CHAPTER I
INTRODUCTION

1.1 State and Significant of the Problem

Now, tablet is one of various pharmaceutical dosage forms that widely used in all country (Lieberman et al., 1989). Tablet is widely accepted as the preferred dosage form among patients and progression in tabletting technology has produced several types of tablet such as chewable, effervescent, and multilayer tablets (Miyamoto, 1998). In pharmaceutical industry, the process of manufacturing is one of various factors, that has been considered. Many procedures of tablet making are not appropriate for the manufactures because the cost of increasing in equipment, labor, time, process validation and energy are important factor. Despite these disadvantages, however the direct compression technique has the distinct advantages. The most obvious advantage of direct compression is economic. Savings can occur in a number of areas, including reduced processing time and thus reduced labor costs, fewer manufacturing steps and pieces of equipment, less process validation, and a lower consumption of power. The most significant advantage in the terms of tablet quality is that of process without the need for moisture and heat which is inherent in most wet granulation procedures, and the avoidance of high compaction pressures involved in producing tablet by slugging or roll compaction. In direct compression, the tablets are compressed directly from powder blends of the active ingredient and suitable excipients (including fillers, disintegrants, and lubricants) which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary. In addition, direct compression procedure is the most efficient process because it is the fastest, simplest for the tablet manufacturing.

However, although this technique seems quite simple, it requires that different properties be observed simultaneously (Göczo et al., 2000):

1) Good flowability and good compressibility of the powder.

2) A suitable bulk density of the powder, in order that the correct amount of drug may be fed into a die cavity.

3) Appropriate particle size distribution.

To solve these problems, several methods were used. Many studies on the tablet excipients that used in direct compression have been reported (Shangraw et al., 1981a; 1981b). There are three general processes that used to develop the tablet excipients for direct compression:

(1) The modification of physical form (as with, for instance, unmilled dicalcium phosphate or sorbital)

(2) The simultaneous modification of both physical and chemical form (pregelatinized starch or microcrystalline cellulose)

(3) The addition of impurities of similar structure to alter crystallization (dextrates or compressible sugar)

In each case, the changes have resulted in material that more closely resemble minigranulations than individualized crystal particles, thus increasing both fluidity and compressibility (Shangraw, 1981a). The evaluation of Emcocel was showed that the physical and binding properties of Emcocel were nearly the same as Avicel PH 101 (Pesonen and Paronen, 1987). However, the another way that can used to improve the powder properties was use the spherical crystals or crystal agglomerates of drug (Gö czo et al., 2000). The crystal habit of drug such as form, surface, size and particle size distribution can be modified during the crystallization process so these properties are changed.

In pharmaceutical technology, it is important to optimize pharmaceutical response relating to the properties of the formulation. Many computer optimization techniques were used to save cost, reduce time, and trial. Numerous studies of optimization techniques were used for selecting pharmaceutical formulation; Factorial Design (Bos et al., 1991; Renoux etal., 1996), Central Composite Design (Down at al., 1980; Matsumura et al., 1994) and Mixture Design (Campisi et al., 1998).

In this study, there are several excipients that use as the component of aspirin tablet formulation. In the formulation, that consists of more than one excipients may be caused some problems because each of excipient is different in its properties. For optimization these properties, the computer optimization technique, base on mixture design was used, aimed to obtain the product with the required characteristics. The direct compression was a selected technique, that used in this study because to avoid the instability of aspirin from heat and moisture.

1.2 Objectives

1. To formulate the optimized aspirin tablet using direct compression by mixture design based on three tablet excipients
2. To compare the optimized aspirin formulation with commercial formulation

1.3 Scope of Study

This study is divided into 5 steps, which as the followings:

1. Design the mixture experiments
2. Study the formulation properties for collect data
   - 2.1 Preparation of aspirin formulations
   - 2.2 Determination the formulation properties
     - 2.2.1 Study the flow properties of powder mixture
       - Angle of repose
       - Percent compressibility
     - 2.2.2 Study the tablet properties
       - Hardness
       - Percent friability
       - Disintegration time
       - Percent drug release
3. Optimization of formulation properties
   - 3.1 Selection the optimal range of each property
   - 3.2 Evaluation of response surface models

4. Scale up the optimized formulation
5. Comparative the scale up formulation with commercial formulation

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1.4 Literature Reviews

1.4.1 Aspirin

Aspirin has the unique standing in the medical world of still being the most widely used drug, even with the advent of modern, highly potent therapeutic agents. Aspirin has superior qualities as an antipyretic and as a general analgesic, but more specifically in the relief of headaches, muscular pain, postoperative and traumatic pain, postpartum pain, dysmennorrhea, malignancy, cold and respiratory disease, rheumatoid arthritis, acute rheumatic fever, and in the field of dental analgesia (Kelly, 1970).

Name : - Acetyl salicylic acid
- Salicylic acid acetate
- 2- (acetyloxy)-benzoic acid

Empirical formula : $C_9H_8O_4$

Structural formula :

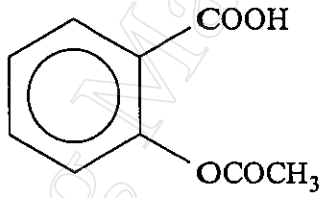

Figure 1.1 Chemical Structure of Aspirin (Florey, 1979)

Molecular weight : 180.16

Description : Aspirin is a white, crystalline powder. It is odorless but might have a faint odor of acetic acid.

Solubility :

in Water at 25° C	0.0033	g/ml
Water at 37° C	0.01	g/ml
Water at 25° C	0.03	g/ml
Ethanol	0.2-0.4	g/ml
Chloroform	0.025-0.06	g/ml
Carbon tetrachloride	0.0004	g/ml

Ether	0.1-0.2	g/ml
Benzene	0.0033	g/ml
Absolute ether	sparingly soluble	
Petroleum ether	insoluble	

pKa : 25° C pKa 2.8×10^{-4} (pKa 3.55)

Partition Coefficients : When aspirin was partitioned between buffers pH 1- and octyl alcohol, partition coefficients ranging from K = 17.7 (pH 1) to K = 0.025 (pH 7). The coefficients is 0.32 in toluene : water and 1.81 in chloroform : water.

Stability : Aspirin is stable in dry air but in contact with moisture or in aqueous solution, it undergoes hydrolysis to yield acetic and salicylic acids. The rate of decomposition is both acid and base catalyzed and is accelerated by heat. Maximum stability is observed at pH values between 2 and 3 (Walter, 1994). The decomposition of aspirin was showed in figure 1.2. When aspirin decomposition that visually the presence of any whiskers (very thin elongated crystals of salicylic acid) observed on the surface of a solid product containing aspirin is definitely an indication that some of aspirin has decomposed and that the resulting salicylic acid has sublimed through the solid material (Kelly, 1970). The linear salicylate oligomers and various other compounds may be products of the thermal decomposition of aspirin (Reepmeyer, 1983). The decomposition of aspirin has been studied in the solid state. The rate equation for the sorbed-moisture model for the degradation of aspirin in the solid state was established (Yang and Brooke, 1982). Decomposition of aspirin in the solid state was later shown to be dependent on the amount of moisture present; in a closed system in the presence of limited amounts of moisture at 62.5°C (Carstensen et al., 1985) and at five other

temperatures (40°C to 65°C) (Carstensen et al., 1988). Significant changes in the disintegration behavior of enteric-coated tablets of aspirin were noted after 4 weeks storage at 30 ° C in cyclic and isothermal heating conditions and under cyclic and constant humidity control (Ondari et al., 1984). Similarly, significant increases in the dissolution rates of enteric-coated aspirin tablets (with a shellac-type coating) were measured following storage at 22 °C and 60% relative humidity, or 33 °C and 60 % relative humidity, for 42 days (Hoblitzell et al., 1985).

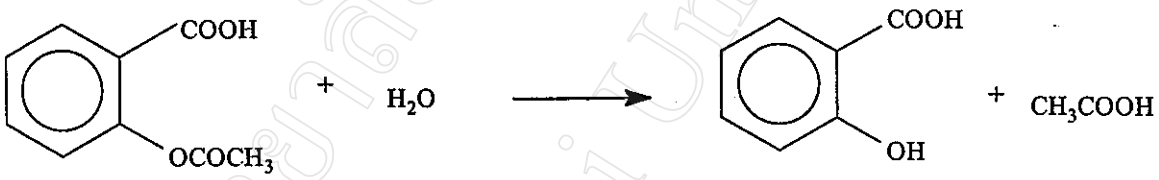

Figure 1.2 The Decomposition of Aspirin (Kelly, 1970)

Pharmacology : Aspirin is analgesic, anti-inflamatory, antipyretic and inhibitor of platelet aggregation. It prolongs the bleeding time. It inhibits fatty acid cyclo-oxygenase (Vane, 1971) by acetylation of the active site of the enzyme (Roth, 1975), and most of their pharmacological effects are due to inhibition of the formation of cyclo-oxygenase products including thromboxanes, protaglandins and prostacyclin. Aspirin has an active metabilite (salicylate) which, in addition to possessing some anti-inflammatory properties its own right, also has important effects on respiratory, acid-base balance and the stomach. Salicylates stimulate respiratory by a direct effect on the medulla, and at high

concentrations, uncouple oxidative phosphorylation in muscle, increasing oxygen consumption and carbon dioxide production. Hyperventilation causes respiratory alkalosis, which is compensated by renal excretion of bicarbonate.When large toxic dose salicylate are ingested and carbohydrate metabolism is deranged, lactic and pyruvic acids accumulate and renal function is impaired, resulting in metabolic acidosis. Salicylates have a direct irritant effect on the gastric mucosa and further predispose to ulceration by inhibiting synthesis of vasodilator and cytoprotective prostaglandins. Large dose of salicylates (greater than 5 g per day) are uricosuric, but such dose are poorly tolerated and salicylates are no longer used to treat gout.

