CHAPTER I
INTRODUCTION

1.1 State and significant of the problem

The most popular of all pharmaceutical dosage form is tablet because of its advantage for the production and consumption of medical products. When the absorption of drug from a tablet is dissolution rate-limited, a more soluble and faster dissolving form may be utilized to improve the rate and extent of bioavailability. The basic knowledge of crystal and dissolution properties of pharmaceutical solids, especially poorly water-soluble drug, could help solve many problems associated with dissolution and absorption characteristics of resultant tablets (Yamamoto and Piyarom, 2000).

For crystal property, many researchers studied the effect of different forms of crystal of drug, called polymorphism, on its bioavailability (Aguiar *et al*., 1967; Miyasaki *et al.*, 1974). It showed that the amorphous form of drug usually dissolves more rapidly than the corresponding crystalline form (Brittain, 2007). Several delivery technologies rely on stabilizing the drug in its amorphous form to increase its dissolution and bioavailability (Aulton, 2002). Moreover, the increasing the available surface area by reducing the particle size can often markedly improve dissolution rates and lead to dramatic improvements in bioavailability. However, particle size reduction as a strategy for enhancing bioavailability does have limitations. Decreasing the drug particle through micronized powder by milling results in an increase in the available area for dissolution, but in some cases, the micronized powder tends to agglomerate (Westerberg and Nyström, 1993) or accelerate the polymorphic conversion (Cheng *et al.*, 2007). Dissolution of very small particles may be retarded because of their tendency to agglomerate occurring air bubbles entrapping and poorly wetted.

Thereafter, surfactants have been used for their solubility-enhancing properties through micellular solubilization of the drug in practice. Unfortunately the toxicity of the relatively high concentrations of surfactant required often makes this approach undesirable (Melia and Davis, 1989). Cyclodextrins offer considerably more promise, and a great deal of work is currently being carried out to investigate their dissolution-enhancing properties. These non-toxic cyclic polysaccharides and their derivatives form water-soluble inclusion complexes with a wide variety of drugs can increase the dissolution rates of poorly soluble drug. The complexes produced are sometimes too stable to be useful, and may decrease the availability of the drug for absorption (Melia and Davis, 1989). The other hand, solid solutions, eutectic mixtures or solid dispersion system are the mechanochemical technique for preparation of ground mixture of drugs (Yamamoto and Piyarom, 2000). They have been used, at least in research laboratories, to increase the rate of dissolution of drugs, presumably by decreasing the particle size of the drug molecules. The liquisolid technique is the method for promoting dissolution rate of poorly water-soluble drugs. The study of liquisolid tablets demonstrated significantly higher drug release rates compared to tablets prepared by direct compression method (Spireas and Sadu, 1998; Javadsadeh *et al.*, 2007). This was due to an increase in wetting properties and surface of drug available for dissolution (Javadsadeh *et al.*, 2005).

Once the oral tablet dosage form reaches the absorption site, it must break down to be a particle of drug which should have the same property before compression in achieving therapeutic efficacy (Hoener and Benet, 2002). The methods of tablet production are able to use both direct compression and indirect compression which are wet and dry granulation techniques (Armstrong, 2007). Nevertheless numerous these unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulating, drying, compaction. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability (Augsburger and Zellhofer, 2007). Especially the compaction will affect therapeutic property of the drug. It is due to the effect of polymorphic forms, crystal habit, size and surface area changed during the processes (Chan and Doelker, 1985; Koivisto *et al*., 2006). In addition, tablet hardness should have an enough amount to withstand mechanical shocks of handling in its

manufacturing, packaging and transportation. At the same time, the hardness may influence tablet disintegration and, perhaps more significantly, drug dissolution rate have become apparent.

In general, the compressed tablet contains solid drug substances and certain excipients selected to aid the processing and improve the properties of tablet such as compressibility, flowability and lubriability including the drug stability. The possible effects of the force used in compressing the drug-diluent mixture into a tablet dosage form on dissolution rate may be considered. As compression force is increased, the particles may be more tightly bound to one another (Hoener and Benet, 2002). Thus, the effect of the compression force on the dissolution rate of a tablet dosage form would appear to be unexpectable. A new technique of tablet preparation was patented, a chargeable pharmaceutical tablet which could solve this problem. The tablet was prepared by immersing a blank tablet in liquid form of the active pharmaceutical ingredient (Lee and Lee, 2002). It concluded that the blank tablet including active ingredients in liquid form unexpectedly exhibits better potency than conventional pharmaceutical tablets containing the same active ingredient. In a specific example, a blank tablet including an anti-foaming active ingredient exhibits superior anti-foaming properties relative to conventional pharmaceutical tablets. Moreover, the blank tablet may be produced in large-scale batches and stored until use and each batch or sub-batch may be loaded with the same or different pharmaceutically acceptable liquid formulations and/or active substances (HOLM et al, 2006).

Preliminary trial in this study was immersing the blank tablet, prepared by direct compression using dicalcium hydrogen phosphate dihydrate as a diluent, in non-aqueous solvent. It was found that this blank tablet did not break down and its hardness still showing the same comparing to that before immersing. Its disintegration time was similar to the blank tablet. According to this result, it was possible to drop a drug-solution on the surface of blank tablet to develop a new method to add up an active ingredient in tablet. In one aspect, it expected that the drug particles could distribute on the surface of the blank tablet and some into the pore of tablet. In another aspect, the particles of drug may be transforming in amorphous form with increasing solubility property after evaporation of a solvent of drug-solution. This so-

called drug-solution-dropping tablet with the certain concentration in drug solution would provide the uniformity of drug in each tablet prepared.

Thus this novel preparation of tablet could be made from the blank tablet prepared by direct compression and wet granulation method with various compression forces. Both soluble and poorly water-soluble drug were used to be the model drugs. The characterization of the drug-dropping-solution tablet was examined to distinguish amorphous form of drug particle. The dissolution test and uniformity of active ingredient was also studied. As well the stability of the preparations was performed.

1.2 Objectives

1. To prepare the pharmaceutical tablet by dropping the low dose of drug solution on the surface of blank tablet.
2. To characterize the drug-solution dropping tablet and compare to the blank tablet.
3. To compare the dissolution profile of the drug-solution dropping tablet with the conventional tablet.
4. To study the uniformity and stability of the drug-solution dropping tablet.

1.3 Scope of Study

This study consists of scope as followings:-

1. Preparation of the blank tablet by two methods , i.e., direct compression using dibasic calcium phosphate dehydrate as water insoluble filler and wet granulation techniques using lactose monohydrate as water soluble diluent.
2. Application three compression forces for each kind of blank tablet.
3. Evaluation of physical properties of blank tablet.
4. Preparation of drug-solution-dropping tablet from direct compression and wet granulation blank tablet of three compression force using chlorpheniramine maleate and diazepam as water soluble and poorly water-soluble low dose model drug respectively.
5. Determination the drug content in drug-solution-dropping tablet.

6. Characterization of tablet such as morphology, thermal analysis and drug released of drug-solution dropping tablet comparing with conventional tablet of the same drug and diluent.
7. Uniformity test of drug-solution-dropping tablet.
8. Dissolution study of drug-solution-dropping tablets of 0, 1, 2 and 3 months storage.

1.4 Literature Reviews

1.4.1 Model Drugs

1.4.1.1 Chlorpheniramine Maleate

Chlorpheniramine maleate (CPM) is an alkylamine antihistamine that is a common ingredient in over-the-counter antitussive formulation. It has a mild sedative action and anticholinergic activity (White, 2000a), it also has antimuscarinic activity. Chlorphenamine maleate and dexchlorpheniramine maleate are used for the symptomatic relief of allergic conditions including mild urticaria and angioedema, vasomotor rhinitis, a allergic reaction to blood and plasma in sensitive patients and allergic conjunctivitis, and in pruritic skin disorders. They are common ingredients of compound preparations for symptomatic treatment of coughs and the common cold. Chlorphenamine may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock.

Chlorphenamine maleate is given by mouth in doses of 4 mg every 4 to 6 hours up to a maximum of 24 mg daily. Doses for children, according to age, are: 1 to 2 years, 1 mg twice daily; 2 to 5 years, 1 mg every 4 to 6 hours (maximum 6 mg daily); 6 to 12 years, 2 mg every 4 to 6 hours (maximum 12 mg daily). Although not licensed in the UK, the BNFC suggests that children aged 1 month and over may be given 1 mg twice daily. Chlorphenamine maleate may be given by intra-muscular, by subcutaneous, or by slow intravenous injection.

