methods may be, in turn, classified into : static methods, like hydration capacity and sedimentation volume, and dynamic methods, like water uptake of powder bed and swelling of pure disintegrant tablet. The latter methods are mostly based on microscopic observation of particles, even though instrumental methods have also been proposed (70). These methods, with a few exceptions, mainly provide an evaluation of particle swelling in static conditions, that is at the equilibrium. Whereas static methods provide only for the quantification of the amount of water uptake at the equilibrium, dynamic methods provide

Table 2 Methods for the evaluation of disintegrant swelling

Water uptake capacity (Swelling in bulk)	Particle swelling (Intrinsic swelling)	
	Microscopic methods	Instrumental methods
Hydration capacity	Optical microscopy	Electrical sensing zone
Sedimentation volume	(Cine) photomicrography	
Water uptake of powder bed		
Swelling of disintegrant tablets		

for the evaluation not only of the extent (amount of water uptake or extent of expansion) but also of the rate of swelling process.

A. Methods for the evaluation of swelling in bulk

1) Hydration capacity

Hydration capacity is the capable for water actually wetting the material which reveals about the same liquid-solid interactions or swelling power. This parameter can be employed as a guideline for the selection of new materials as potential tablet disintegrants. Kornblum and Stoopak (71) describe a method for determining the hydration capacity of cross-linked polyvinylpyrrolidone in comparison with starch and alginic acid. The procedure utilized are developed for materials that do not contain appreciable water-soluble constituents. In this method the amount of water taken on by one gram of disintegrant after shaking, centrifuging and decanting is determined. The advantage of this method is that it can be carried out quickly and easily, whilst being very reproducible.

2) Sedimentation volume (1)

In the past, investigators have used sedimentation volumes of slurry as a measure of swelling. This test gives a fair appraisal of swelling capacity

but does not provide for dynamic measurement of the swelling itself. As a result, many disintegrant studies cannot correlate rank-order sedimentation volumes with disintegrant efficiency.

3) Water uptake

The rate of disintegration of compressed tablets can be limited by the rate and extent of liquid absorption by the system. The penetration rate of a liquid into a porous structure depends on the balance between capillary and opposing viscous forces. If the total cross-sectional area of the pores does not vary with their length, there is a linear relationship between the square of volumetric uptake (v) and the time (t) :

$$V^2 = \frac{2 m \gamma \cos \theta}{k_o \cdot n} \cdot t$$

where m = the hydraulic pore radius

γ = the surface tension of the penetrating liquid

θ = the contact angle between liquid and solid in the pores

n = the liquid viscosity

k_o = a constant dependent on pore shape

This equation derived by Washburn (72), indicates that water penetration in pharmaceutical tablets is determined by the controlling factors like porosity, pore size distribution, and contact angle with the pore wall.

Many studies are carried out water uptake in this way :- on pure disintegrants, and on tablets batches, each one containing a different disintegrant (16). The affinity of samples for water uptake is tested :- either by measuring the weight increase of the sample after storage at 100 % relative humidity (25), or by the evaluation of water intake of a powder bed (or of a tablet) after contact with water through a sintered glass filter. But the studies caried out on the pure disintegrants cannot be sufficient for the disintegration time optimization. Other factors must be involved such as the disintegrant concentration, the wettability of the other components of the tablet, and the porosity of the system. Consequently, it seems that the whole structure of the tablet must be invaded by water owing to an hydrophilic continuous network of disintegrant particles.

4) Swelling of disintegrant tablets

During the water uptake measurement, the swelling of tablets of pure disintegrants is studies with a linear inductive transducer in contact with the

tablet and connected with a recorder, as shown in Figure 10 (32). The swelling of tablets is recorded at the time determined. The swelling measure is given in percent, according to the relation :

$$\% G = \frac{h_t - h_o}{h_o} \times 100$$

where h_o is the height of the tablet at the beginning of the test and h_t is the height of the tablet at the time t.