Clinical Pharmacology: Aspirin is generally well tolerated at doses up to 2 g daily. Higher doses are associated with numerous side effects, including tinnitus, abdominal discomfort, nausea, vomiting and gastrointestinal bleeding. Increasingly toxic concentrations cause deafness, vertigo, headache, hyperpnoea, acid-base disturbance, fever, sweating, tachycardia, hallucinations, delirium, loss of consciousness, circulatory collapse, respiratory failure and death. Because aspirin irreversibly acetylates cyclo-oxygense, its duration of action may, in some circunstances, substantially outlive its presence in the body. In particular, its effect on platelet thromboxane biosynthesis persists for many days, recovery being determinated by the entry of new platelets into the circulation (Patrono et al., 1980). Prostaglandin and prostacyclin biosynthesis in other tissues may recover from inhibition by aspirin much more rapidly, presumably because of synthesis of new enzyme (Weksler et al., 1985; Ritter et al., 1989). An intermittent dosage schedule may therefore cause selective

inhibition of platelet thromboxane biosynthesis throughout much of the dosage interval (Moncada, 1982). When aspirin is used as an analgesic in postoperative dental pain, large doses are required (around 1200 mg), analgesic is reversible within a few hours and there is a significant correlation between analgesia and plasma salicylate concentration (Seymour and Rawlins, 1982). However, that the correlation between analgesia and salicylate concentration was fortuitous, and subsequently showed that sodium salicylate does not cause significant analgesia (Seymour at al., 1984).

Indication :

- Mild to moderate pain
- Chronic disease accompanied by pain and inflammation
- As an antipyretic for symptomatic use in adults with febrile illness
- Prophylaxis against arterial occlusive events including stroke and myocardial infarction in patients at high risk (unstable angina, following myocardial infarction and transient cerebral ischemic attacks)

Mode of Use :

The usual dose for analgesia is 300 to 900 mg, every 4-6 hours as needed, with a maximum daily dose of 4 g.

Incompatibility:

A sticky mass is produced when aspirin is triturated with acetanilide, amidopyrine, phenacetin, phenazone, hexamine, phenol, salol, potassium acetate, or sodium phosphate. Aspirin is incompatible with free acids, iron salts, phenobarbitone sodium, quinine salts, potassium and sodium iodides, and with alkali hydroxides, carbonates, and stearates. In solid mixture, aspirin has been reported to acetylate other drug such as paracetamol, homatropine, ephedrine, phenylpropanolamine, and codeine

phosphate. Aspirin has also been reported to be incompatible with histamines (Walter, 1994).

1.4.2 Chitin

Chitin is a very widely distributed, especially in animals, and exists also in less evolved taxonomic groups, such as protozoa (Muzzarelli, 1977). It is a structural constituent in the shells of crustacean and insect, is an acetylated polyamine, which is biodegradable and non-toxic. It is the most abundant natural polymer, after cellulose. It is a close chemical relative of cellulose, and likes cellulose, can be modified both chemically and physically to produce materials with a wide variety of potentially useful properties (Ritthidej et al., 1994). The repeating unit of chitin is N-acetyl-D-glucosamine as shown in Figure 1.3.

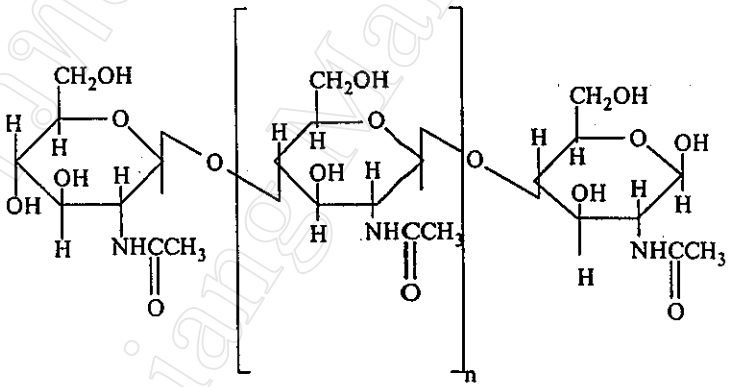

Figure 1.3 The Chemical Structure of Chitin (Lower, 1984)

Chitin is insoluble in water, diluted acid, diluted alkaline, alcohol and other organic solvents, but it can be soluble in concentrate hydrochloric acid, sulfuric acid, phosphoric acid, formic acid. The molecular weight of chitin is more than 1×10^6. Chitin is slowly N-deacetylated and degraded by strong alkali to gave a complex mixture of

partially deacetylated products collectively called as chitosan, a completely deacetylated chitin being referred to chitan (Lower, 1984).

A variety of applications of chitin have been proposed. There are many studies of chitin, that using in many fields (Muzzarelli, 1977). In pharmaceutical, chitin can used as tablet excipient. The study of using chitin and chitosan as disintegrants in paracetamol tablets was found that, tablets containing chitosan showed faster disintegration, greater dissolution and was slightly softer than those containing chitin. Crystallinity, degree of acetylation, chain length and particle size were attributed to the efficiency of chitin or chitosan (Ritthidej et al, 1994). In direct compression, the fluidity of combined powders with chitin and chitosan was greater than that of the powder with crystalline cellulose (Sawayanagi et al., 1982). It is suggested that chitin and chitosan may be suitable for use as diluents with friction-lowering properties in direct compression process. In the studies of chitosan as filler or binder, chitosan fulfills the general requirements for auxiliary substances in the process of direct tableting. On addition in the proportion of 50 % of tablet mass, rapid tablet disintegration resulted (Knapczyk, 1993). In direct compression of salicylic acid tablet, the chitosan affected on crushing strength as well as the release profile of salicylic acid (Rege et al., 1999). In the evaluation of chitosan as binder for chlorpheniramine maleate tablets in comparison with other cellulose binders, it was found that, the rank order correlation for binder efficientcy was: hydroxypropylmethylcellulose > chitosan > methylcellulose > sodium carboxymethylcellulose (Upadrashta et al., 1992).

1.4.3 Starch

Starch is one of the most widely used tablet excipients, but it does not in its natural state possess the two properties necessary for making good compacts: compressibility and fluidity. There have been many attempts to modify starch to improve its binding and flow properties. Starch is widely used as an excipient primarily in oral solid dosage formulations where it is utilized as a binder, diluent and disintegrant.

As a diluent, starch is used for the preparation of standardize triturated of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.

In tablet formulations, freshly prepared starch paste is used at a concentration of 5-25% w/w in tablet granulation as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameter such as granule friability, tablet friability, hardness, disintegration rate and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentration 3-15% w/w. However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. Because of the rounded surfaces of many of large starch grains appear to be flattened or collapsed, it make that, starch's lack of compressibility often weakens the tablet structure sufficiently to preclude its use in direct compression (Shangraw et al., 1981). In granulated formulations, about half the total starch content is included in the granulation mixture and the another half as part of the final blend with the dried granulation (Wade and Weller, 1994).

1.4.4 Direct Compression Excipients (Shangraw, 1989)

1.4.4.1 Lactose

Spray-dried lactose

Spray-dried lactose has excellent fluidity, among the best for all direct compression fillers. It contains approximately 5 % moisture, but most of this consists of water of hydration. The free surface moisture is less than 0.5 % and does not cause any significant problems. It is relatively nonhygroscopic. Spray-dried lactose is available from a number of commercial sources in a number of forms. Because the processing conditions used by different manufacturers may vary, all spray-dried lactose does not necessarily have the same properties particularly in term of degree of agglomeration, which influences both fluidity and compressibility. Alternative sources of supply should be validated, as is true of all direct compression fillers.

Anhydrous lactose

Anhydrous lactose is a free-flowing crystalline lactose with no water of hydration. The most common form of anhydrous lactose is produced by crystallization above 93 ° C, which produces the β form. This carried out on steam-heated roller, the resultant cake being dried, ground, and sieved to produce the desire size. It is available in a white crystalline form that has good flow properties and is directly compressible.

1.4.4.2 Sucrose

Various modified sucrose have been introduced into the direct compression market place. One of the first such product was Di-Pac®, which is a cocrystallization of 97 % sucrose and 3 % highly modified dextrins. Each Di-Pac® granule consists of hundreds of small sucrose crystals " glued " together by the dextrin. Di-Pac® has good flow properties and needs a glidant only when atmospheric moisture levels are high (greater than 50 % relative humidity). It has excellent color and stability on aging probably the best of all the sugars.