CPM is a racemic mixture of optical isomers and is known by the chemical names, i.e., (±)-3-(4-Chlorophenyl)-NN-dimethyl-3-(2-pyridyl) propylamine hydrogen maleate; 1-p-Chlorophenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate; 1-(N,N-Dimethyl-amino)-3-(p-chlorophenyl)-3-(alpha-pyridyl) propane maleate. The synonyms are Chlorphenamine hydrogen maleate and Chlor-Trimeton. Its molecular

formula is $C_{16}H_{19}ClN_2$, $C_4H_4O_4$ with 390.87 as molecular weight. The structure formula is shown in Figure 1.1

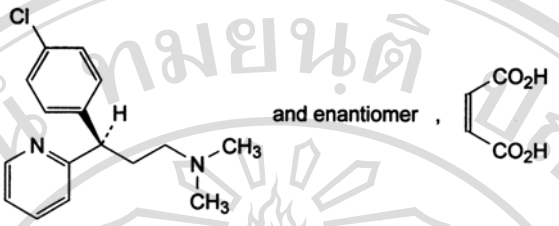


Figure 1.1 Chemical Structure of Chlorphenamine maleate (BP 2007).

CPM is a white or almost white, crystalline powder. It is freely soluble in water; soluble in alcohol (BP 2007) or soluble 1 in 4 of water and 1 in 10 of alcohol and of chloroform; slightly soluble in ether and in benzene (Rochville, 2007 USP 30). CPM is 'high solubility'' drug as one which at the highest human dose is soluble in 250 ml (or less) water throughout the physiological pH range (1–8) at 37 °C (Armstrong, 2007). The solution of CPM is acid to litmus (pH 4 to 5). Its melting point is about 130°C and 113 -115 °C for d-form of CPM which is recrystallized from ethyl acetate. The pK_a of CPM are as follows: $pKa_1 = 9.2$, $pKa_2 = 4.0$. The liquid-liquid partitioning data were accumulated and are tabulated in Table 1.1. Ultraviolet absorption of CPM, it is found the maximum absorption at 265 nm in 0.1N HCl.

The Differential Scanning Calorimetry (DSC) curve exhibits a single sharp melting endothermic with the onset temperature of 133°C and peak temperature is 136°C. The maximum intensity of X-Ray powder diffraction is 19.214 and 20.215 degree at an angle 2Θ (Eckhart and McCorkle, 1978).

Table 1.1 Liquid -liquid partitioning data percent of chlorpheniramine maleate in organic phase

Aqueous pH	n-Butanol	Chloroform	n- Heptane
0.1	-	0.6	-
1.3	-	-	0.8
1.7	-	1.0	-
2.7	35.4	-	-
3.5	73.8	44.0	-
3.6	-	-	8.5
4.3	79.2	70.0	-
5.8	-	-	74.7
6.2	83.3	91.2	-
6.7	-	-	81.5
7.1	92.7	99.0	-
7.7	-	-	94.9
8.0	99.4	-	-
8.7	-	99.6	97.4
9.4	-	-	99.4
10.8	-	99.7	-
11.9	-	99.6	-
12.5	-	99.6	99.8

CPM is stable in the solutions, over pH 2 to 13 range when were stored for one week at 95°C and in aqueous buffer, over pH 2 to 8 range, when stored for three months at 25°C in a light box under a fluorescent light of about 350 candle power. However it should be store in airtight containers and protect from light.

CPM has been reported to be incompatible with calcium chloride, kanamycin sulfate, noradrenaline acid tartrate, pentobarbital sodium, and meglumine adipiodone.

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported (Sean Sweetman, 2007). Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide interindividual variation in the pharmacokinetics of chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS.

Chlorphenamine maleate is extensively metabolized. Metabolites include desmethyl- and didesmethyl-chlorphenamine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

1.4.1.2 Diazepam

A benzodiazepine indicated for the symptomatic relief of tension and anxiety, acute alcohol withdrawal, and adjunctive therapy in skeletal muscle spasms and preferred to many clinician for the management of status epilepticus. It is used preoperatively because of its ability to relieve anxiety, sedate, and cause light anesthesia and a terograde amnesia. The BNF recommends a dose of 5 to 15 mg by mouth at bedtime, although doses up to 30 mg are licensed. Doses of 1 to 5 mg at bedtime have been used in children and adolescents aged from 12 to 18 years to control night terrors and sleepwalking. It is absorbed well after single oral dose leading to rapid onset of clinical effects. Initially these effects may be transient due to extensive distribution to body tissues. Patients on the drug should be cautioned not to drive automobile or to operate dangerous machinery until a few days after the drug has been discontinued (White, 2000 b)**.**

Synonyms of diazepam are Diatsepaami; Diazepám; Diazepam; Diazepamas; Diazepamum; LA-III; NSC-77518; Ro-5-2807; Wy-3467. Chemical

name of diazepam is 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one with $C_{16}H_{13}ClN_2O$ as molecular formula. The molecular weight is 284.7 and structure formula is shown in Figure 1.2.

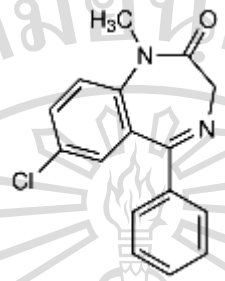


Figure 1.2 Chemical Structure of Diazepam. (Sweetman, 2007)

Diazepam is a white or almost white, crystalline powder. It is very slightly soluble in water and soluble in alcohol (BP 2007). An off-white to yellow, practically odourless, crystalline powder or soluble 1 g in 333 ml of water, 16 ml of alcohol, 2 ml of chloroform, and 39 ml of ether ((Rochville, 2007 USP 30). The solubility of diazepam in WFI was 0.041 mg/ml after equilibration for 24 hours at 25 °C (Newton *et al.*, 1981). Diazepam is a ‘‘low solubility’’ drug thus one which requires more than 250 ml of water to dissolve the largest human dose at any pH within the physiological range. The solubility of diazepam is 1:333 in water or 0.041 mg/ml in WFI ((Rochville, 2007 USP 30). Its dose is 5 mg which dissolve in water 1.665 ml or 121.95 ml of WFI. pka of diazepam is 3.7, 3.2 so it is high permeability at stomach (Armstrong, 2007). As a rule of thumb, a compound with an average potency of 1mg/kg should have a solubility of at least 0.1g/L to be adequately soluble. If a compound with the same potency has a solubility of less than 0.01g/L it can be considered poorly soluble. Diazepam is weakly acidic drug or acid soluble basic drug which is insoluble in intestinal fluids. Its melting point is about 131 - 135°C ((Rochville, 2007 USP 30). Partition coefficient of diazepam is 2.7 in term of log *P*.

The differential scanning calorimetry (DSC) curve exhibits a single sharp melting endotherm with the onset temperature of 129°C using energy 5.9 kcal/mole and peak temperature is 136°C. It is degraded at 180°C and by acid hydrolysis (Macdonal *et al*., 1972).

Diazepam is stable in the air. However it should be store in airtight containers and protect from light. Care should be observed when diluting diazepam injections for infusion because of problems of precipitation. The manufacturer's directions should be followed regarding diluent and concentration of diazepam and all solutions should be freshly prepared.

Incompatibility has been reported between diazepam and several other drugs. Manufacturers (*Roche*) of diazepam injection have advised against its admixture with other drugs. Substantial adsorption of diazepam onto some plastics may cause problems when giving the drug by continuous intravenous infusion. More than 50% of diazepam in solution may be adsorbed onto the walls of PVC infusion bags and their use should, therefore, be avoided. Giving sets should contain the minimum amount of PVC tubing and should not contain a cellulose propionate volume-control chamber. Suitable materials for infusion containers, syringes, and giving sets for diazepam include glass, polyolefin, polypropylene, and polyethylene.

Talc and dibasic calcium phosphate had the lowest adsorptive power for diazepam while magnesium trisilicate exhibited the highest adsorptive capacity for the drug. The antacid decreased obviously the dissolution of diazepam (Naggar, 1981).

A correlation of in vitro dissolution and in vivo absorption of diazepam tablets with either slightly swelling disintegrant, potato starch or the strongly swelling sodium starch glycolate has been found for the model with a relatively high stirring rate, which is less discriminating in vitro (Proost *et al*., 1983).

