CHAPTER I

INTRODUCTION

The history of solid dosage forms dates back will over a thousand years, and tablets have been in wildspread use since the latter part of the 19^{th} century. Today they still remain the most popular of all medicinal preparations intended for oral usage. The advantage of tablets include relative ease and economy of manufacture, compactness, ease of handling and ingestion, convenience to the patient, generally good palatability, and therapeutic desirability resulting from precision of dosage, stability and acceptable bioavailability (1).

Tablets are prepared by compressing a formulation containing drug with or without excipients using available equipments. It is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. The characteristics include the ability to flow freely, cohesiveness and lubrication. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material which to be compressed into tablets.

In general, there are three methods for tablet preparation : wet granulation, dry granulation and direct compression. Wet granulation is the most wildely used method. The purposes of wet granulation is to enlarge the particle size of a powder and obtain uniform particles which have free-flowing. It improves the cohesiveness, compatability, prevents segregation and reduces dust (2,3).

The appearance, elegance and tablet properties are directly related to the granulation form which tablets are compressed. The quality of granulation is depend on the materials, processing techniques and various equipments utilized. All these variables mentioned above none is more critical than the binders used to form granulation. Tablets binders impart a cohesiveness to the tablet formulation which ensure the tablet remaining intact after compression, as well as improving free-flowing qualities by the formulation of granules of desired hardness and size (4). Because of the importance of binders in tablet preparation, numerous materials have been evaluated as tablet binders.

Recently, Pongsamart et al (5) elucidated slightly off white powder, extracted from durian rinds (Durio zibethinus Linn.) by using alcohol (D_1) and acid alcohol (D_2). The authors found that extracts mainly composed of carbohydrate and no acute or subchronic toxicity observed after oral administration in mice . Umprayn et al (6) established that both forms of durian rind extracts appeared to be an effective disintegrating agent in tablet preparations. Furthermore , it is reasonable to assume that they may have some binding properties which can be employed in tablet formulations. The reason may be due to both exhibited water absorbing ability, swelling properties and forming a mucilagenous mass in the presence of water.

The persent study intend to evaluate binding properties of durian rind extracts (D_1 and D_2) in wet granulation process as comparing with various cammonly used binding agents.

LITERATURE REVIEWS

TABLET BINDERS

THE PURPOSES OF ADDING BINDER IN TABLET FORMULATION (2-4,7)

There are four main reasons of adding binder :

1. To adhere the powder to each other so they can be formed into agglomerate, called granules.
2. To improve flow property of powder.
3. To insure the tablet remaining intact after compression by imparting cohesive quality to the powder.
4. To increase tablet hardness and reduce friability.

BINDER INCORPORATION METHOD (2)

Binder are utilized as a solution and in dry form depending on the other ingredients in the formulation and the method of preparation.

1. Solution Incorporation Method. Binders solution are prepared with water or suitable solvent and added to the powdered mixtures.

2. Dry Incorporation Method. Powder and binder are pre-dry mixed and then the mixture were moistened with water or suitable solvent.

TYPE OF BINDERS (2-4)

Binders are either sugars or polymeric materials. The latter fall into two categories : 1) natural polymers such as starchs and gums, including acacia and tragacanth, and 2) synthetic polymers such as polyvinylpyrrolidone (povidone), methylcellulose (Methocel$^{(R)}$) and hydroxypropylcellulose (Klucel$^{(R)}$). Binders of both types may be added dry to the powder mix, and the mixture

wetted with aqueous, alcohol, and aqueous alcohol mixtures or the binder may be put into solution in the suitable solvent and added. A list of commonly used binders in wet granulation process is shown in Table 1.

1. Starch is a polymeric carbohydrate obtained from the roots, seeds, and fruits of various plants, including corn potato, wheat, tapioca and rice. It, probably the most commonly used binder in the past, has been employed in form of starch paste, in a concentration range of 5 or 10% (4). A simple way to make starch paste is to suspend starch in 1 to 1 1/2 parts of cold water, then add 2 to 4 times as much boiling water with constant stirring. The starch swells almost immediately to make a translucent paste which can then be diluted with cold water to the desired concentration. Starch paste may also be prepared by suspending the starch in cold and heating to boiling in a steam-jaketted kettle with constant stirring. Starch paste is a versatile binder, yielding granules and tablets which disintegrate readily. It forms tablets which are generally soft and brittle.