Nutab® is a directly compressible sugar consisting of processed sucrose, 4 % invert sugar (equimolecular mixture of levulose and dextrose), and 0.1 to 0.2 % each of corn starch and magnesium stearate. It has a relative large particle size distribution which makes for good fluidity but could cause blending problems if cofillers and drugs are not carefully controlled relative to particle size and amounts. In formulating Nutab® has poor color stability relative to other direct compression sucroses and lactoses.

1.4.4.3 Dextrose

Emdex® is a modification of natural dextrose for improving tablet characteristics. This product is spray-crystallized and consists of 90 to 92 % dextrose, 3 to 5 % maltose, and the remainder higher glucose polysaccharides. It is available as both an anhydrous and a hydrous product (9 % moisture). The anhydrous form is slightly more compressible than the monohydrate, but the compressibility of both is excellent. The most widely used product is the monohydrate and the water of hydration does not

appear to affect drug stability. At approximately 75 % relative humidity both forms of Emdex® become quite hygroscopic. Above 80 % relative humidity both products liquefy.

Emdex® possesses the largest particle size of all the common direct compression excipients. Blending problems can occur if blends of other smaller particle size excipients are not used to fill in voids.

1.4.4.4 Sorbitol

Sorbitol is one of the most complex of all direct compression fillers. It exists in a number of polymorphic crystalline forms as well as an amorphous form. Both compressibility and stability has caused major problems among users. The less stability (α and β) polymorphic forms of sorbitol will convert to the more stability form (γ), which often results in dendritic growth (small, hairlike crystals). This causes a caking of particles and is accentuated by the presence of moisture.

Sorbitol is widely used as the sole ingredient in "sugar-free" mints and as a vehicle in chewable tablets. However, it is hydroscopic and will clump in the feed frame and stick to the surfaces of the die table when tableted at humidities greater than 50 %.

1.4.4.5 Mannitol

Mannitol is widely used in the direct compression of reagent tablet in clinical test kits where rapid and complete solubility is required. It does not make as hard a tablet as sorbitol but is less sensitive to humidity. Mannitol use as filler in chewable tablets is limited by its cost, although its cool mouth feel is highly attractive. It also exists in a number of polymorphic forms and the different forms were shown to have different compression characteristics.

1.4.4.6 Maltodextrin

A free-flowing agglomerated maltodextrin is available for direct compression tableting under the name Maltrin®. The product is highly compressible, completely soluble and has very low hygroscopic characteristic.

1.4.4.7 Modified Starch

The only modification of starch, which has received widespread acceptance in direct compression, is Starch 1500®. Starch 1500® is more fluid than regular starch and meets the specifications for Pregelatinized Starch, NF. Starch 1500® consists of intact and ruptured starch grains that have been partially hydrolyzed and subsequently agglomerated. It has an extremely high moisture content (12 to 13%), but there is little indication that this moisture is readily available to accelerate the decomposition of moisture-sensitive drugs.

Although Starch 1500® will readily compact by itself, it does not form hard compacts. Its dilution potential is minimal, and it is not generally used as the filler-binder in direct compression, but use as disintegrant. The major advantage of Starch 1500® is that it retains the disintegrant properties of starch without decreasing the fluidity and compressibility of the total formulation, as is the case with a compression force is applied, it imparts little strength to compacts. As few clean surfaces are formed during compaction; lubricants, particularly the alkaline stearate lubricants, tend to dramatically soften tablets containing high concentration of Starch 1500®. Lubricants such as stearic acid or hydrogenated vegetable oils are preferred in such formulations.

1.4.4.8 Cellulose

Solka-Floc® was a floc cellulose product that introduced as filler disintegrant. Solka-Floc® consists of cellulose that has been separated from wood by digestion and formed into sheets, which are mechanically processed to separate and break up individual fibers into small pieces. This converts the cellulose into a free flowing powder. However, this material has poor fluidity and compressibility and is not used as a direct compression excipient.

The most important modification of cellulose for tableting was the isolation of the crystalline portions of the cellulose fiber chain. This product, microcrystalline cellulose (Avicel®), was introduced as a direct compression tableting agent in 1960s and stands as a direct compression excipient developed in modern times. Microcrystalline

cellulose is derived from a special grade of purified alpha wood cellulose by several acid hydrolysis to remove the amorphous cellulose portions, yielding particles consists of bundles of needlelike microcrystals. Microcrystalline cellulose for direct compression tableting comes in a number of grades. PH 101, which was the original product, is the most widely used. PH 102 is more agglomerated and possesses a large particle size, resulting in slightly better fluidity but no significant decrease in compressibility.

1.4.4.9 Inorganic Calcium Salt

The most widely used inorganic direct compression filler is unmilled dicalcium phosphate. This material is available in a tableting grade under the name Emcompress® or DiTab®. Dicalcium phosphate is relatively inexpensive and possesses a high degree of physical and chemical stability. It is nonhygroscopic at a relative humidity of up to 80%. Dicalcium phosphate in its directly compressibility form exists as a dihydrate. Although this hydrate is stable at room and body temperature, it will begin to lose small amounts of moisture when exposed to temperatures of 40 to 60° C.

Tablets produced with dibasic calcium phosphate do not disintegrate readily and disintegrant is necessary, it gave a range of disintegrating times based on type of disintegrating agent and tablet hardness (Rubinsteine and Bodey, 1976; Manudhane et al., 1969). In high temperature and high relative humidity, the tablet made with dibasic calcium phosphate resulted in significant changes of physical properties (Lausier et al., 1977; Horhota et al., 1976).

The fluidity of dicalcium phosphate is good, and glidants generally are not necessary. Tricalcium phosphate (TriTab®) is less compressibility and less soluble than dicalcium phosphate, but it contains a higher ratio of calcium ions. Calcium sulfate is also available in a direct compression form (Delaflo®).

Cel-O-Cal® is the first significant direct compression tablet filler specifically designed to combine the advantages of dissimilar materials by the method of coprocessing. It consists of 30 parts of microcrystalline cellulose and 70 parts of

anhydrous calcium sulfate coprecessed in a spray-dryer. It combines the compressibility and disintegrant advantages of microcrystalline cellulose with the cost advantages of calcium sulfate. The product is significantly more compressible than a physical mixture of its component parts and produces tablets of much lower friability.

Calcium carbonate has been used as tablet filler in the past. It is available in a number of forms, including precipitated, ground-up oyster shells, and mined limestone. They do differ in terms of degree of whiteness, particle size, and impurities. A number have been coprocessed with various binders to make them directly compressible.

1.4.5 Experimental Design

1.4.5.1 The Mixture Design

In a mixture experiment, the independent factors are proportions of different of a blend. The fact that the proportions of the different factors must sum to 100% complicate the design as well as the analysis of mixture experiments. When the mixture components are subject to the constraint that they must sum to one.

In mixture experiments, the measured response is assumed to depend only on the relative proportion of the ingredients or components in the mixture and not on the amount of the mixture (Trutna et al., No date)

The response can be related to the mixture composition with the use of a special-cubic equation (Lahdenpää, 1996)

$$Y= \beta_1X_1 + \beta_1X_2 +\beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 +\beta_{23}X_2X_3 + \beta_{123}X_1X_2X_3 \ldots\ldots (1.1)$$

Where Y is the modeled response, β_1 to β_{123} are the regression coefficients, and X_1, X_2, and X_3 are the fractions of the three mixture components.

The seven regression coefficients in this model can be estimated by use of multiple regression. This requires at least seven measurements of each response located in the experimental space. After calculating the models for each criterion the values of the response can be predicted at every mixture composition within the experimental space.

When experimenting with mixtures, special constraints are placed on the compositional variables; that is, the sum of the fractions of all the mixture components equals one, as shown in Equation 1.2 (Kristl, 1993). None of the fractions can be negative.

$$\sum_{i=1}^{k} m_i = 1 \qquad \text{.....(1.2)}$$

The first constraint results in a special type of polynomial, as has been derived by Scheffe'. Because a change of one fraction m_1 in a mixture implies change of another fraction, there are no quadratic (e.g. $m_1 * m_1$) interaction terms in these polynomials. The two-factor, second-order, polynomial model, shown in Equation 1.3,

$$E(y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \qquad \text{.....(1.3)}$$

with six parameters to be estimated, using the constraint $m_1 + m_2 = 1$, yields a new polynomial with three new parameters β_1^*, given in Equation 1.4.

$$E(y) = \beta_1^* m_1 + \beta_2^* m_2 + \beta_{12}^* m_1 m_2 \qquad \text{.....(1.4)}$$

The three-factor second-order polynomial, depicted as Equation 1.5,

$$E(y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2 \ldots \quad (1.5)$$

has ten parameters to be estimated. Using the constraint m1+m2+m3 = 1, it yields a new polynomial with six new parameter β^*, as on Equation 1.6.

$$E(y) = \beta_1^* m_1 + \beta_2^* m_2 + \beta_3^* m_3 + \beta_{12}^* m_1 m_2 + \beta_{13}^* m_1 m_3 + \beta_{23}^* m_2 m_3 \ldots\ldots (1.6)$$

For three-factor third-order polynomials more terms have to be added; a three-factor, full cubic Scheffe′ model with ten terms is used. A frequently used "special cubic" Scheffe′ model consists of the terms given in Equation 1.6 to which the special cubic three-factor cross-product term has been added in Equation 1.7.

$$E(y) = \beta_1 m_1 + \beta_2 m_2 + \beta_3 m_3 + \beta_{12} m_1 m_2 + \beta_{13} m_1 m_3 + \beta_{23} m_2 m_3 + \beta_{123} m_1 m_2 m_3 \ldots\ldots (1.7)$$

It should be noted that in these models the intercept, represent in normal model equations, has disappeared. As a consequence it is not possible to evaluate Scheffe′ models with linear regression, using standard regression software. Special regression algorithms can, however, be implemented in some software packages, for example SAS® because of the mixture constraints, the number of parameter to be estimated (and thus the number of experiments that are the minimum necessary for regression analysis) has decreased considerably. Whereas in normal polynomials the cross-product terms describe the interaction of factors, in Scheffe′ polynomials these terms are said to describe "non-linear blending". This phenomenon should not be termed an interaction, because as a consequence of the mixture constraint it is not possible to vary the components and thus to evaluate their effects independently (Doornbor and Dehaan, 1995).