1.4.2 Tablet excipients (Raymond *et al*., 2006)

1.4.2.1 Dibasic calcium phosphate dihydrate

Dibasic calcium phosphate dihydrate (DCP dihydrate) is widely used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements. Synonyms of DCP dihydrate are Calcium hydrogen ortho-phosphate dihydrate; calcium mono-hydrogen phosphate dihydrate; *Di-Cafos*; dicalcium ortho-phosphate; DI-TAB; E341; Emcompress; phosphoric acid calcium salt (1 : 1) dihydrate; secondary calcium phosphate. Its chemical Name is

dibasic calcium phosphate dihydate with empirical formula:$CaHPO_4 \cdot 2H_2O$ and molecular Weight: 172.09. Structural formula is shown in Figure 1.3

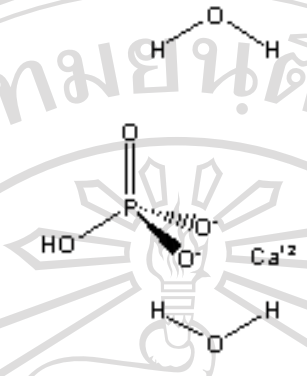
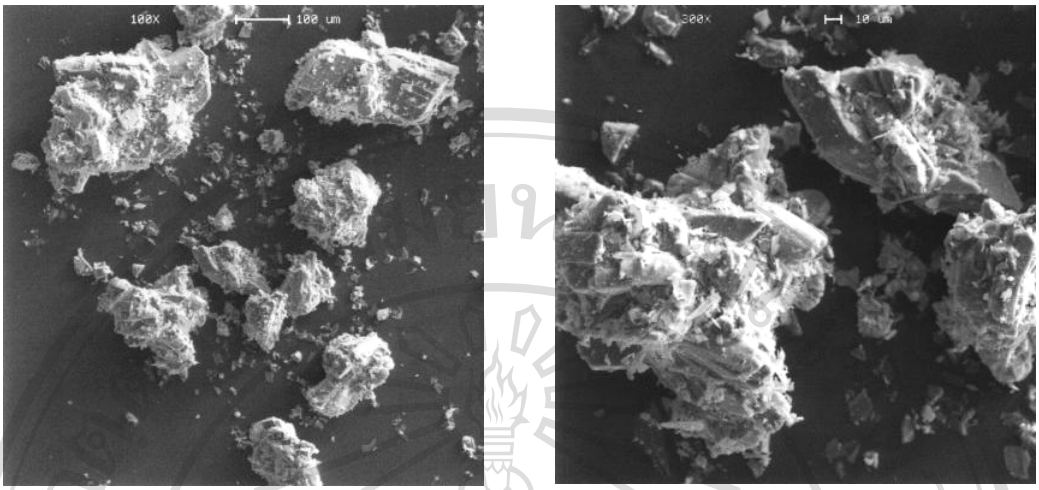


Figure 1.3 Structure Formula of DCP dihydrate (Ametch Industry, 2009)

Dibasic calcium phosphate dihydrate is practically insoluble in ethanol, ether, and water, alkaline medium and soluble in dilute acids. It is a neutral (Shangraw, 1989), white, odorless, tasteless powder or crystalline solid. It occurs as monoclinic crystals as its SEM shown in Figure 1.4. The particle size distribution lies primarily between 75 and 420 μm, with an average particle size of about 130 μm. Table 1.2 shows the typical properties of dibasic calcium phosphate. It is nonhygroscopic at a relative humidity of up to 80%, contains about 0.5% moisture and posses a high degree of physical and chemical stable at room temperature. Although the hydrate in this material 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. However, under certain conditions of temperature and humidity, it can lose water of crystallization below 100°C.



Magnification: 100× *Magnification*: 300×

Figure 1.4 SEM of dibasic calcium phosphate dihydrate, coarse grade. *Manufacturer:* JRS Pharma LP. *Lot No.:* W28C

Table 1.2 Typical properties of dibasic calcium phosphate dihydrate

Item	Specification	Remarks
Acidity/alkalinity	pH = 7.4	(20% slurry of *DI-TAB*)
Angle of repose	28.3°	for *Emcompress*
Density (bulk)	0.915 g/mL	
Density (tapped)	1.17 g/mL	
Density (true)	2.389 g/mL	
Flowability	27.3 g/s 11.4 g/s	for *DI-TAB* for *Emcompress*[9]
Melting point	decomposes below 100°C with loss of water	
Moisture content	dibasic calcium phosphate dihydrate contains two molecules of water of crystallization, which can be lost at temperatures well below 100°C	
Particle size distribution	average particle diameter 180 µm Fine powder: average particle diameter 9 µm	*DI-TAB*
Specific surface area	0.44–0.46 m^2/g	for *Emcompress*

It was reported that DCP dihydrate is incompatible with indomethacin, aspirin, aspartame, antibiotics, i.e., tetracycline, ampicillin, cephalexin, and erythromycin. In addition, the surface of dibasic calcium phosphate dihydrate is alkaline and consequently it should not be used with drugs that are sensitive to alkaline pH.

DCP dihydrate, ummilled or coarse powder is the normally used in solid dosage form as tablet and capsule diluent because of its advantage such as compaction properties, the good flow properties of the coarse-grade material, and glidants are generally not necessary. It is more compressible than spray-dried lactose and compressible starch (Shangraw, 1989; Carstensen and Ertell, 1990). Consolidation is principally by fragmentation, so although a lubricant is needed, tablet strength loss is low thus allowing easier transition from the laboratory to production scale (Bolhuis and Holzer, 1996). DCP dihydrate is abrasive and a lubricant is required for tableting, for example about 0.5 to 1% w/w of magnesium stearate or about 1% w/w of sodium stearyl fumarate is commonly used. A commercially available free-flowing form is marketed as Emcompress® and has been described for use in tablet (Mendell, 1972).

DCP dihydrate can be used with salt of most organic bases, such as antihistamines, with both water- and oil-soluble vitamins. The tablets may be developed an acetic odor on aging if inorganic acetate salts are present in the formulation. It is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may cause abdominal discomfort.

DCP dihydrate tablets are rapidly and completely penetrated by the liquid when placed in water. Nevertheless the tablets do not disintegrate because DCP dihydrate as the excipient is relatively insoluble in water and no disintegration force is developed. This also indicates that a disintegrant with an active mechanism such as swelling or disintegration force is needed (Caramella *et al*., 1986). The disintegration properties of DCP dihydrate tablets employing insoluble and soluble disintegrating agents. The insoluble disintegrants showed a greater effect when compressional forces were varied than did the soluble disintegrants (Khan and Rhodes, 1975).

Increasing the ratio of dibasic calcium phosphate (DCP) to microcrystalline cellulose (MCC) in a system containing an "insoluble" drug, indomethacin USP revealed the negative effect on dissolution (Bavitz and Schwartz, 1976). The ratio 50:50 of DCP : MCC released 66% of the drug in 30 min. The amount released decreased to 18% and 10% in 30 minutes when the ratio of DCP to MCC increased to 70:30 and 84:16, respectively. This study suggests the importance of carriers when insoluble drugs are employed.

1.4.2.2 Lactose monohydrate

Lactose is the most frequently used as diluent for solid dosage forms. An inexpensive disaccharide obtained from milk or as a by-product of the cheese industry which consists of one galactose and one glucose moiety. It is available in a number of forms and may contain varying proportion amorphous lactose, though *a*-Lactose monohydrate is the variety that is normally used as the diluent in tablets made by wet granulation. It is freely albeit slowly soluble in water and as such it is a suitable diluent for active ingredients of low water solubility. The synonyms of lactose monohydrate are Lactochem, Pharmatose and its chemical name is *O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate (BP 2007). The empirical formula is $C_{12}H_{22}O_{11}{\cdot}H_2O$ with 360.31 as molecular weight. Structural formula of α lactose monohydrate is shown in Figure 1.5

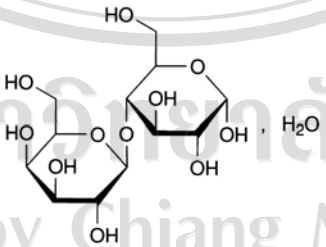
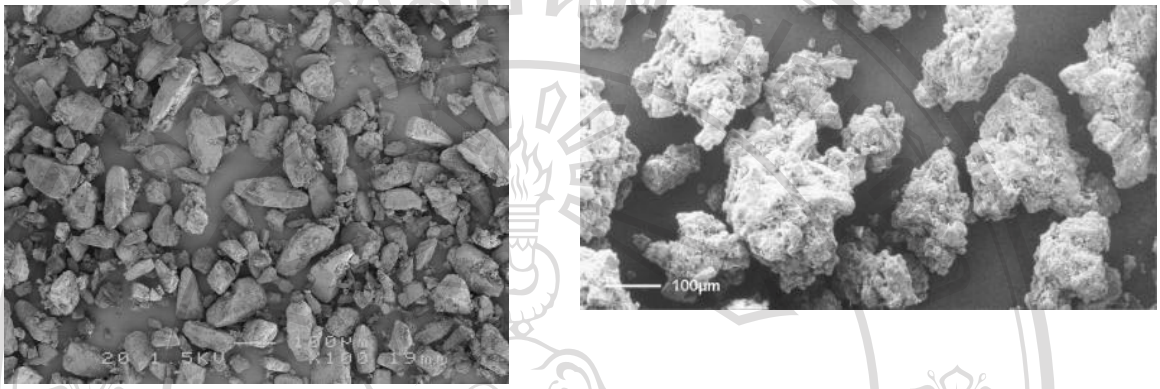


Figure 1.5 Structure Formula of α lactose monohydrate (BP 2007)

Lactose exists as white to off-white crystalline particles or powder as SEM shown in Figure 1.6. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet. Various lactose grades are commercially available that have different physical

properties as shown in Table 1.3 such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application.