2. Pregelatinized starch is a partially hydrolyzed starch, which can be used in placed of starch as starch paste. Its binding properties are slightly greater than starch paste, and it offers the advantage of being soluble in warm water without boiling. It may also be used as a binder by adding dry form to powder mix and wetting with water to granulate.

3. Acacia is natural gum produces hard tablet but without increasing hardness with times. One of the disadvantages of acacia is that it is a natural product and is often highly contaminated with bacteria which makes it objectable as a binder. Now it has been largely replaced by recently developed polymers.

Table 1

Commonly used Tablet binders in Wet granulation process (3)

Name	Form Used	Tablet Concentration Range (%)	Solvent / Moistener	Class*
Starch	Warm paste	1-5	Water	V
Pregelatinized Starch	Dry/Solution	5-10	Water	V
Acacia	Dry/Solution	5-20	Water	I
Gelatin	Warm Solution	1-5	Water	I
Sucrose	Solution	2-20	Water	I-II
Dextrose	Dry/Solution	5-10	Water	IV
Polyvinylpyrrolidone	Dry/Solution	Ø.5-5	Water or alcohol or hydro-alcohol	III
Methylcellulose	Solution paste	1-5	Water	III
Ethycellulose	Solution	Ø.5-2	Alcohol	III
Hydroxypropylmethyl cellulose	Solution paste	1-5	Water	III

* The class of binders, base on properties, are as follow : I very hard tablets that retard disintegration; II very hard tablets that promote disintegration; III hard tablet that retard disintegration; IV soft tablets that retard disintegration; V soft tablet that promote disintegration.

4. Gelatin is a product obtained by the partial hydrolysis of collagen. Gelatin solutions should be made by first allowing the gelatin to hydrate in cold water for several hours or overnight, then heating the solution to boiling . Gelatin solution must be kept warm until used otherwise they will gel on cooling. Gelatin has a tendency to produce hard granules and has the disadvantage that tablets made with gelatin tend to harden after storage. It may be used as 2 to 10 % solution (4).

5. Sugars such as sucrose or dextrose form the hardnest granules. They are also good carriers for soluble dyes , producing granulations and tablets of uniform colors. Sucrose is used in a formulation where the preponderance of ingredients are water soluble. The tablet prepared from sucrose will frequently fail to disintegrate and will instead dissolved by erosion. As a result, It may prolong disintegration time while providing good dissolution properties.

6. Polyvinylpyrrolidone (PVP) has become a popular binder. This compound is a high molecular weight polymer, unreactive and has the advantage of being soluble in both water and alcohol. PVP form hard tablets with some tendency toward retardation of disintegration . Although it tend to be slightly hygroscopic, tablets prepared with it do not, as a rule, harden with age. Generally, it is better to granulate insoluble powders with aqueous or hydroalcoholic solutions of PVP and to granulate soluble powder with PVP in alcohol solution.

7. Methylcellulose is the methyl ether of cellulose. It is commercially available in a variety of viscosity grades from several sources. The methylcellulose solution is prepared by wetting methylcellulose in hot water, and bringing it to final volume with cold water to allow for dissolution. A 5 % solution

produces granulations similar in hardness to 10 % starch paste (4). It has the advantage of producing granulations which compress readily, producing tablets which generally do not harden with age.

8. Ethylcellulose is a ethyl ether of cellulose containing 40-50 % of ethoxy groups. It is insoluble in water and is used in alcohol solutions. Ethylcellulose is available in several viscosity grades. Tablets prepared from ethycellulose granulations have relatively short disintegration times without hardening tendencies. Ethylcellulose is useful as a binder in the nonaqueous wet granulations of moisture sensitive drugs.

9. Hydroxypropylmethylcellulose (HPMC) is the propylene glycol ether of methylcellulose. It is soluble in water and hydroalcoholic solutions. It is also available in a range of viscosities. HPMC solution is prepared with the same method as methylcellulose. In a tablet, at concentration between 1-5 % HPMC forms hard tablets and a tendency to retard disintegration (3). Similar to ethylcellulose HPMC can be used as a binder in the nonaqueous wet granulation of moisture sensitive drugs.