Steps in Planing a Mixture Experiment (Trutna et al., No date)

Planning a mixture experiment typically involves the following steps

1. Define the objectives of the experiment.
2. Select the mixture components and any other factors to be studied. Other factors may include process variables or the total amount of the mixture.
3. Identify any constraints on the mixture components or other factors in order to specify the experimental region.
4. Identify the response variables to be measured.

5. Propose an appropriate model form for modeling the response data as functions of the mixture components and other factors selected for the experiment.
6. Select an experimental design that is sufficient not only to fit the proposed model form but allows a test of model adequacy as well.

1.4.5.2 The Augmented Simplex Centroid Design

The augmented simplex centroid is superior for studying the response of complete mixtures in the sense that it can detect and model curvature in the interior of the triangle that can not be accounted for by the terms in the full cubic model.

Simplex design are used to study the effects of mixture components on the response variable. The simplex centroid design has 2^p-1 points, corresponding to the p permutations of (1, 0, 0,..., 0), the $\binom{p}{2}$ permutations of (1/2, 1/2, 0,..., 0), the $\binom{p}{3}$ permutations of (1/3, 1/3,1/3, 0,..., 0),..., and the overall centriod (1/p, 1/p, ...,1/p).

In Figure 1.4a, the simplex centroid design consists of 7 points. A criticism of the simplex centriod design is that most of the experimental runs occur on the boundary of the region and, consequently, include only p-1 of the p components. It is usually desirable to augment the simplex centroid with additional points in the interior of the region where the blends will consists of all p mixture components (Montgomery, 2001). In augmented simplex centroid design, three points are added into the simplex centriod design (as seeen in Figure 1.4b) (Doornbos and Dehaan, 1995).

In the augmented simplex centroid design, there are 10 points that each point represents each formulation. The proportion of the components in each formulation can be seen in Table 1.1.

Table 1.1 The Proportion of Each Component in Each Formulation

Formulation	Component		
	X1	X2	X3
1	1.0000	-	-
2	-	1.0000	-
3	-	-	1.0000
4	0.5000	0.5000	-
5	-	0.5000	0.5000
6	0.5000	-	0.5000
7	0.1666	0.1666	0.6667
8	0.6667	0.1666	0.1666
9	0.1666	0.6667	0.1666
10	0.3333	0.3333	0.3333

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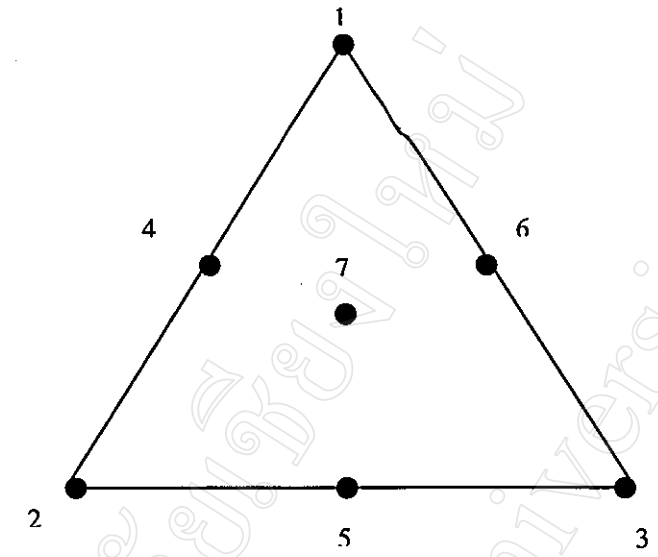
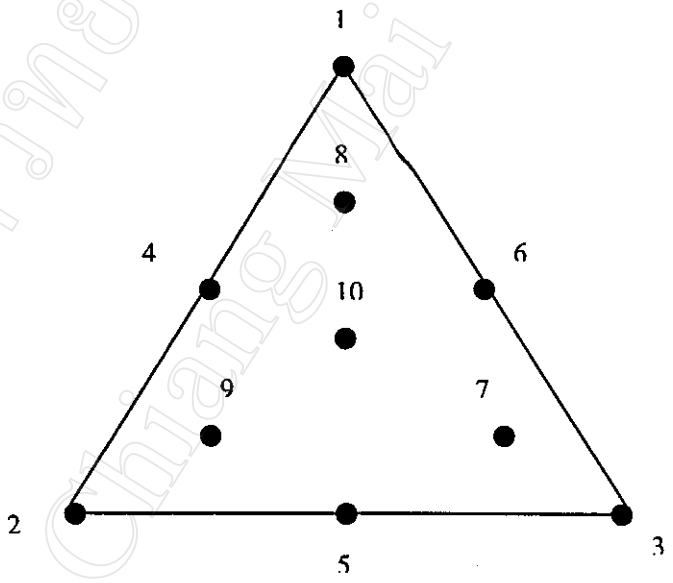


(a)



(b)

Figure 1.4 (a) The Simplex Centriod Design (Montgomery, 2001)
(b) The Augmented Simplex Centriod Design (Doorbos and Dehaan, 1995)

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1.4.6 Mixing

Almost every industry have a blending or mixing operation in some stages of manufacture. In pharmacy, the basic objectives in mixing are to obtain dosage units each of which contain the same ratio of ingredients, and to replicate this procedure with batch (Lantz and Schwartz, 1989).

The definitions of mix and blend are as follows:

Mix: to put together (substances or things, or one substance or thing with another) in one mass or assemblage with more or less through diffusion of the constituent elements among one another.

Blend: to mix smoothly and inseparably together.

The mixing of solid particles is accomplished through three principle mechanisms.

1. Diffusion: the redistribution of particles by the random movement of particles relative one to the other
2. Convection: the movement of groups of adjacent particles from one place to another within the mixture
3. Shear: the change in the configuration of ingredients through the formation of slip planes in the mixture

These three principle mechanisms are illustrated in Figure 1.5

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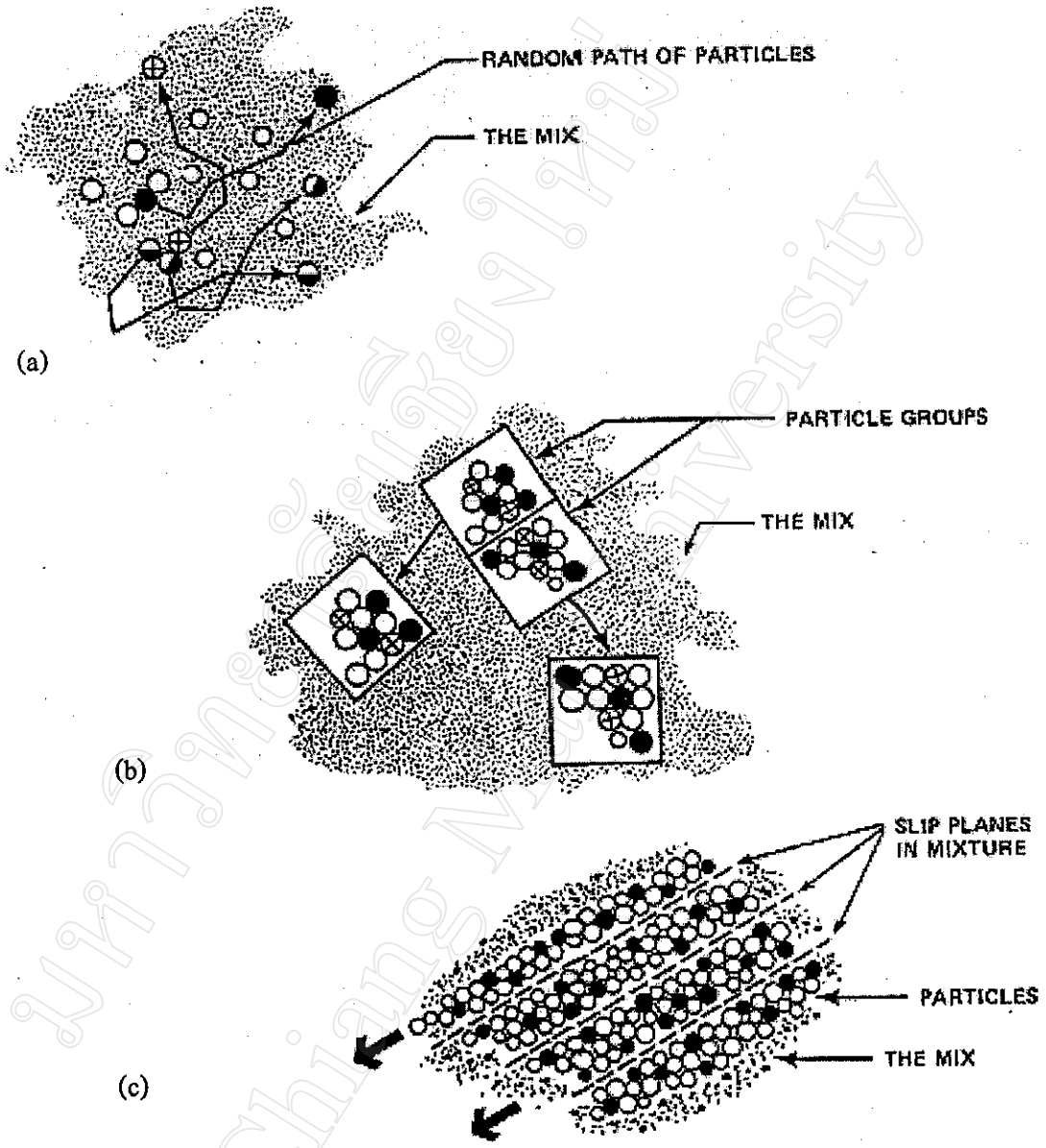