Pharmatose 125M Pharmatose DCL 15

Magnification: 100×

Figure 1.6 SEM of Pharmatose (Manufacturer: DMV International)

Lactose monohydrate is practically insoluble in chloroform, ethanol and ether. The solubility in water is 1 in 5.24**,** 1 in 3.05 at 40°C, 1 in 2.30 at 50°C, 1 in 1.71 at 60°C and 1 in 0.96 at 80°C. In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e., α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. All of them are stable in crystalline forms

Table 1.3 Typical properties of lactose monohydrate

Item	Specification	Remarks
Angle of repose	33° 32°	for *Pharmatose DCL 15* for *Tablettose 70* and *Tablettose 80*
Brittle fracture index	0.0749 0.0883	at compression pressure 189.5 MPa at compression pressure 191.0 MPa
Bonding index	0.0081 0.0052	at compression pressure 189.5 MPa at compression pressure 191.0 MPa
Compression pressure	18.95–19.10 kN/cm^2	
Density (true)	1.545 g/mL	α-lactose monohydrate
Density (bulk)	0.76 – 0.48 g/ mL	Pharmatose 80M – 450M
Density (tapped)	0.75 – 0.91 g/ mL	Pharmatose 80M – 450M
Melting point	201–202°C	for dehydrated α-lactose monohydrate
Moisture content	5.2% w/w water	lactose monohydrate
Particle size distribution	average particle diameter 10 – 150 μm	lactose monohydrate
Permanent deformation pressure	370.0 MPa 485.0 MPa	at compression pressure 189.5 MPa at compression pressure 191.0 MPa
Reduced modulus of elasticity	1472 5155	at compression pressure 189.5 MPa at compression pressure 191.0 MPas
Specific surface area	0.23 m^2/g	for *Pharmatose 200M*.
Specific rotation $[\alpha]_D^{20}$	+54.4° to +55.9°	as a 10% w/v solution. Lactose exhibits mutarotation and an
Tensile strength	2.987 MPa 2.517 MPa	at compression pressure 189.5 MPa at compression pressure 191.0 MPa

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products and thus its use is contraindicated in such formulations (Armstrong, 2007). Lactose is also incompatible with amino acids, aminophylline, amphetamines,

and lisinopril. Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also are differing.

Fine grades of lactose are usually used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. α-lactose monohydrate has a place in tableting by the wet granulation method in the sense that on wetting some goes into solution thereby coating the drug and offering an amount of protection and slow release where rapid dissolution is not required (Bandelin, 1989).

1.4.2.3 Croscarmellose Sodium

Croscarmellose sodium is derived from internally crosslinking a cellulose ether, sodiumcarboxymethylcellulose, which is a water soluble polymer (Augsburger *et al*., 2007). Its synonyms are *Ac-Di-Sol;* crosslinked carboxy-methylcellulose sodium; *Explocel*; modified cellulose gum; *Nymcel ZSX*; *Pharmacel XL*; *Primellose*; *Solutab*; *Vivasol*. The chemical name is cellulose, carboxymethyl ether, sodium salt, crosslinked. Empirical formula is R_nOCH_2COONa which a crosslinked polymer of carboxymethylcellulose sodium or carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose with 90,000–700,000 as its molecular weight. The structural formula is shown in Figure 1.7

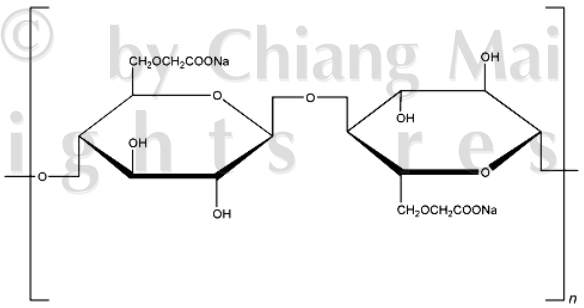
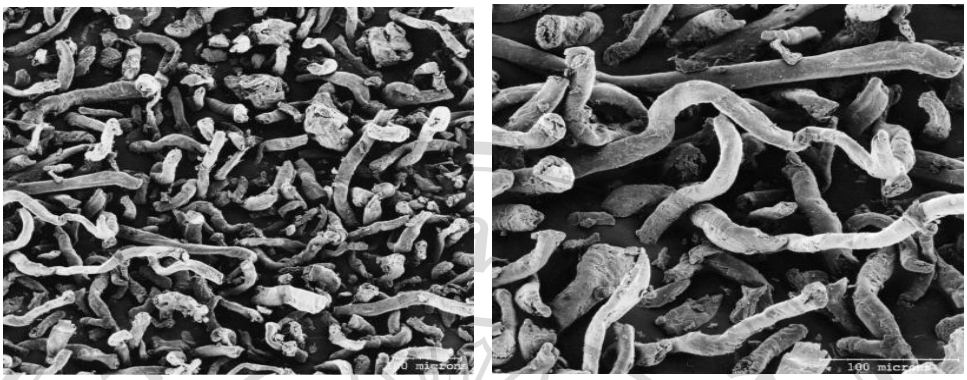


Figure 1.7 Structure Formula of Carboxymethylcellulose sodium (Raymond et al., 2006)



Magnification: 100× *Magnification:* 1000×

Figure 1.8 SEM of Croscarmellose sodium (Ac-Di-Sol®).
Manufacturer: FMC Biopolymer

Table 1.4 Typical properties of croscamellose sodium

Item	Specification	Remarks
Acidity/alkalinity	pH = 5.0–7.0	aqueous dispersions
Bonding index	0.0456	
Brittle fracture index	0.1000	
Density (bulk)	0.529 g/mL	for *Ac-Di-Sol*
Density (tapped)	0.819 g/mL	for *Ac-Di-Sol*
Density (true)	1.543 g/mL	for *Ac-Di-Sol*
Particle size distribution	not more than 2% retained on a #200 (73.7 μm) mesh and not more than 10% retained on a #325 (44.5 μm) mesh	
Specific surface area	0.81–0.83 m^2/g	

Croscarmellose sodium particles are odorless white or grayish-white fibers with fairly sharp ends, probably because of the milling process which SEM and typical properties shown in Figure 1.6 and Table 1.4, respectively. It is insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water; practically insoluble in acetone, ethanol and toluene.

Ac-Di-Sol® or croscarmellose sodium has a high affinity for water which results in rapid tablet disintegration. It has been classified as a super-disintegrant (Peck *et al*., 1989). Croscarmellose sodium may be used in both direct-compression and wet-granulation processes in tablet formulations. It should be added in both the wet and dry stages of the process (intra- and extragranularly) when used in wet granulations, so that the wicking and swelling ability of the disintegrant is best utilized (Gordon *et al*., 1993, Khattab *et al*., 1993). The concentrations of croscarmellose sodium may be up to 5% w/w as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months (Gordon and Chowhan, 1990).

Tablet formulations that contain hygroscopic excipients such as sorbitol, and prepared by either the wet-granulation or direct-compression process may slightly reduced the efficacy of croscarmellose sodium (Johnson *et al*., 1991). Also it is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc. It is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

1.4.2.4 Polyvinyl pyrrolidone

Povidone is used in pharmaceutical manufacturing as a suspending and dispersing agent and as a tablet binding, granulating, and coating agent (Sweetman, 2007). Povidone as a synthetic polymer consists essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, in the range 10–120. Its synonyms are E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer. The chemical name is 1-Ethenyl-2-pyrrolidinone homopolymer with $(C_6H_9NO)_n$ as empirical formula and 2,500–3,000,000 as molecular weight. The structural formula is shown in Figure 1.9.