GRANULE FORMATION IN WET GRANULATION

In wet granulation , solution containing a binder generally added to the powder mixture . The liquid play an important role in the granulation process. Addition of a granulating liquid to a mass of powder may be characterized in a series of stages as described in Figure 1 by Newitt and Conway-Jones as follows (8).

1. Pendular State At the initial stage, the powder particle are wetted with the granulating liquid . The liquid films will be formed on the surface and may combine to produce discrete liquid bridges at points of contact (Figure 1-A). The surface

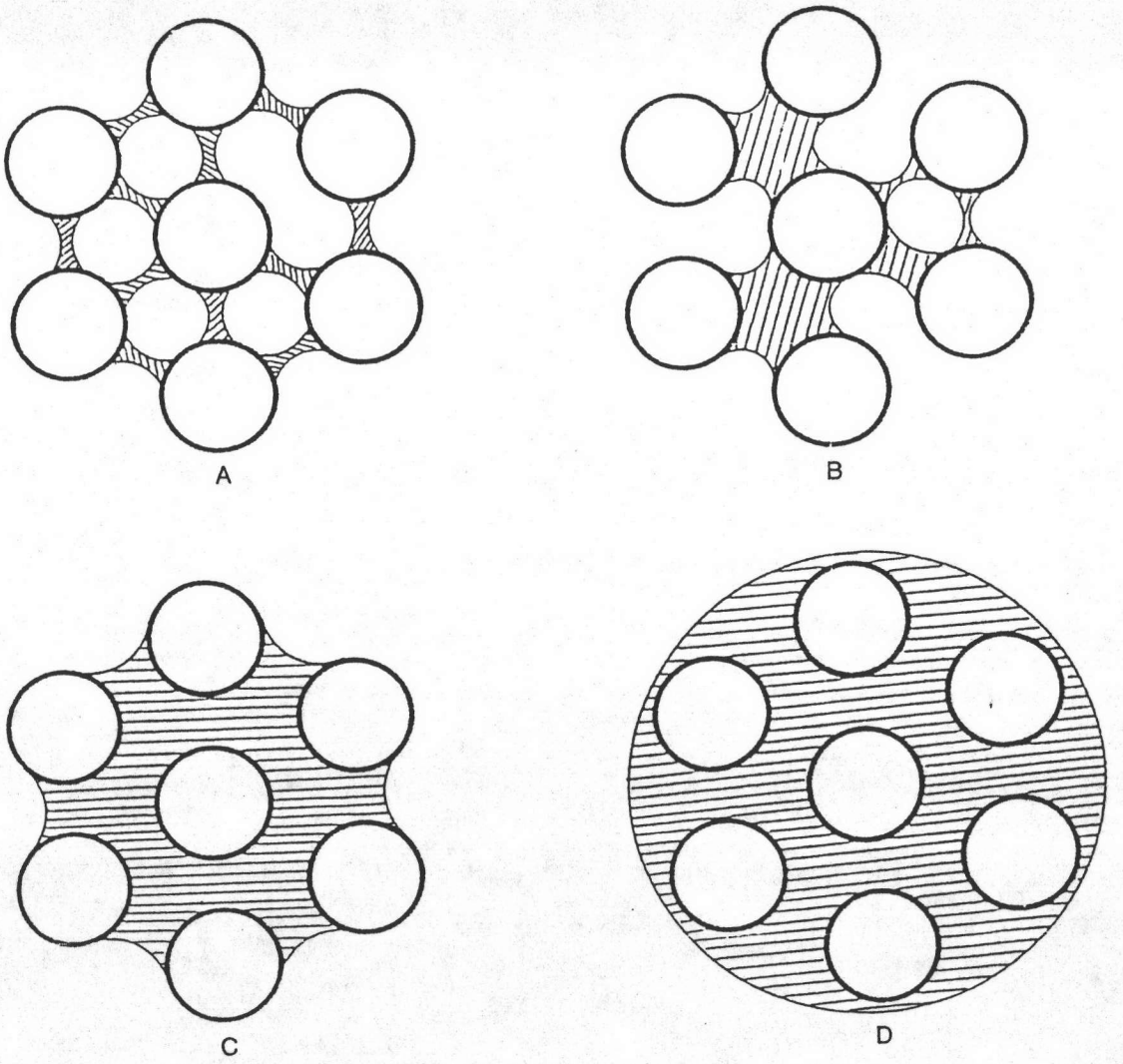

Figure 1 Stage in the Development of Moist Granules as the Proportion of Liquid is Increased in Wet Granulation Process. (Key : A Pendular, B Funicular, C Capillary, D Droplet).

tension and negative capillary pressure in such bridge provide the cohesive force. In this state, the granules have comparatively low mechanical strength.