Figure 1.5 Principle Mechanism of Mixing (Lantz and Schwartz, 1989)

a) Diffusion: random action of individual particles in the mix

b) Convection: transfer of adjacent particles groups in the mix

c) Shear: configuration change through slip planes

The unit operation of solid-solid mixing can be separated into four principle steps.

1. The bed of solid particles expand
2. Three dimensional shear forces become active in the powder bed
3. The powder bed is mixed long enough to permit true randomization of particles
4. Randomization (no segregation), of the particles is maintained after mixing has stopped

Initially, when dry materials or particles are loaded into a mixer, they form a static bed. Before mixing or interparticulate movement can take place, this static bed must expand as shown in Figure 1.6, as a result of mixing forces. It must be noted that before a particle bed can expand for mixing, there must be room for it to expand, i.e., there must be enough additional void space remaining in the mixer for expansion after it has been charged with the ingredients to be blended.

Once particle movement is made possible with the expansion of the powder bed, shear forces are necessary to produce movement between particles. Tension and compression forces merely change the bed volume (Figure 1.6).

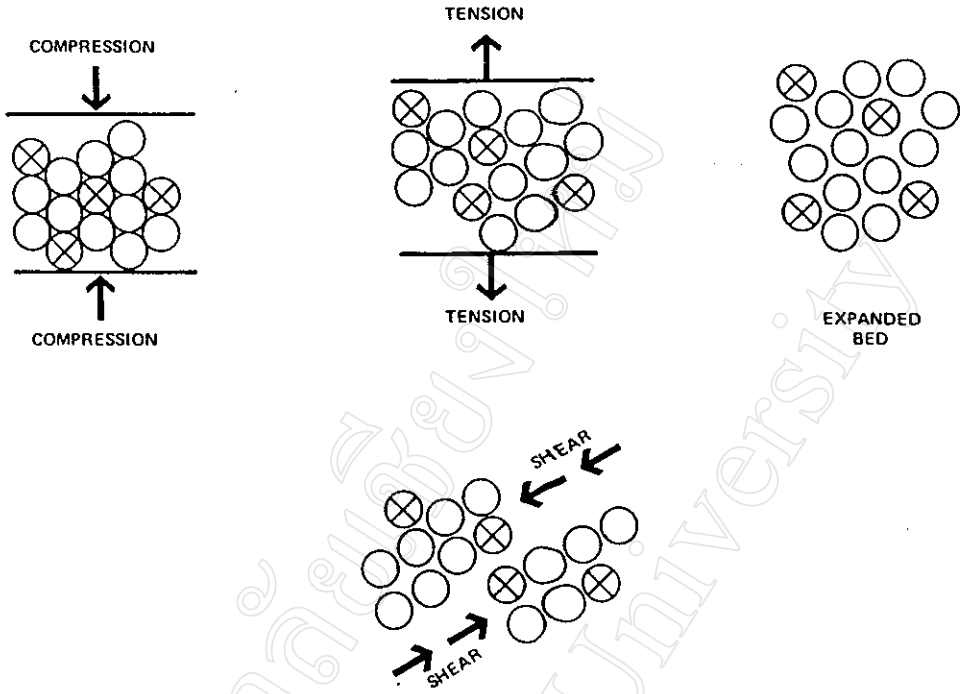

Figure 1.6 Mixing Forces and Bed Expansion (Lantz and Schwartz, 1989)

1.4.6.1 Cube Mixer

Cube mixer is one of the common type mixer (Figure 1.7). It can be rotated about an axis. The resulting tumbling motion is accentuated by means of buffles or simply by virtue of the shape of the container.

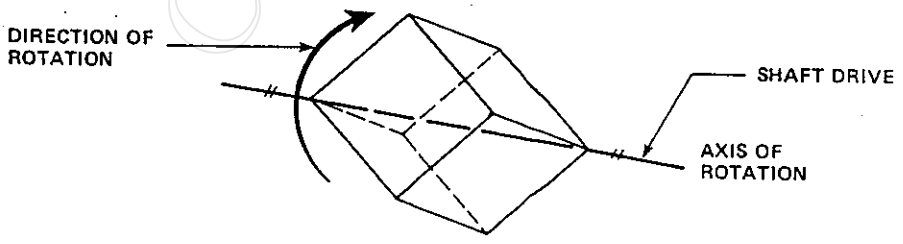

Figure 1.7 Cube Mixer (Lantz and Schwartz, 1989)

The efficiency of tumbling mixers is highly dependent on the speed of rotation. Rotation that is too low does not produce the desired intense tumbling or cascading motion, nor does it generate rapid shear rates. On the other hand, rotation that is too rapid tends to produce centrifugal force sufficient to hold the powder to the sides of the mixer and thereby reduce efficiency. The optimum rate of rotation depends on the size and shape of the tumbler and also on the type of material being mixed, but is commonly in the range of 30 to 100 rpm (Rippie, 1986).

1.4.7 Compression Process (Parrott, 1989)

Compression is the process of applying pressure to a material. In pharmaceutical tabletting an appropriate volume of granules or powders in a die cavity is compressed between an upper and lower punch to consolidate the material into the single solid matrix, which is subsequently ejected from the die cavity as an intact tablet. The subsequent events that occur in the process of process of compression are:

1) Transitional repacking
2) Deformation at points of contact
3) Fragmentation and/or deformation
4) Bonding
5) Deformation of the solid body
6) Decompression
7) Ejection

1.4.7.1 Transitional Repacking (Particle Rearrangement)

First, the powders or granules are delivered into the die cavity. In the initial event the punch and particle movement occur at low pressure. The powder flow with respect to each other, with the finer particles entering the void between the large particles and the bulk density of powders is increased. Spherical particles undergo less particle rearrange than irregular particles, as the spherical particles tend to assume a close packing arrangement initially.

1.4.7.2 Deformation at Points of Contact

When a stress (force) is applied to a material, deformation (change of form) occurs. If the deformation disappears completely (returns to the original shape) upon release of the stress, it is an elastic deformation. A deformation that does not completely recover after release of the stress is known as a plastic deformation. The force required to initiate a plastic deformation is known as the yield stress. When the particles are so closely packed that no further filling of the void can occur, a further increase of compressional force causes deformation at the points of contact. Both plastic and elastic deformation may occur although one type predominates for a given material. Deformation increases the area of true contact and the formation of potential bonding areas.

1.4.7.3 Fragmentation and Deformation

At higher pressure, fracture occurs when the stresses within the particles become great enough to propagate cracks. Fragmentation furthers densification, with the infiltration of the smaller fragments into the void space. Fragmentation increases the number of particles and forms new, clean surfaces that are potential bonding areas.

With some materials fragmentation does not occur because the stresses are relieved by plastic deformation. Plastic deformation may be thought of as a change in particle shape and as the sliding of groups of particles in an attempt to relieve stress (viscoelastic flow). Such deformation produces new, clean surfaces that are potential bonding areas.

1.4.7.4 Bonding

The dominating bond types adhering particles together in compression of dry powders could for simplicity be limited to three types (Nystrom and Karehill, 1995).

- Solid bridges (due to, e.g. melting)
- Distance attraction forces (intermolecular forces)
- Mechanical interlocking (between irregularly shaped particles)

Solid bridges that contribute to the overall compact strength can be defined as areas of real contact, i.e., contact at an atomic level between adjacent surfaces in the compact. Different type of solid bridges have been proposed, such as solid bridge due to melting, self diffusion of atoms between surfaces, and recrystallization of solution materials in the compacts.

The intermolecular forces are as a collective term for all bonding forces that act between surfaces separated by some distance. Thus, the term includes van der Waals forces, electrostatic forces, and hydrogen bonding. The dominant interaction forces between solid surfaces is the van der Waals force of attraction. This force operates in vacuum gas, and liquid environments up to a distance of approximately 100-1000 °A. Hydrogen bonding is predominantly an electrostatic interaction and may occur either intramolecularly or intermolecularly. Electrostatic force arises during mixing and compaction due to triboelectric charging. These electrostatic forces are neutralized with time by electrostatic discharging.