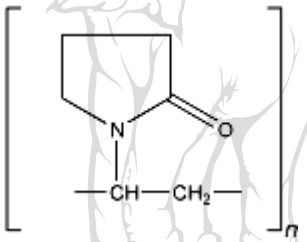
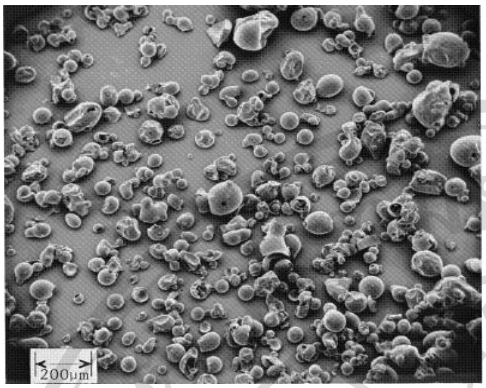
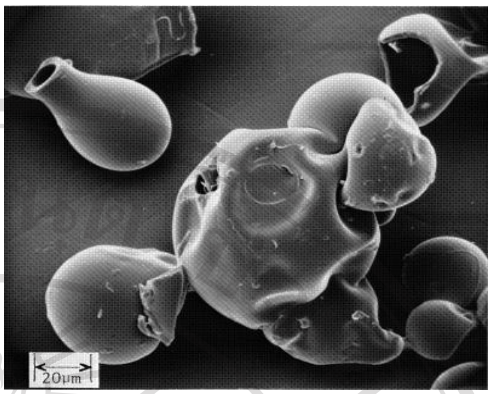


Figure 1.9 Structure Formula of Povidone
(Raymond et al., 2006)

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres which SEM shown in Figure 1.11. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates. Table 1.5 shows the typical properties of povidone.



Magnification: 60×



Magnification: 600×

Figure 1.10 SEM of Povidone K-30 (*Plasdone K-30).*
Manufacturer: ISP *Lot No.:* 82A-4

Table 1.5 Typical properties of povidone

Item	Specification	Remarks
Acidity/alkalinity	pH = 3.0–7.0	5% w/v aqueous solution
Density (bulk)	0.29–0.39 g/mL	for *Plasdone*
Density (tapped)	0.39–0.54 g/mL	for *Plasdone*
Density (true)	1.180 g/mL	
Particle size distribution	90% >50 µm, 50% >100 µm, 90% >200 µm, 95% >250 µm	*for Kollidon 25/30* *for Kollidon 90*
Flowability	20 g/s 16 g/s	for povidone K-15 for povidone K-29/32
Melting point	Softens at 150°C	
Moisture content	very hygroscopic	significant amounts of moisture being absorbed at

Povidone is freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. Povidone solutions are used as binders in wet-granulation processes in tableting (Becker *et al*., 1997). Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms (Lu *et al.,* 1995; Iwata and Ueda H., 1996). Povidone solutions may also be used as coating agents.

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. It should be stored in an airtight container in a cool, dry place since the powder is hygroscopic. The mixtures in tablet containing sodium starch glycolate and HPMC are more stable than those containing croscarmellose sodium and povidone, respecttively (Lewis, 2007).

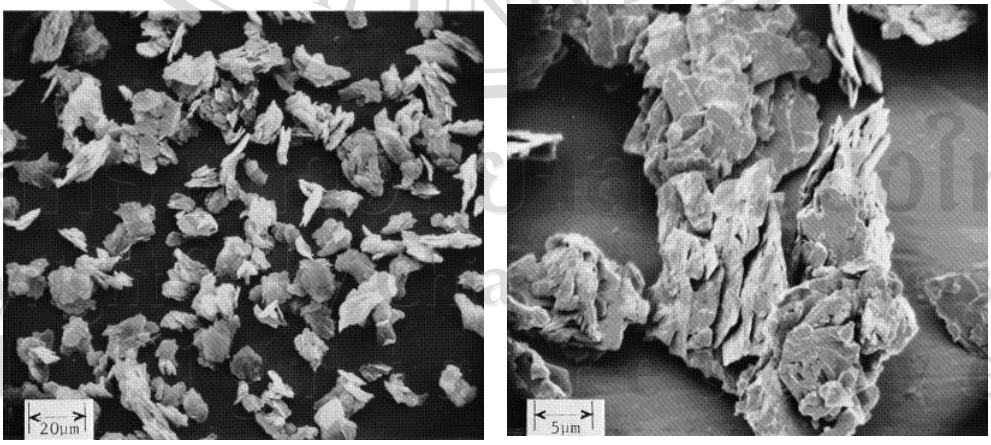
Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone. When consumed orally in tablet or solution forms, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization.

1.4.2.5 Magnesium stearate

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Its synonyms are Magnesium octa-decanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt. The chemical name is Octadecanoic acid magnesium salt with $C_{36}H_{70}MgO_4$ as empirical formula and 591.34 as molecular weight. The structural formula is $[CH_3(CH_2)_{16}COO]_2Mg$

Magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid ($C_{36}H_{70}MgO_4$ = 591.2) and palmitic acid ($C_{32}H_{62}MgO_4$ = 535.1) and in minor proportions other fatty acids. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90.0%

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density as shown in Figure 1.11, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin. Typical properties are shown in Table 1.6. It is practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).



Magnification: **600×** ***Magnification:*** **2400×**

Figure 1.11 SEM of Magnesium stearate

Table 1.6 Typical properties of magnesium stearate

Item	Specification	Remarks
Density (bulk)	0.159 g/mL	
Density (tapped)	0.286 g/mL	
Density (true)	1.092 g/mL	
Flowability	poorly flowing	cohesive powder
Flash point	250°C	
Melting range	117–150°C 126–130°C	commercial samples high purity magnesium
Specific surface area	1.6–14.8 m^2/g	

Although magnesium stearate is stable, it should be stored in a well-closed container in a cool, dry place. It is incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations (Levy and Gumtow, 1963; Ganderton, 1969).

Dissolution rate and crushing strength of tablet decreased as the increasing time of blending of magnesium stearate with a tablet granulation and magnesium stearate may also increase tablet friability. Therefore the blending times with magnesium stearate should be carefully controlled (Ragnarsson *et al*., 1979; Bolhuis *et al*., 1980; Bossert and Stamm, 1980; Sheikh-Salem and Fell, 1981, Chowhan and Chi, 1986a; 1986b; Muzikova, 2002; Muzikova and Horacek, 2003). Decreasing in dissolution caused by the effects of magnesium stearate in some cases can be overcome by including a highly swelling disintegrant in the formulation. (Desai *et al*., 1993)

The existence of various crystalline forms of magnesium stearate has been established. A trihydrate, a dihydrate, and an anhydrate have been isolated from high-purity magnesium stearate (Ertel and Carstensen, 1988), and an amorphous form has been observed (Leinonen *et al*., 1992). While the hydrate forms are stable in the presence of moisture, the anhydrous form adsorbs moisture at relative humidity up to 50%, and at higher humidities rehydrates to form the trihydrate. The anhydrate can be formed by drying either of the hydrates at 105°C.

It has not been conclusively established which form of pure magnesium stearate possesses the best lubricating properties. Commercial lots of magnesium stearate generally consist of mixtures of crystalline forms. Because of the possibility of conversion of crystalline forms during heating, consideration should be given to the pretreatment conditions employed when determining physical properties of magnesium stearate powders such as surface area. Physical properties of magnesium stearate can vary among batches from different manufacturers because the solid-state characteristics of the powder are influenced by manufacturing variables. Variations in the physical properties of different lots of magnesium stearate from the same vendor have also been observed (Barra and Somma 1996). It has not been possible to conclusively correlate the dissolution rate retardation with observed lubricity because of these variations, (Billany and Richards, 1982). Various physical properties of different batches of magnesium stearate such as specific surface area, particle size, crystalline structure, moisture content, and fatty acid composition have been correlated with lubricant efficacy.

1.4.2.6 Talc

Purified talc is used as a lubricant and diluent in making tablets and capsules and to clarify liquids. Its synonyms are hydrous magnesium calcium silicate; hydrous magnesium silicate; magnesium hydrogen metasilicate; powdered talc; purified French chalk. Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder which SEM shown in Figure 1.12. It adheres readily to

the skin and is soft to the touch and free from grittiness. The typical properties are shown in Table 1.7. It is practically insoluble in dilute acids and alkalis, organic solvents, and water.