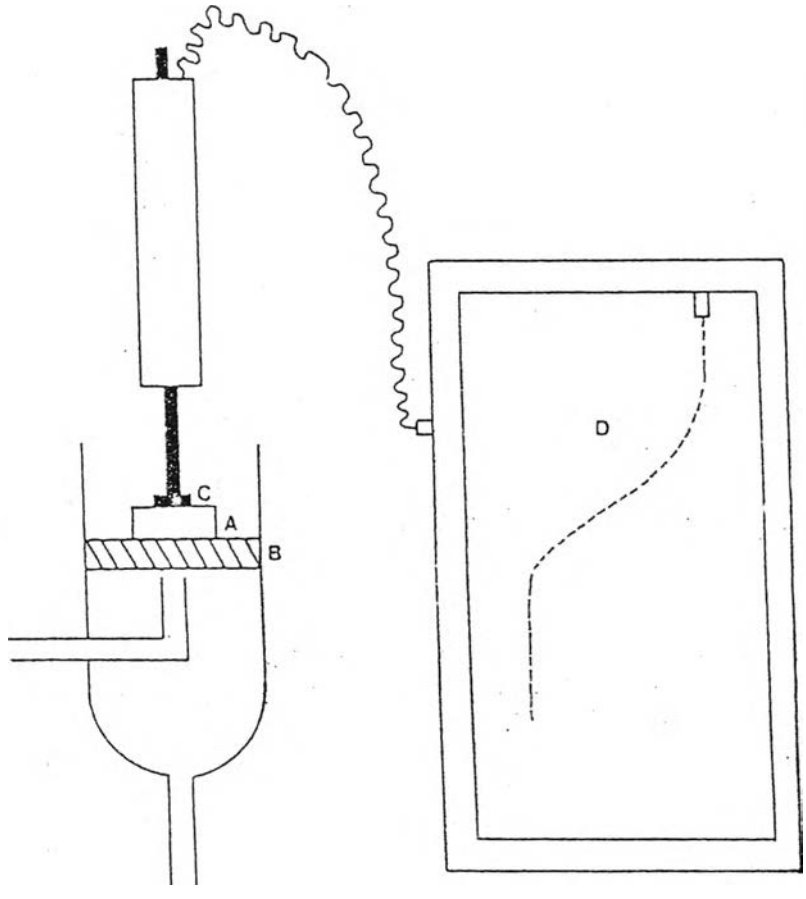
B. Methods for the evaluation of particle swelling

(intrinsic swelling)

1) Microscopic methods

a) Optical microscopy (36)

The measurement is carried out on the microscope. The substance under test is placed on the microscope slide, covered with cover glass and put under the lens. One of the grains is introduced on the crossing of the scales and its length and width are measured in microns. Subsequently, a bit of water is carefully introduced between the glasses. The wetted grain swells rapidly and reaches its maximum size within a few seconds. The outline of the swollen grain may be measured again accurately. There are, however, some difficulties as regards the calculation of volume of the grain observed. The volume of the sphere is calculated as follow :



Swelling recorder A : Tablet ; B : Water penetration ;
C : Transducer ; D : Recorder

Figure 10 Apparatus for determining the swelling of pure disintegrant tablet

$$V = \frac{4}{3}\pi r^3$$

where r is the radius of the sphere.

b) Cinephotomicrography (73)

A cinephotomicrographic technique is used to study microscopically the swelling characteristics of individual tablet disintegrant particles in water. Feret's diameter, projected area, and dimensionless shape factor such as elongation ratio, bulkiness factor and surface factor of various particle profiles are determined. In this method, groups of disintegrant particles are photographed under a microscope by a high speed movie camera with the resultant film being analysed by a special computer technique which allows the size of both individual and all particles, in any given visual field, to be followed over the very short period of time which elapses during the interaction of the disintegrant particle with water.

The microscopic method may be employed for the determination of swelling power both of the agents insoluble and soluble in water. This method cannot be used for testing material composed of very tiny grains or fibers as bentonite and sponge.

2) Instrumental methods

a) Electrical sensing zone (74)

An instrumental method that is based on the employment of a Coulter Counter has recently been proposed. This method allows the combine measurements of particle volume increase (particle swelling) and granulometric characterization of disintegrants. The choice of the Coulter Counter method is advised by the fact that it provides facilities for counting and sizing particles and that its counting principle is on a volume basis, which should allow an exact calculation of particle volume. The measurement of particle swelling is based essentially on the comparison between calculated (from density) and measured (from the particle size distribution provided by a Coulter Counter) total particulate volume. The main problems are represented by the possibility to particle conductivity changes on swelling and by the accuracy of total particulate volume measurements.

Basically, the first problem is related to the Coulter Counter operating principle : it is conceivable that if particle conductivity changes on swelling, the Coulter Counter response may be impaired. To deal with this problem the method must be validated, either by optical microscopy or by other granulometric techniques, for example, laser diffraction in order to assess its applicability for the evaluation of particle swelling of

a given swelling polymer in a given swelling medium. This method is rapid, satisfactorily accurate and reproducible and seems to be useful especially for materials which swell to a limited extent, which can be hardly evaluated by optical microscopy.

3.2.2 Methods for the qualitative evaluation of disintegrant swelling

These methods are less well known than the former, although a few have appeared in the literature, including swelling energy, swelling pressure, and swelling force (75). These methods may also be defined as dynamic, in which case the term is used in its etymological sense, i.e., relating to the observation that a swelling force or pressure develops inside disintegrating compacts following water penetration.