The term mechanical interlocking is used to describe the hooking and twisting together of the packed material. Materials bonding predominantly by this mechanism require high compression forces and have low compact strength and an extremely long disintegration time. However, a more limited of this bonding mechanism is that it is dependent on the shape and surface structure of the particles; i.e., long needle-formed fibers and irregular particles have a higher tendency to hook and twist together during compaction compared with smooth spherical ones.

1.4.7.5 Deformation of the Solid Body

As the applied pressure is further increased, the bonded solid is consolidated toward a limiting density by plastic and/or elastic deformation of the tablet within the die.

1.4.7.6 Decompression

The success or failure to produce an intact tablet depends on the stresses induced by elastic rebound and the associated deformation process during decompression and ejection. Often, if capping or lamination of the ejected tablet has

occurred, the individual pieces are dense, hard, and strongly bonded indicating that sufficient areas of true contact existed during compression. As the upper punch is withdrawn from the die cavity, the tablet is confined in the die by radial pressure. Consequently, any dimensional change during decompression must occur in the axial direction.

Ideally, if only elastic deformation occurred, with the sudden removal of axial pressure the powders would return to their original form breaking any bonds that may have formed under pressure. Also the die wall pressure would be zero as the elastic material recovered axially and contracted radially. Actually under nonisostatic pressure, pharmaceutical materials undergo sufficient plastic deformation to produce a die wall pressure in excess of that may be relieved by elastic recovery accompanying removal of the upper punch. As the movement of the tablet is restricted by the residual die wall pressure and the friction with the die wall, the stress from the axial elastic recovery and the radial contraction causes splitting (capping) of the tablet unless the shear stress is relieved by plastic deformation.

Thus, capping is due to uniaxial relaxation in the die cavity at the point where the upper punch pressure is released (Hiestand et al., 1977) and some may also occur at ejection. It has been demonstrated that if decompression occurs simultaneously in all directions capping is reduced or eliminated (Amidon, 1981; Carstensen, 1985).

1.4.7.7 Ejection

As the lower punch rises and pushes the tablet upward there is a continued residual die wall pressure and considerable energy may be expanded due to the die wall friction. As the tablet is removed from the die, the lateral pressure is relieved, and the tablet undergoes elastic recovery with an increase (2 to 10 %) in the volume of that portion of the tablet removed from the die. During ejection that portion of the tablet within the die is under strain, and if this strain exceeds the shear strength of the tablet, the tablet caps adjacent to the regions in which the strain had just been removed. The compression process has been seen in Figure 1.8.

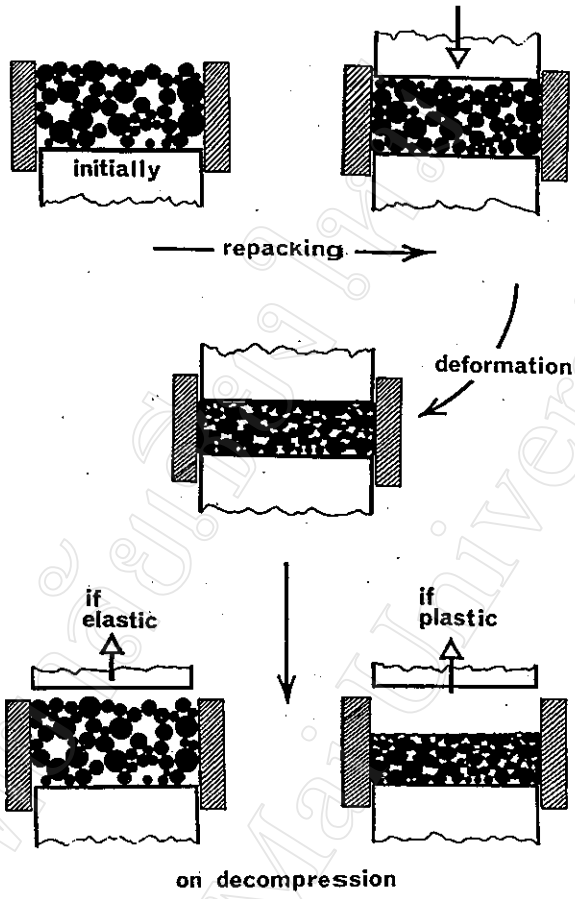

Figure 1.8 The Compression Process of Tablet (Marshall, 1986)

1.4.8 Powder Evaluation

1.4.8.1 Angle of Repose (Carr, 1965)

The angle of repose is the angle between the horizontal and the slope of heap of solid dropped from some elevation. It can be defined as the constant angle to the horizontal assumed by a conelike pile of the material. The pile is carefully built up by dropping the material from a point above the horizontal.

The lower angle of repose of a dry material indicates that, the more flowable material. In conversion, the higher angle of repose occurs from less flowability material.

The angle of repose is a direct indication of the potential flowability of a material and its determination is an easy and simple method of indirectly measuring the following properties affecting flow: shape, size, porosity, cohesion, fluidity, surface area, bulk. The repose angle can be predicting the flowability of material by Table1.2.

Table 1.2 Relationship of Repose Angle and Flow (Wells, 1988)

Repose Angle	Flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

1.4.7.2 **Percent Compressibility**

Compressibility is defined as the ability of a powder to reduce in volume under pressure (John, 1996). The lower percent compressibility material indicates that, the more flowable material. In conversion, the higher percent compressibility occurs from less flowability material. The percent compressibility can be calculated from Equation 1.8. The Relationship of percent compressibility and flowability can be seen in Table 1.3.

$$\% \text{ Compressibility} = \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}} \quad \text{.....(1.8)}$$

Percent compressibility indirectly affecting uniformity in size and shape, deformability, surface area, cohesion, and moisture content.

Table 1.3 Relationship of Compressibility to Flowability (Jones, 1977)

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very Poor
>40	Very Very Poor

1.4.9 Tablet Evaluation (Gordon et al., 1989)

1.4.9.1 Size and Shape

The size and shape of a tablet can be influenced by the particle size of the granulation that can be used, the type of tablet press required, production lot sizes, the type of tablet processing that can be used, packaging operations, and overall production costs. The shape of the tablet alone can influence the choice of tablet machine that can be used. For example, because of the nonuniform forces experienced within a tablet during compression, the more convex the tablet surface, the more likely one is to observe capping problems, thus necessitating the use of a slower tablet press or one with precompression capabilities (Hiestand et al., 1977).

1.4.9.2 Tablet Thickness

Once the tablet size (weight) and shape have been established, tablet thickness remains the only overall dimension variable. Although thickness specifications may be set on an individual product basis, as a general rule, the thickness should be controlled to within 5% or less of an established standard value. Variation in tablet thickness can also indicate formulation or processing problems. At a constant compression load, variations in tablet thickness are indicative of changes in die fill and, consequently, tablet weight, whereas with a constant die fill, thickness variations reflect changes in compressive force. Several factors influence tablet thickness and tablet thickness control. These include

a) the physical properties of raw materials, including crystal form and true and bulk density
b) the granulation properties, including bulk density, particle size, and particle size distribution
c) the physical and mechanical properties of the final compressing mix, including powder flow
d) consistency of the upper and lower punch lengths, which should be appropriately standardized

Since tablet thickness cannot be independently adjusted because of the interrelationships between thickness, weight, compressional force, tablet porosity, etc., it is obvious that appropriate control of raw materials, granulation and final mix properties, and machine operation are fundamental to the satisfactory control of the tablet thickness in practice.

1.4.9.3 Color

Most pharmaceutical companies use variations in tablet color as a mean of identifying distinct products as well as different strengths within a given product line. Tablet colors are generally selected such that the tablets have an aesthetic appeal to consumers, thus requiring that the color of a product be uniform

a) Within a single tablet (nonuniformity is generally referred to as mottling)
b) From tablet to tablet
c) From lot to lot

Nonuniformity of coloring not only lacks aesthetic appeal but also could be associated by the consumer with nonuniformity of content and general poor quality of the product.

1.4.9.4 Hardness

Tablet hardness must be an important consideration because it can have a significant influence on quality of tablet parameters such as disintegration and

dissolution properties. In pharmaceutical industry, general definition of tablet hardness is being the force required breaking a tablet in a diametrical compression test.

The hardness of a tablet is a function of many things all working together. The variation of tablet thickness may also produce variations in tablet hardness. Hardness is a function of applied compressional force and is therefore a function of those factors that cause the force to vary. As additional force is applied to compress a tablet, the tablet hardness will increase. This relationship will hold up to a maximum value beyond which increases in pressure will not cause an increase in hardness, but will cause the tablet to laminate or cap, thus destroying its integrity.

Tablet size, shape and orientation in the tester will also affect the measured hardness values for a given formulation. Large tablets require a greater force to cause fracture and are therefore often considered harder than small tablets.

Factors that may alter tablet hardness in the course of a production run are substantial alterations in machine speed, a dirty or worn cam track, and changes in the particle size distribution of granulation mix during the course of the compressing run. These latter changes affect the die fills. Dies having a light fill (large particles, low density) will produce a softer tablet than dies receiving a heavy fill (small particles, high density).