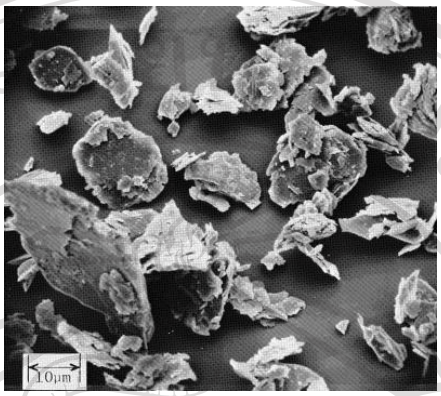


Figure 1.12 SEM of Talc (*Purtalc*). Magnification: 1200×
Manufacturer: Charles B Chrystal Co., Inc

Table 1.7 Typical properties of talc

Item	Specification	Remarks
Acidity/alkalinity	pH = 7–10	for a 20% w/v aqueous dispersion
Refractive index	n^{20}_{D} = 1.54–1.59	
Specific gravity	2.7–2.8	
Specific surface area	2.41–2.42 m^2/g	
Particle size distribution	varies with the source and grade of material. Two typical grades are ≥99% through a 74 μm (#200 mesh) or ≥99% through a 44 μm (#325 mesh)	
Hardness (Mohs)	1.0–1.5	
Moisture content	talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%	

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It is incompatible with quaternary ammonium compounds.

Talc was once widely used in oral solid dosage formulations as a glidant, tablet lubricant at concentration 1.0 – 10.0%, and diluent at concentration 5.0 – 30.0% although today it is less commonly used. It is also widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant.

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants.

Although talc has been extensively investigated for its carcinogenic potential, and it has been suggested that there is an increased risk of ovarian cancer in women using talc, the evidence is inconclusive. However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products. Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.

1.4.3 Solvents (Sweetman, 2007)

1.4.3.1 Absolute alcohol

Alcohol is widely used as a solvent and preservative in pharmaceutical preparations. Its synonyms are dehydrated alcohol; anhydrous ethanol; ethanol. The molecular formula and molecular weight is C_2H_5OH and 46.07, respectively. The Structure formula is shown in Figure 1.13

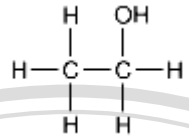


Figure 1.13 Structure Formula of ethyl alcohol
(Sweetman, 2007)

Ethanol contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH at 20 degrees, (specific gravity not more than 0.7962 at 15.56 degrees). It is colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame, boiling point about 78 degrees. It is miscible with water and with dichloromethane. It should be store in airtight containers and protect from light. The typical properties are shown in Table 1.8.

Ethanol and aqueous ethanol solutions of various concentrations are widely used in pharmaceutical formulations and cosmetics.

Reports of interactions between alcohol and other drugs are not consistent, possibly because acute alcohol intake may inhibit drug metabolism while chronic alcohol intake can enhance the induction of drug-metabolizing enzymes in the liver.

Table 1.8 Typical properties of absolute alcohol

Item	Specification	Remarks
Autoignition temperature	365°C	
Boiling point	78.5°C	
Explosive limits	3.5–19.0% v/v in air	
Flash point	12°C	closed cup
Melting point	−112°C	
Refractive index	$n^{20}{}_{D} = 1.361$	
Specific gravity	0.7904–0.7935	at 20°C
Surface tension	22.75 mN/m at 20°C	(ethanol/vapor)
Moisture content	absorbs water rapidly from the air	
Vapor density (relative)	1.59 (air = 1)	
Vapor pressure	5.8 Pa at 20°C	
Viscosity (dynamic)	1.22 mPa s (1.22 cP)	at 20°C

1.4.3.2 Dichloromethane

Dichloromethane is used as a pharmaceutical and industrial solvent. It is also employed as an extraction solvent in food processing. Its synonyms are dichlormethan; methylene chloride (Rochville, 2007 USP 30) with molecular formula as CH_2Cl_2 and molecular weight as 84.93. The Structure formula is shown in Figure 1.14

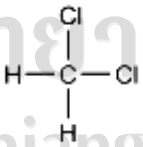


Figure 1.14 Structure Formula of dichloromethane (Sweetman, 2007)

Dichloromethane is a clear, colourless, volatile liquid having an odour resembling chloroform. Relative density is 1.320 to 1.332 (BP 2007). It may contain not more than 2% of alcohol and/or not more than 0.03% of 2-methylbut-2-ene as stabilizers. It is sparingly soluble in water; miscible with alcohol, with ether,

and with fixed and volatile oils. It should be store in airtight containers and protect from light. Phosgene is produced on heating of dichloromethane. The liquid is irritant and high concentrations of the vapour are irritant to the eyes.

1.4.4 Tablet Manufacturing

Tablets are prepared by three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression (Niazi, 2004) as following.

1.4.4.1 Wet granulation

Drug powders are often not easily compressible. The purpose of wet is to improve flow of the mixture and to enhance its compressibility. A flow diagram of the wet granulation process together with appropriate excipients is shown in Figure 1.15 (Armstrong, 2007).

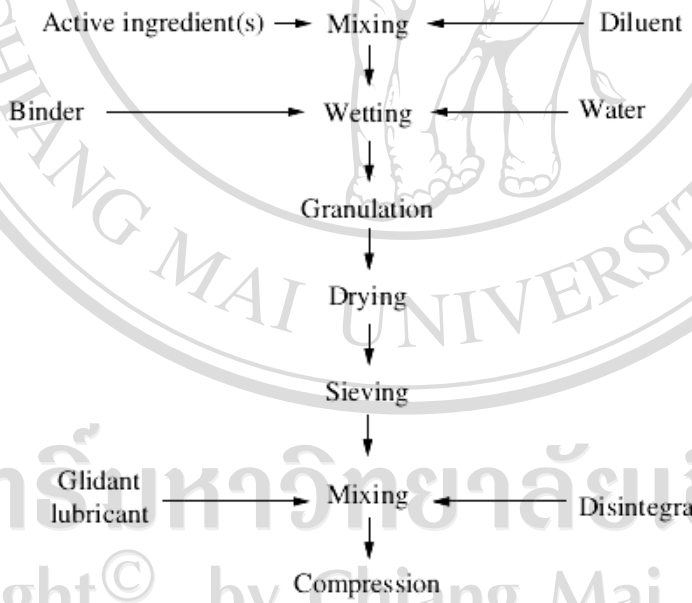


Figure 1.15 Diagram of wet granulation process.

The example of formulation and wet granulation procedure of Diazepam Tablets preparation, 10 mg (Niazi , 2004 b) are shown in the following:

Material Name	Quantity	
	mg/tablet	g/1000 tablets
Diazepam	10.00	10.00
Potato starch	70.00	70.00
Lactose	150.00	150.00
Potato starch, cold swelling	1.50	1.50
Polysorbate 80	0.076	0.076
Microcrystalline cellulose	48.00	48.00
Magnesium stearate	0.75	0.75
Talc, QS	QS	300.00

Manufacturing processes

1. Granulation

a. Weigh and mix for 10 min the potato starch, lactose, potato starch (cold swelling), and diazepam in a suitable mixer.

b. Pass the mixture through a high speed fitz mill.

c. Dissolve polysorbate 80 in purified water.

d. Wet the mixture from b. with the solution from c., adding more water if necessary.

e. Pass the wet mass through a fitz mill sieve, and dry in a drying oven at 35°C for 20 h.

f. Pass the dried granulation through a fitz mill.

g. Separately pass microcrystalline cellulose, magnesium stearate, and talc through a fitz mill sieve (0.3-mm screen).

h. Mix the granules from f. with the mixture from g. for 15 min.

2. Compression

Compress using round, flat punches with beveled edges and a break line on one side. Theoretical weight of 300 mg (290 to 310 mg); thickness 3.2 mm (range: 3.1 to 3.3 mm); diameter 9.5 mm (range 9.3 to 9.7 mm). For 2-mg and 5-mg tablets, adjust fill weight accordingly; for larger tablet size, adjust proportionally with lactose and starch.

1.4.4.2 Dry granulation

Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. Dry granulation process is shown in Figure 1.16 (Armstrong, 2007).

1.4.4.3 Direct compression

Direct compression avoids many of the problems associated with wet and dry granulations which are complex multistage processes. The process of direct compression is shown in Figure 1.17. A major component of the formulation already possesses the necessary degree of fluidity and compressibility.