2. Funicular State As the amount of granulating liquid increases, several bridges of granules also further increase. (Figure 1-B)

3. Capillary State Eventually as more liquid is added and the mass is kneaded to bring particles into closer proximity, the void space within the granule are entirely eliminate (Figure 1-c). At this point, bonding is effected by interfacial forces at the granule surface by a negative capillary pressure throughout the interior liquid filled space . The maximum strength of the wet granules is obtined in this state . Consequently, optimization of granulation process ensuring that this state has been achieved .

4. Droplet State Further addition of granulating liquid result in droplet formation (Figure 1-D). The particles are still held together with surface tension but without intragranular forces; such structures are weaker.

During drying, solid bridges of soluble materials (eg. drug, diluent binder etc.) will be formed in the granule. It may be crystallize or precipitate out. This process results in the increasing in granule strength.

EFFECTS OF BINDER ON GRANULE PROPERTIES

The effects of binder on granule properties have been reported by many researchers (9-23).

EFFECT ON PARTICLE SIZE AND SIZE DISTRIBUTION

Chalmers and El worthy (9) studied PVP as binder and they found that the average granule size of oxytetracycline increased when , a) increasing binder concentration at a constant volume utilized, b) increasing the volume of the granulating solution at a fixed binder concentration , and c) increasing the volume of granulating solution while decreasing the PVP concentration but maintaining the same amount of PVP employed in each granulation. El-Gindy et al (10) studied the binder activity of PVP on the physical properties and compaction characteristic of granules prepared by wet granulation and fluidization. The results are in agreement with the above authors. Furthermore, types of binder are significantly effect on granule size. Ritala et al (10) stated that PVP and hydrolysed gelatin produced granules with a high mean granule size than polyvinylpyrrolidone-polyvinylacetate copolymer and hydroxypropylmetheyl cellulose.

EFFECT ON BULK DENSITY , TAPPED DENSITY AND COMPRESSIBILITY

Previous work (2) presented that the increasing in the average granule size at higher binder level yielded a lower bulk density granules. Stanley - wood and Shubair (13) found that as the concentration of starch paste increased to 10 % w/w bulk density, tapped density and percent compressibility tend to increase. But the results were conversely when the concentration over 10 % w/w. Harwood and Pilpel (14) investigated the effect of size and shape on bulk density and tapped density of granules. As granule size increased, bulk density was found to decrease. These attributed to the fact that smaller granules were able to form a closer , more intimate packing than those larger granules.

EFFECT ON FLOW PROPERTIES

In general , the angle of repose normally increases as particle size reduced, and this effect is usually quite dramatic in the small particle size range . Value for angle of repose $\leqslant 30^{\circ}$ generally indicate a free-flowing material, and angle of repose $\geqslant 40^{\circ}$ suggest poorly flowing material (15). Increasing binder concentration, flow rate was decreased as angle of repose was increased (10). Davis and Gloor (12) in a series of publications, have described that increasing binder concentration such as povidone, acacia, gelatin and hydroxypropylcellulose tend to decrease hopper flow rates . The authors concluded that the decrease in hopper flow rates are a result of increasing average granule size that occurs as binder concentration increased. Marks and Sciarra (16) like Harwood and Pilpel(14) also found that flow rate was inversely proportional to average granule size.

EFFECT ON GRANULE FRIABILITY

Granule strength and friability are somewhat important, as they affect change in particle size distribution and consequently compressibility into cohesive tablets. Granule should possess sufficient strength to withstand normal handling and mixing process without breaking down and producing large amount of fine powder. The resultant strength of a granule is, of course, dependent upon the excipient employed, the kind and amount of binding agent, the granulating equipments, and so on (15). In a batch of granules it would appear that the larger granules possess more strength than the smaller ones (14,16). This may attribute that the smaller granules are more poorly formed and thus less robust than their larger counterparts.