Lubricants can have a significant affect on tablet hardness when used in too high a concentration or when mixed too long. The lubricants will coat the granulation particles and interfere with tablet bonding (Lerk and Bolhuis, 1977; Shah and Mlodozeniec, 1977).

1.4.9.5 Friability

Friability is a measure of the tablet's ability to withstand both shock and abrasion without crumbling during the handling of manufacturing, packaging, shipping, and consumer use. Tablets that tend to powder, chip, and fragment when handled lack elegance and, hence, consumer acceptance. These tablets can also create excessive dust and dirt in processing areas such as compressing, coating, and packaging, and can add to a tablet's weight variation or result in content uniformity problems.

1.4.9.6 Disintegration

It is generally accepted that in order for a drug to be available to the body, it must first be in solution. For most conventional tablets, the first important step in the sequence is the breakdown of the tablet into smaller particles or granules. This process is known as disintegration. Figure 1.9 illustrates a scheme of the ways in which drugs formulated into a tablet become available to the systemic circulation.

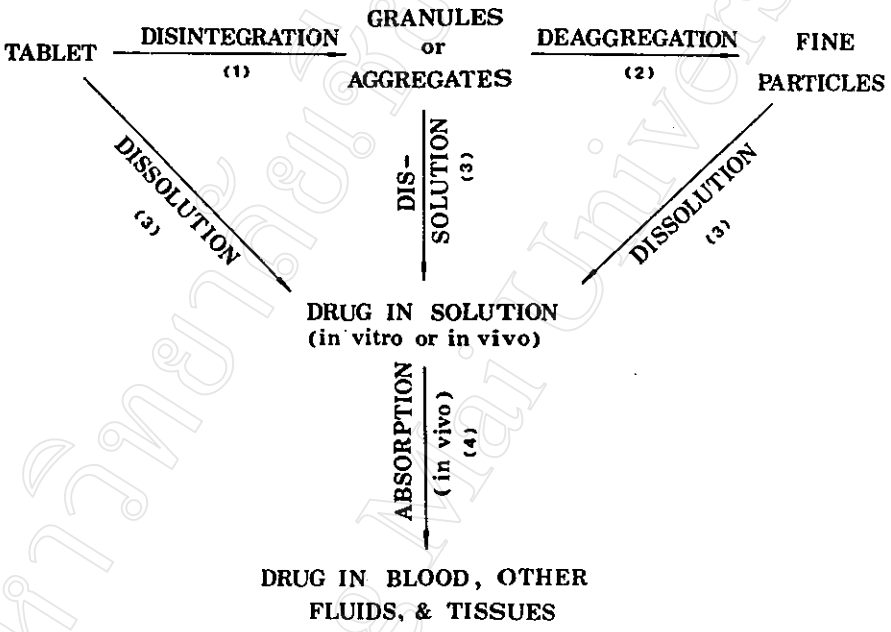

Figure 1.9 Drug available in the body (Gordon et al., 1989)

The medium used, the temperature of the medium, and the operator performing the test all can have a significant effect on disintegration times. In addition, many factors involved with a tablets's formulation and method of manufacture can affect the disintegration. The disintegration times can be affected by the nature of the drug, the diluents used (Lerk et al, 1974), the binders or amount of binder, as well as the manner in which these are incorporated into the tablet (Rubinsteine and Wells, 1977). The type and amount of disintegrating agent can profoundly affect disintegration time. The presence of excess amounts of lubricants or excessive lubrication time can increase

disintegration times. The compaction pressure used to compress the tablets also influence disintegration, with an increase in pressure generally resulting in an increase in disintegration times.

1.4.9.7 Dissolution

Figure 1.9 was presented the processes involved in making a drug administrated as a solid dosage form available for absorption. It was point out that the original rationale for using tablet disintegration tests was that as the tablet broke down into small particles, a greater surface area was exposed to the dissolving medium, and therefore disintegration must be related to the availability of the drug to the body. However, the disintegration tests offer no assurance that the formulation will release the drug, even in the form of small particles. In pharmaceutical, the design of the tablet and the dissolution profile may determine the total amount of drug absorbed as well as the rate of absorption. Thus, the rate of dissolution may be directly related to the efficacy of the tablet product.

The primary objectives of an *in vitro* dissolution test are to demonstrate that

a) Essentially 100% of the drug can be released from the dosage form.

b) The rate of drug release is uniform from batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.

Various parameters are affected the dissolution of drug as the following;

1) pH of dissolution medium
2) Volume of dissolution medium
3) Temperature
4) Agitation

1.4.9.8 Weight Variation

A tablet is designed to contain a specific amount of drug in specific amount of tablet formula. Within the composite sample weighed, there could be tablets that are

excessively overweight and tablets that are excessively underweight but with an average value that is acceptable.

Weight uniformity can be considered indicative of dosage uniformity provided:

a) The major component of the tablet is active drug.

b) The uniformity of drug distribution of the granulation or powder from which the tablets are made is perfect.

1.4.9.9 Content Uniformity

The potency of tablet is generally expressed in term of gram (g), milligram (mg), or microgram (μg) of drug per tablet, and is given as the label strength of the product. Compendial or other standards provide an acceptable potency range around the label potency. For very potent, low-dose drugs, the range is usually not less than 90% and not more than 110% of the labeled amount. For most drugs in tablet dosage form, the stated compendial range for acceptability is not less than 95% and not more than 105% of the labeled amount.

Three factors can contribute directly to content uniformity problems in tablets:

a) Nonuniform distribution of the drug substance throughout the powder mixture or granulation

b) Segregation of the powder mixture or granulation during the various manufacturing processes

c) Tablet weight variation

The precision and variation of the assay used in the content uniformity test is also a factor that enters as an error factors in the determination of content uniformity.

The problem of nonuniform distribution is illustrated in Figure 1.10. The irregularly shaped drug particles are dispersed in irregularly shaped diluent particles of various sizes, and it is not difficult to comprehend why a perfect physical mixture never occurs geometrically (uniform physical placement of the drug particles) or statistically (equal probability that all sections of the mix will contain a certain number of drug particles). The squares drawn in the picture illustrate various possible random samples

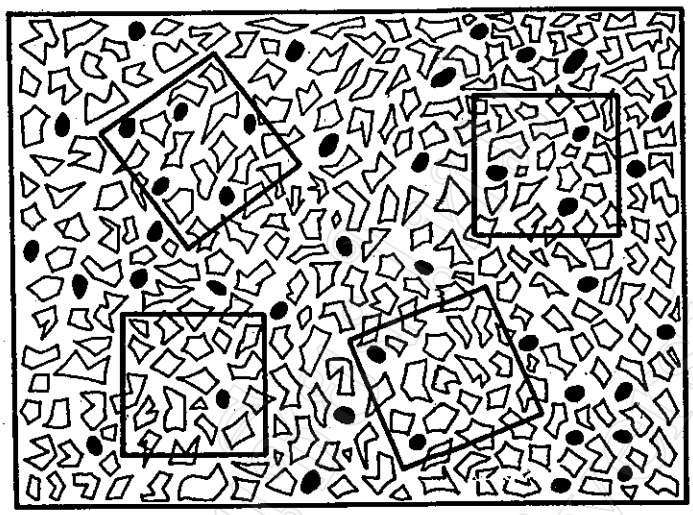

Figure 1.10 Non Uniformity of Powder Mixture (Gordon et al., 1989)

that might be drawn from the mixture and represent the amount of the mixture required for one tablet. The squares contain as many as five particles and as few as one drug particle.

1.4.10 Tabletting Problems (Rawlins, 1977)

Tablets may exhibit a number of defects, which are immediately apparent, or as is often the case with capping appears only after storage. It is important therefore that the appropriate tests be applied at the start of and during a production run in order that remedical action may be promptly taken.

1.4.10.1 Binding in the Die

When this occurs, ejection of the tablet is difficult and is often accompanied by a characteristic grunting noise; the tablet edges are rough or scored. The problem results from those conditions, which give rise to high die-wall friction namely, poor lubrication, underdried granules and a dirty or the blemished die. Poor lubrication includes inefficient blending of the lubricant with the granules as well as wrong quantity or choice

of this adjuvant. An alternative source of trouble is too large a clearance between the lower punch and the die-bore as a result of excessive wear. Fines sap downwards through the gap and compact to form a tough film which hinders free movement of the punch.

1.4.10.2 Picking and Sticking

These problems are caused by adhesion of material to the punch faces. If localized, portions of the tablet surface are seen to be missing; this is called picking. The tablet has a dull rough appearance when sticking occurs due to adhesion of the tablet to the whole punch face. In either case, if not corrected, the defect worsens progressively and a layer of compacted granules builds up on the punch face. This effectively is equivalent to an increase in punch length that causes high compaction pressure and eventual jamming of the press if not promptly rectified. The fault can usually be traced to under-dried granules, poorly maintained punch faces or the use of a lubricant lacking in anti-adherent properties

1.4.10.3 Capping and Lamination

These faults can often be traced to inadequate removal of air from the granules in the die-cavity before and during compression. The entrapped air interferes with granule bonding while its subsequent expansion at the ejection stage detaches the top, the cap of the tablet. In other cases the tablet splits into a number of layers (laminates). Excessive fines, incorrectly prepared or overdried granules or too small a top punch/die-bore clearance all hinder escape of air from the die cavity and may be the cause of capping or lamination (seen in Figure 1.11).