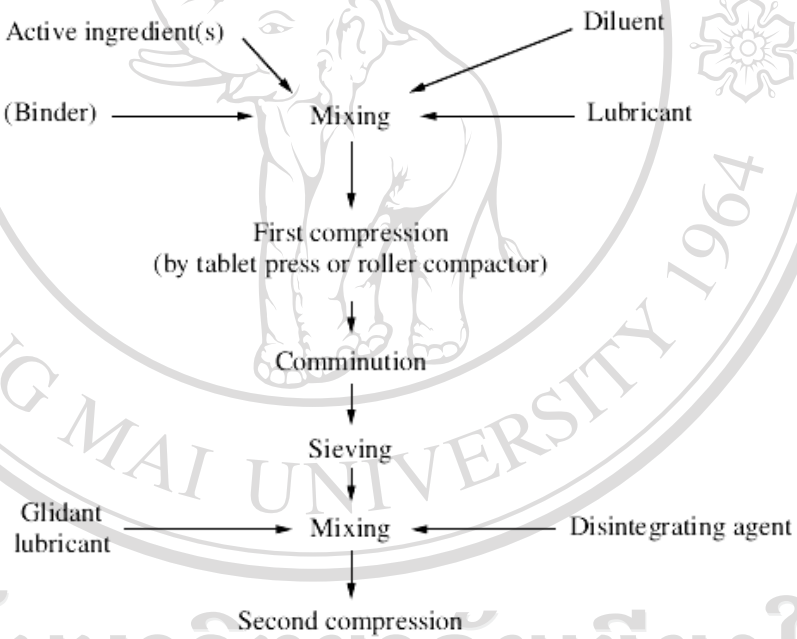


Figure 1.16 Diagram of dry granulation process

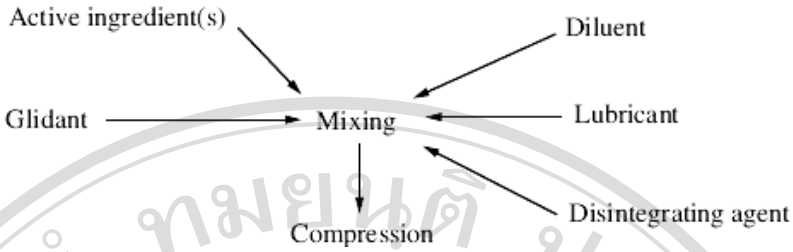


Figure 1.17 Diagram of direct compression process

There are many factors associated with these processes effect on content uniformity, bioavailability, or stability (Augsburger and Zellhofer, 2007). Some of these are given in the following list:

1. Particle Size Reduction

– Non-uniform particle size can lead to segregation problems

– Development of electrostatic forces inhibits complete blending

– Changing the crystalline state can affect solubility *

2. Blending

– Non-homogeneous distribution of drug substance is the result of poor blending or unblending *

– Overblending of lubricant lowers dissolution rates and affects compactibility

3. Granulation

– Non-homogeneous distribution of binder and drug substance gives drug-rich or drug-poor fines

– Decomposition of drug substance due to residual moisture *

– Uneven granule size (too many or to few fines) leads to compaction or uniformity problems

4. Tableting

– Uneven compaction pressures affect disintegration and dissolution *

– Loss of mix quality in hopper and feed frame gives poor content uniformity

– Additional shearing of lubricant in feed frame lowers dissolution rates

* These problems which occur during tablet process may be solved by another method which adding drug after tablet forming.

In the other hand, the potential for excipients to cause chemical and physical instability in drugs has been recognized for over 30 years (Lee, 2008). Drug compatibility studies have been used as an approach for accepting/rejecting excipients for use in pharmaceutical formulations (Jackson *et al*., 2000; Patel *et al*., 2003; Verma and Garg, 2004).

This is necessary for consistency in manufacturing procedures and in bioavailability. The right polymorph, at times, is not necessarily the most stable polymorph; unstable forms like amorphous forms (that are most constrained) are often used because of their higher solubility and often a better bioavailability profile.The manufacturing factors that may be affected by the choice of a particular polymorphic form include milling, granulation such as kneading time (Ertel *et al*., 1990), and compression including crystallization from different solvents at different speeds and temperature, precipitation, concentration or evaporation, crystallization from the melt, grinding and compression, lyophilization, and spray drying.

In the manufacturing processing, crystallization is a major problem and it can be avoided by a careful study of polymorphic transition (in tablet characterization), particularly in supercritical fluids. The solvent molecules fill the spaces in the crystal lattice, and generally reduce the solubility and dissolution rates. This phenomenon is thermodynamically driven.

Because of problems encountered with the bioavailability of hydrophobic drugs of low water solubility, water-soluble diluents are used as fillers for these tablets.

1.4.5 Tablet Evaluation (Lee, 2008)

1.4.5.1 Weight variation

Tablets are required to meet a weight variation test where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity, where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar coated. Thus, the pharmacopoeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage-form unit,

pass a content uniformity test, wherein individual tablets are assayed for actual drug content.

1.4.5.2 Hardness testing

A tablet requires a certain amount of mechanical strength to withstand the shocks of handling in its manufacturing, packing, shipping, and dispensing. Hardness and friability are most common measures used to evaluate tablet strength. The same instrument must be used consistently throughout a particular study.

1.4.5.3 Tablet friability

This test is intended to determine, under defined conditions, the friability of uncoated tablets, the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test. Generally, the test is done once. If cracked, cleaved, or broken tablets are obvious, then the sample also fails the test.

1.4.5.4 Tablet porosity

The *porosity* or *voids* (ε) of a powder is also defined as the ratio of the void volume to the bulk volume of the packing given below. Porosity is frequently expressed in percent, ε × 100 (Niazi, 2007).

$$\varepsilon = 1 - \frac{V_p}{V_b}$$

V_b is known as the bulk volume

V_p is the *true volume* of the particles.

A typical relationship is shown in Fig. 1.18. As force is increased from zero, the porosity of the tablet falls rapidly, but then further increase in force has a progressively smaller effect. The porosity value at which the curve becomes virtually horizontal is dependent on the solid being compressed. Substances

that deform plastically typically give tablets of lower porosity than those which fragment (Armstrong, 2007).

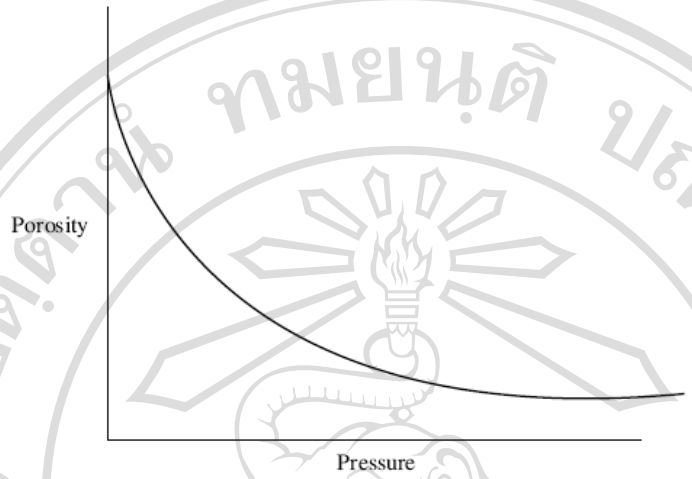


Figure 1.18 A force-porosity diagram.

Many equations have been derived in attempts to provide a mathematical expression of Fig. 1.19. These have been reviewed by Kawakita and Ludde, 1970. It must be stressed that such equations are simply mathematical descriptions of the data, and they have no underlying physical significance. The most widely used of these equations is the Heckel relationship (Heckel, 1961).

$$\text{Ln } 1 / (1 - D) = kP + A$$

where D is the relative density of the tablet and hence (1 – D) is the porosity, P is the applied pressure, and k and A are constants.

1.4.5.5 Disintegration test

A disintegration test is a test to establish how fast a tablet disintegrates into aggregates and/or finer particles. The test assumes that if product disintegrates within a short period of time, such as within 5 min, then the drug would be released as expected and one should not anticipate a problem in the quality of a drug product. The test is conducted using a specially designed instrument known as disintegration apparatus.

1.4.5.6 Determination of the active ingredient content

One may assume that this test as a quantitative version of the identification test. Although the specifications for assay results differ from product to product, generally the expected range for individual active ingredient is to be within 90%–110% of the labeled amount.