3.3 The mechanisms of disintegrant action

The mechanisms of action of tablet disintegrants have been variously hypothesized, stated and debated. But as yet no theory has been able to explain the apparent divergent observations. It now seems obvious that no single mechanism of disintegrant action is applicable to all disintegrants. In some instances, a combination of mechanisms may be operative. Those mechanisms can be referenced by the physical and chemical properties of the different disintegrants. An overview of current thinking on the mechanisms of

disintegrant action is presented. The concepts that will be discussed are

3.3.1 Heat of immersion and wettability

It has been proposed that the heat generated by the wetting of the ingredients that occurs when the tablet is immersed in a fluid causes the entrapped air in the tablet to expand pushing the tablet apart, thus producing tablet disintegration (76,77). There has been reported that as compression force increased, the heat of absorption and disintegration times decreased. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents. List and Muazzam (78) study this phenomenon and also find that exothermic reactions upon wetting are not universal for all disintegrants and that when significant heat of wetting is generated, there is not always a corresponding decrease in disintegration time.

3.3.2 Effect of water sorption

Water sorption has been implicated as an important mechanism of action for tablet disintegrants. This finding is given credence by Khan and Rhodes (25). They conclude that the ability of particles to draw up water into the porous network of a tablet is essential for efficient disintegration.

It has been stated that substances that absorb about 20% water and are insoluble in water are good disintegrants, i.e., alginic acid, calcium alginate, methylcellulose and various starches. Those that absorb about 40% water and are soluble in water increase disintegration time, i.e., carboxyvinyl polymer, sodium carboxymethyl cellulose, sodium alginate, while those that absorb water poorly reportedly are poor disintegrants, i.e, ethylcellulose (9). There has been reported that the rate of water uptake showed difference between soluble and insoluble disintegrators. The rate of disintegration using either soluble and insoluble disintegrants is thought to be related to the rate of liquid penetration into the tablet.

It can conclude that water uptake is the important mechanism but water sorption by itself will not cause tablet disintegration (76).

3.3.3 Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegrants is swelling. Primarily this is because almost all disintegrants swell to some extent, and swelling has been reported quite universally in the literature. The following disintegrants have been reported as swelling or increasing in particle size in the presence of moisture (76) : carboxymethyl dextran, sodium carboxymethyl

cellulose, cross-linked polyacrylic and polymethacrylic acids, cross-linked gum arabic, cold water soluble and ungelatinized starch, silicates, gums, formaldehyde casein, cation-exchange resin, ultra amylopectin, dextran, natural sponge, carboxymethyl starch, and starches.

Swelling is found by Bolhuis and coworkers (17) to be the primary mechanism of action for tablet disintegrants. In addition, they found that rapidly swelling particles such as sodium starch glycolate and croscarmellose sodium are capable of overcoming the negative effects of hydrophobic tablet components that normally block the passage of aqueous fluids through the porous network within a tablet matrix. Many investigations have placed importance not only on the extent of swelling, but also on the rate at which that swelling develops. In addition, it is important to understand that, as particles swell, there must be little or accommodation by the tablet matrix of that swelling; if the matrix yields elastically to the swelling, little or no force will be expended on the system and disintegration will not take place. If the matrix is rigid and does not accommodate swelling, however, deaggregation or disintegration will occur (1).

The swelling of some disintegrant particles is dependent upon pH (79). Shangraw and coworkers report (30) that the volumes of anionic cross-linked starches and

celluloses are significantly altered in acidic media while polyplasdone and starches remained unchange.

3.3.4 Porosity and capillary action

Tablet porosity is an important influence on water penetration and tablet disintegration. Porosity depends on the pressure at which tablets are compressed as well as on the nature of the material being tabletted. The effect of porosity is different to interpret because of the effect of pressure, materials, methods of measurement and types of pores. Studies of porosity have often involved penetration of various fluids into tablets. Permeation of tablets is also affected by the above variables in addition to the fluids used. Porosity (void space and pore size) decreases with an increase in compression. The rate of penetration of fluids into a tablet is proportional to mean pore diameter or porosity and permeability of tablets decreases as pressure increases.

It is generally agreed that as porosity or pore diameter decreases in tablet compression, disintegration time goes through a minima. It is thought that at low compression forces, tablet have a high porosity due to the large void space. Thus, the swelling disintegrant particles exert very little pressure against other components in the tablet matrix, and disintegrant is slow. At medium pressures, however,

the void space is reduced, and the swelling disintegrant particles exert enough pressure on the adjacent granules to cause more rapid disintegration. High force produces tablets with low porosity and decreases the ability of fluid to enter the tablet, increasing disintegration time even further. The phenomenon of an initial decrease in disintegration times with increasing compression force is more pronounced for insoluble fillers because the rate - determining step is water penetration with subsequent swelling of the disintegrant. No correlation is found between disintegration and penetration times, but generally short disintegration times have rapid fluid penetration times. Penetration of fluid into tablets is affected by the interfacial tension of liquid-solid boundary, contact angle, pore size distribution, and geometry of the pore surface. In addition, viscosity of the liquid and electrostatic charging may affect flow of liquids in capillaries.