Numerous reports exists in the literature to show that increasing amount of binder produced granules of greater strength (12,14-20). The quantity of granulating fluid used , and the concentration of any added binder are the two major factors contributing to an increase in granule strength. At a constant binder concentration in the final formula, dilution of the binder solution increase granule strength or reduces granule friability (22-23).

EFFECT ON PERCENT FINE OF GRANULE

Granule flowability and tablet uniformity were significantly effected by amount of fine particles. The optimum amount of percent fine lead to a maximum flow rate (8). From comparative data of Agrawal and Prakasdam's work (24) showed that granules prepared from PVP as compared with starch, ethylcellulose and acacia have the mininum percent fine, low compressibility and the best flow rate.

EFFECT OF BINDERS ON TABLET PROPERTIES

The influences of binders on tablet characteristics were investigated by many workers (22-47).

EFFECT ON TABLET STRENGTH AND FRIABILITY

A tablet requires a certain amount of strength, or hardness, to withstand mechanical shocks of handling in its manufacture, packing and shipping. Adequate tablet hardness and resistant to powdering and friability are necessary requisties for consumer acceptable. In addition, hardness are significantly influence on disintegration and dissolution rate of tablets.

Previous investigations have shown the effect of binders on tablet strength and friability. In general, it was found that the increase in binder concentration caused an enhance in the hardness, tensile strength and decresse in friability. Sakr and his co-workers (25) cleary emphasized that type of binder used are influence on those properties. Sodium alginate compared favourably with both acacia and gelatin in increasing the mechanical strength of lactose tablets, as demonstrated by the increase in hardness and decrease in friability values. In addition, varying the starch mucilage fluid volume, but not the total fluid added, also affected on these two properties (25).

EFFECT ON TABLET DISINTEGRATION TIME

Although the complete disintegration of a tablet does not necessarily mean complete dissolution, however the tablet that failed to disintegrate completely will not be able to permit the full availability of the active portion at the absorption site. The effect of binder on disintegration time of tablet has been studied by many workers (10-11,24-25,27-32). It generally increased with higher binder concentration. This probably due to a corresponding increase in the binder's adhesiveness. The effect of various binder types and concentrations on granulations and compressed tablets in fluidized bed was investigated (11). The result indicated that the rank of disintegration time of various binders is hydroxypropylcellulose > gelatin > acacia > PVP and the disintegration time increase as binder concentration increased.

EFFECT ON DISSOLUTION TIME

It is generally accepted that in order for a drug to be available to the body, it has to be in solution. Figure 2 illustrates a scheme of the way in which drugs formulated into a