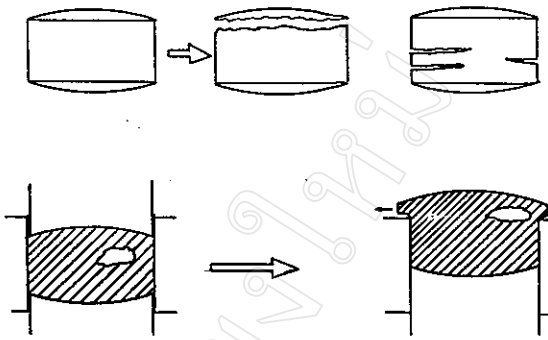

Figure 1.11 Defects of Tablet (Carstensen, 1980)

A second cause of the problem is associated with undue elastic compression of the tablet due to the use of too high a pressure at the compaction stage. During ejection, elastic recovery of that part of the tablet protruding from the die gives rise to both lateral and longitudinal forces (Figure 1.12) which rupture the intergranule bond and the tablet then caps or laminates. Finally, on occasion, these faults may be traced to distortion of the tablet during ejection from a ringed die or to the use of burred punches.

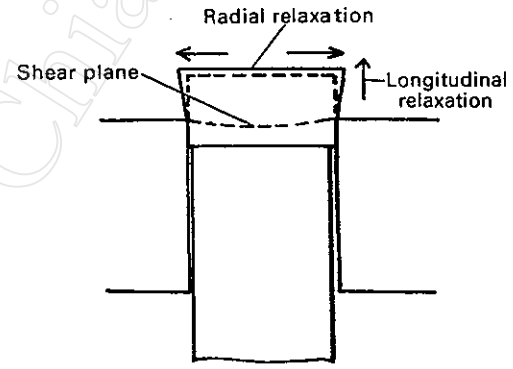

Figure 1.12 Elastic Recovery of a Compaction from a Die (Rawlins, 1977)

1.4.10.4 Excessive Weight Variation

This problem is associated with poor granule flow and separation of granule constituents. Thus granules, which are under-dried, too large, and too fine or contain a large proportion of fines, are incorrectly lubricated or comprise elements with widely differing densities or sizes, may all be suspected as possible causes of excessive weight variation. If the fault occurs with a rotary machine and granule flow appears to be satisfactory, then it is worth considering the possibility that one or more punches are of different length to the others due, for example, to inadvertent mixing of mixing of bottom punch sets. Occasionally, difficult granules are produced in spite of care in processing and tablets of more uniform weight and improved appearance may be obtained at a slower machine speed that allows more time for die-cavity filling.

1.4.10.5 Fissured or Pitted Surface

If this is not due to sticking or picking the most likely cause is the presence of granules, which are uniform in size and lack the fines necessary to fill the voids. Generally, the problem may be cured by the use of granules with a broader size distribution but care must be taken to see that this does not lead to other problems such as capping or lack of uniformity in the tablet weight.

1.4.10.6 Soft Tablets

A part from the use of too low a compaction pressure this problem usually arises when granules have been inadequately dried or the intergranule bonds have been weakened either by traces of air in the granule bed (insufficient to cause capping) or by excessive proportion of fatty lubricant such as magnesium stearate.

1.4.10.7 Protracted Disintegration

In this case the tablet either rapidly breaks down to form large particles that persist for a long period, or fine particles are produced, but the overall disintegration time is excessive. The fault can usually be traced to;

1) an adhesive granulating agent which is too strong

2) conditions that inhibit the penetration of water; high degree of compaction, hydrophobic tablet ingredients, excessive quantities of fatty lubricant or gelling of the granulating agent
3) inefficient bursting action resulting from the use of wrong type of disintegrating agent or insufficient of it

If the granules are intrinsically hydrophobic or have become so due to the unavoidable use of fatty lubricant, small amounts of surfactant may be included in the tablet formulation to facilitate penetration by aqueous fluids. Alternatively, a hard polyethylene glycol may be employed to provide soluble points in the tablet structure.

1.4.10.8 Mottled Tablets

These may be produced if the granule size distribution is discontinuous; the finer particles provide a background of slightly different, which shows up the larger granules in the tablet surface. The effect is more marked with colored tablets and is particularly noticeable if dye migration has occurred. If the problem arises when the tablets are stored, instability of one or more ingredients should be suspected.

1.4.10.9 Variation of Drug Content

If the content shows excessive variation and those factors contributing to weight variation can be eliminated as a cause, the most likely sources of trouble are migration of solute, physical adsorption with separation at some stage of production process and inefficient mixing.

1.4.11 The Tablet Compression of Single Punch Tablet Machine (Carstensen, 1980)

The compression cycle of a single punch tablet machine was described as following procedures (as seen in Figure 1.13).

1.4.11.1 Collection and Filling

Granules or powders flow from the hopper into a feedshoe which, oscillates over the die to promote uniform flow of material into the die cavity. For a given granule the

volume of the cavity, which is adjustable, governs the weight of tablet. At the end of the filling stage, the toe of the feedshoe is deflected so that it smoothes the surface of the granules or powders in the die.

1.4.11.2 Compression

In next step, the top punch is lowered to compact the granules or powders. The penetration of the top punch into the cavity can be adjusted to regulate the degree of compaction, that is tablet hardness.

1.4.11.3 Ejection

The top punch is then quickly raised and, after a short delay, the bottom punch moves upwards to eject the tablet. The bottom punch drops to the filling position and the ejected tablet is pushed towards the collection chute by the toe of the feedshoe as it moves forwards to commence the filling cycle of the next tablet.

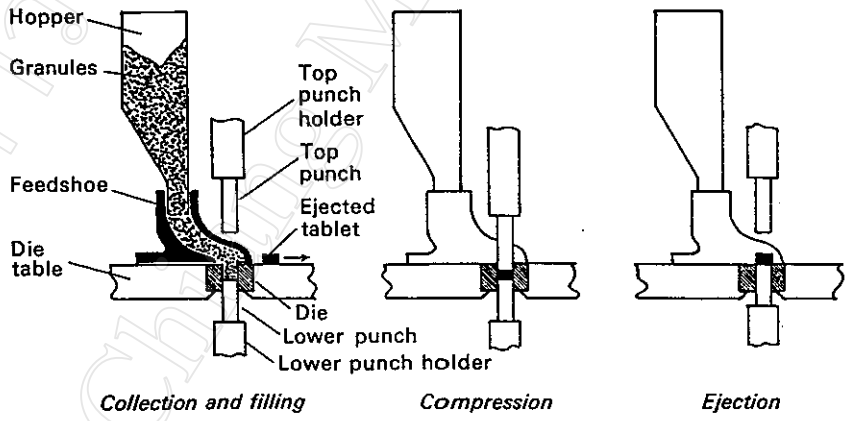

Figure 1.13 The Compression Cycle for a Single Punch Tablet Machine (Rawlins, 1977)

1.4.12 Drug Release Kinetic

1.4.12.1 Weibull Distribution (Langerbucher, 1972; Costa et al., 2001)

The equation of Weibull can be successfully applied to almost all kinds of dissolution curves (Goldsmith et al., 1978). When applied to drug dissolution or release from pharmaceutical dosage forms, the Weibull equation expresses the accumulated fraction of the drug (m) in solution at time (t) by:

$$m = 1 - \exp\left[-\frac{(t-Ti)^b}{a}\right] \quad \text{..... (1.9)}$$

Where a = the scale parameter

Ti = lag time

b = the shape parameter

The scale parameter (a) defines the time scale of the process. The location parameter (Ti) represent the lag time before the actual onset of the dissolution process which, in most case, will be equal to zero. The shape parameter (b) characterizes the curve as Table 1.4.

Table 1.4 The Summary of b Parameter Characteristic (Grant and Leavenworth, 1980).

B	Curve	Release Characteristic
< 1	Steeper initial slope than consistent with the exponential	The dissolution rate decrease during the time (Jorgensen and Jacobsen, 1992)
= 1	Exponential	First order kinetic (Racz et al., 1997; Dredan et al., 1996)
> 1	S-shape with upward curvature followed by a turning point	The maximum rate occurs after some time and decrease in the next time

The Equation 1.9 may be rearranged into:

$$\text{Log } [-\ln (1-m)] = b \log (t-Ti) - \log a \quad \text{.....(1.10)}$$

From this equation a linear relation can be obtained for a log-log plot of – ln (1-m) versus time (t). The shape parameter (b) is obtained from the slope of the time and the scale parameter (a) is estimated from the ordinate value (1/a) at time t =1. The parameter, a, can be replaced by the more informative dissolution time, Td, that is defined by $a = (Td)^{b}$ and is read from the graph as the time value corresponding to the ordinate – ln (1-m) = 1. Since – ln (1-m) is equivalent to m = 0.632, Td represents the time interval necessary to dissolve or release 63.2 % of the drug present in the pharmaceutical dosage form. To pharmaceuticals systems following this model, the logarithm of the dissolved amount of drug versus the logarithm of time plot will be linear.

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