Lowenthal and Burruss (80) conclude that, the decrease in mean pore diameter with increasing the compression force and the increase in mean pore diameter with increase in disintegrant concentration, vary with disintegrant, compression force, drug and disintegrant concentration. For example, only corn starch with aspirin give a constant increase in mean pore diameter with increasing concentration. Only at 1,000 psig did the mean pore diameter consistently increase with disintegrant

concentration. The rate of mean pore diameter increases due to corn starch concentration drops as compression force increases. A cation-exchange resin produces larger mean pore diameters and lower porosities than corn or waxy maize starches. Tablet that has the largest change in mean pore diameters shows minimal change in disintegration times. Large pore diameters or porosities do not always give rapid disintegration, nor does small pore diameters and porosities imply poor tablet disintegration.

3.3.5 Deformation

The existence of plastic deformation under the stress of tabletting has been reported for many years. Evidence that disintegrant particles deform during tablet compression is demonstrated by Hess (37). The deformed particles are shown to return to their normal shapes when exposed to moisture. Potato starch is found to plastically deform under pressure, but the individual grains could still be recognized (81). Corn and waxy maize starches also deform when compressed and the degree of deformation increares with increasing pressure (82). It is stated that compression decreases grain stability, resulting in energy rich grains being formed, so that no more energy is required for swelling to occur. It is the reason that ordinary starch will require heat to swell, whereas deformed starch will not require any extra energy. It is also indicated that the

deformed grains appear as layers or streaks. The grains were not broken and apparently did not decrease in size (82).

3.3.6 Physicochemical bonding

Another theory of tablet disintegration attempts to explain the swelling of tablets made with "nonswellable" disintegrants such microcrystalline cellulose. Shangraw and coworkers (40) conclude that in microcrystalline cellulose tablets, disintegration is due to entrance of water into the tablet by means of capillaries. The water breaks the hydrogen bonds holding the cellulose fibers together, thus causing tablet disintegration. It is suggested that pressure caused the matchsticklike bundles of cellulose to line themselves up into layers, decreasing bond distances and increasing interparticle forces. Tablet disintegration occurs when these bonds are broken by water. It is disclosed that as the polarity of disintegration fluids decreased, the disintegration times of microcrystalline tablets increased. Similar results have been reported for starch (35,83). The swelling of starch is reportedly due to the filament micelles of the grains being pushed apart to exert pressure sufficient to cause tablet disruption.

3.4 Disintegrating force

Colombo and coworkers (84) study tablet

disintegration mechanisms by measuring the disintegration force developed by a tablet after immersion in water or other biological fluids. This research shows that, of all the mechanisms describes above, only the swelling of disintegrant particles can be clearly demonstrated. The tablet disintegrates when a certain amount of disintegration force is developed and this force arises only when the excipients swell. Further data indicate that water uptake and disintegration force development are directly connected.

Caramella and coworkers (85) stated that "a force must develop inside the compact to promote disintegration". They divide the various mechanisms on the basis of dynamic considerations, that is on the basis of their capability to promote disintegrating force development. They are grouped in the following manner (5) :

a) the pressure exerted by the air entrapped in pore structures due to a hydrodynamic process or the heat of wetting
b) the swelling of the disintegrating agent
c) the repulsion among particles caused by the contact between solid and liquid.

They also stress the concept that force is not a mechanism by itself but the outcome of a series of events beginning with water penetration and leading to the activation of one of the mechanisms cite.

Bolhuis and collaborators (17) propose a scheme of disintegrant action for strongly swelling materials suggesting that these disintegrants act not only by promoting water penetration but also by causing a chain reaction of disruption of the tablet. The scheme propose by Bolhuis is enlarged by introducing the force development between the various steps, are shown in Figure 11, since, swelling has to be capable not only of promoting water penetration but also of producing enough disintegration force to cause bond disruption. They conclude that "The role of swelling in the disintegration process is to make pore walls hydrophilic so as to provide enough disintegrating force to produce interparticle bonds disruption. A continuous network formation around the active principle particles determines efficient disintegration only when it promotes a rapid disintegrating force development" (86).

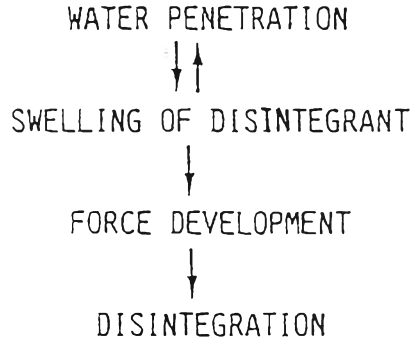


Figure 11 Disintegration process scheme