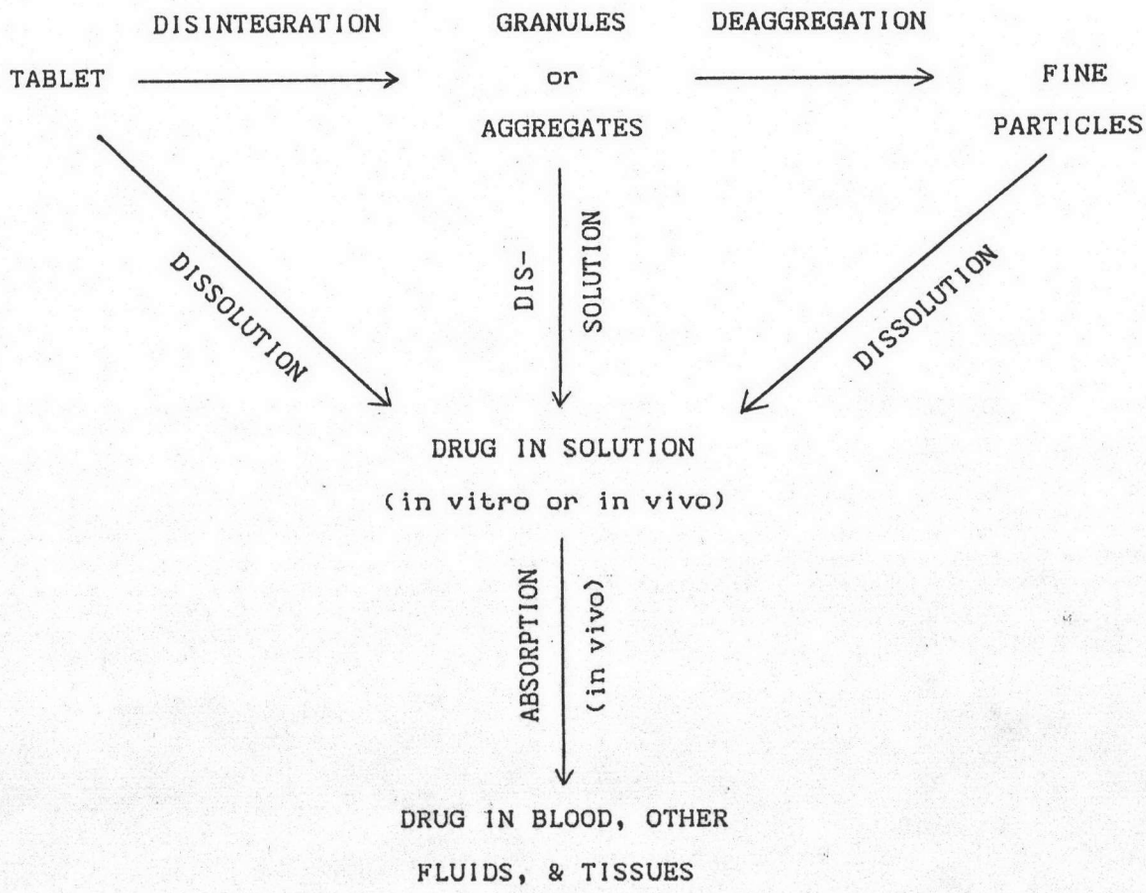

Figure 2 Illustrate a Scheme of the Way in which Tablets Become Available to the Body.

tablets become available to the body. For most tablet the first step is to breakdown into small particles and then dissolve in the content of the gastrointestinal tract before the absorption of the drug occurs. Usually, the rate of drug absorption is determined by the rate of drug dissolution from the tablet. Therefore, it is important to obtain rapid drug dissolution from the tablet. Many reports concerned with the effect of binder on tablet dissolution (30-47).

Jacob and Plein (32) investigated the effect of various binders,such as gelatin,acacia,ethylcellulose,hydroxyethylcellulose, and hardness on tablet dissolution. It could be noticed that increasing in binder concentration and hardness retarded the dissolution rate of phenobarbital tablets.

Esezobo et al (33) indicated that T 50 % of paracetamol tablets is increased as percent amount of binder, such as PVP, gelatin and Tapioca, increased.

Shubair and Dingwall (34) found that dissolution of erythrosine from lactose compacts was adversely affected by amount of starch paste except at high level and by compressional force. They also reported that amount of binder fluid used affect the release patterns of active drug (35).

Sakr and Elsabbagh (36) employed acacia and sodium alginate as binder to formulate nicotinic acid tablet. The result showed that acacia had little or no effect on the dissolution time while sodium alginate had a marked delaying effect.

Rubinstein et al (37) studied the effect of four tablet binders, such as PVP, starch, stearic acid and

methylhydroxyethylcellulose, on the dissolution rate and bioavailablity of frusemide tablets. The results indicated that the choice of binding agent in tablet formulation siginificantly affect the bioavailability of frusemide. In addition, bioavailability differences between each formulation can best be detected in vitro by dissolution rate measurements.

PURPOSE OF THE STUDY

The purpose of the study is to evaluate binding property of durian rind extracts , useless material, as the new binding agent in wet granulation process comparing with five different commonly used binders,such as PVPK30, corn starch , Starch 1500(R), Methocel E15LV(R) and gelatin.

The study of binding property emphasized with granules and tablets physical characteristics such as particle size distribution, density, flow property, granule friability, tablet strength, weight variation, porosity, disintegration and dissolution prepared by each binders.

Paracetamol and pyridoxine hydrochloride, which are slightly water soluble and water soluble active drug were employed as model drugs. Furthermore, Paracetamol was choosen due to poor compressibility as indicated by the capping problem which usually occurred during compression.

In addition, binder index (θ_b index) which is a new parameter, combines four tablet characteristics, including tensile strength, percent porosity, median dissolution time, and percent friability, is presented. The proposed index allow an overall simpler quatitative evaluation of a binder activity.