1.4.5.7 Uniformity of dosage units

This test is conducted to establish consistency in the content of active ingredient from tablet to tablet. There are generally two approaches taken in establishing this: weight variation or content uniformity. It is mandatory to use content uniformity for tablets with less than 50 mg of active ingredient and/or representing less than 50% total mass of the tablets. The content uniformity approach is preferred over the weight variation approach as it more precisely reflects the variation of the active ingredient from tablet to tablet. The required specification for this test is that uniformity of dosage unit should be within a range of 85%–115% with a relative standard deviation of less than or equal to 6%.

1.4.6 Tablet Characterization

It is generally agreed that crystallography, microscopy, thermal analysis and solubility studies are the most useful for characterization of polymorph and solvates. Instrumental analyses such as scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and powder X - ray diffraction (PXRD) can be very useful to characterize powder properties such as purity, polymorphism, salvation, degradation, drug – excipient compatibility, and other desirable characteristics (Brittain, 2007; Lee, 2008). SEM can also gives information on surface morphology and shape of the powder and readily measure in submicrometer range (0.01 – 100 micron). A number of parameters can be measured from the various thermal events detected by DSC (Niazi, 2007). DSC profile would yield such physical properties as melting (endothermic), solid-state transitions (endothermic), glass transitions, crystallization (endothermic), decomposition (exothermic) and dehydration or desolvation (endothermic) which shown in Figure 1.20 (a).

Powder X-ray diffraction data collected on crystalline samples gives information about peak intensities and peak positions. The powder pattern consists of a series of peaks that have been collected at various scattering angles, which are related to d-spacing. X-ray diffractometry identify polymorphs; quantification of degree of crystallinity; crystal lattice geometry and solid-state transformations. In XRD, the amorphous form shows a shallow peak or halo, as opposed to sharp and intense peaks for a crystalline drug compound in Figure 1.20 b (Omathanu, 2008).

Although XRPD analysis is a relatively straightforward technique for the identification of solid-phase structures, there are sources of error, including the following such as:-

Variations in particle size: Large particle sizes can lead to nonrandom orientation, and hence particles, 10 mm should be used.

Size of sample: Using this technique, the diffraction pattern of approximately 10 mg of the compound can be obtained. Nevertheless, there is no expectation that such data will be available at this early stage of development.

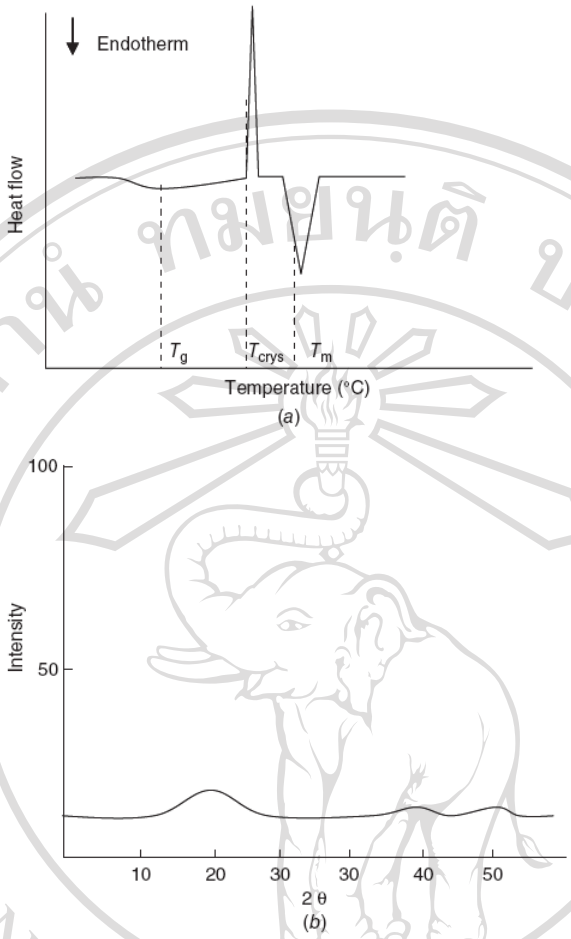


Figure 1.19 Characterization of amorphous form. (*a*) DSC thermogram of amorphous substance. Thermogram is characterized by a glass transition temperature (*T*g) above which the amorphous form is mobile and recrystallizes (*T*crys) into a crystalline form which finally melts (*T*m). (*b*) Amorphous form that does not show any peaks in XRD as it does not have regular arrangement of molecules. Shallow peaks are indicative of an amorphous drug substance.

In vitro dissolution testing is one of the tests in the characterization of drugs in certain dosage forms. It is also used to confirm drug consistency and identify the formulations are good or not. During the preformulation stage, an understanding of the dissolution rate of the drug candidate is necessary, as this property of the compound is recognized as a significant factor involved in drug bioavailability. Dissolution of a solid usually takes place in two stages: salvation of the solute molecules by the solvent molecules followed by transport of these molecules from the

interface into the bulk medium by convection or diffusion. The major factor that determines the dissolution rate is the aqueous solubility of the compound; however, other factors, such as particle size, crystalline state (polymorphs, hydrates), pH, and buffer concentration can affect the rate. Moreover, physical properties, such as viscosity and wettability can also influence the dissolution process. Ideally, dissolution should simulate in vivo conditions. To do this, it should be carried out in a large volume of dissolution medium, or there must be some mechanism whereby the dissolution medium is constantly replenished by fresh solvent. Provided this condition is met, the dissolution testing is defined as taking place under sink conditions. Conversely, if there is a concentration increase during dissolution testing, such that the dissolution is retarded by a concentration gradient, the dissolution is said to be nonsink. A number of analytical techniques can be used to follow the dissolution process; however, UV-visible spectrophotometry and HPLC with fixed or variable wavelength detectors (or diode array) appear to be the most common.

1.4.7 Improving Drug Dissolutions (Melia and Davis, 1989)

Whilst it may be important to control the above parameters, there are many approaches which have been investigated to enhance drug dissolution rates. An overall summary of the principal approaches is provided in Table 1.9 (Melia and Davis, 1989).

Table 1.9 Approaches to improving the dissolution properties of poorly soluble drugs to be given orally

Chemical modification
Soluble prodrugs
Salts
Particle size and crystal form modifications
Milling/micronization of drug substance
Crystal habit
Polymorphic form
Pseudopolymorphs (including solvates)
Crystal poisoning
Dispersing the drug with carrier excipients
Ordered mixes
Freeze drying
Milling
Solvent deposition
Solid solutions (molecular)
Solid dispersions (non-molecular)
Eutectic mixtures
Cornplexing and solubilizing agents
Surfactants
Cyclodextrins

This review is therefore only some approaches such drug particle size, surface wetting, crystal habit and solid dispersion as the following:

Drug particle size

Erratic bioavailability is a common problem with tablets and capsules containing poorly soluble drugs. With these materials, it has been found that increasing the available surface area by reducing the particle size can often markedly improve dissolution rates and lead to dramatic improvements in bioavailability. As a

result of these and several other experiences, it has been recommended that particle size be controlled in oral formulations of new drugs if the solubility of the new drug substance is below 10 mg/L. However, particle size reduction as a strategy for enhancing bioavailability does have limitations. Dissolution of very small particles may be retarded (Leuner and Dressman, 2000) because of their tendency to (1) agglomerate such as two micronized drugs, oxazepam and griseofulvin (Westerberg and Nyström, 1993), piroxicam powder (Swanepoel *et al*., 2000), (2) entrap air bubbles and (3) be poorly wetted which improve by subsequent item.

The common way for micronization is the milling of previously formed larger crystals. However, milling shows several disadvantages as the newly created surfaces are thermodynamically activated due to the high energy input, not naturally grown (Rasenack *et al*., 2003) and polymorph conversion (Cheng *et al*., 2007).

The other method, preparation of nifedipine nanoparticles has been achieved using high pressure homogenization (Hecq *et al*., 2005). The dissolution characteristics of nifedipine nanoparticles were significantly increased in regards to the commercial product. Leading to the reduction in particle size of cilostazol and increased specific surface area after supercritical antisolvent (SAS) process which mean micronized particle size ranging between 0.90 and 4.52 μm were obtained by varying process parameters such as precipitation vessel pressure and temperature, drug solution concentration, solvent type (dichloromethane, glacial acetic acid), feed rate ratio of CO_2/drug solution. (Kim *et al*., 2007). Amorphous atorvastatin calcium nanoparticles were also successfully prepared using the supercritical antisolvent (SAS) process (Kim *et al*., 2008).

Microcrystals were also prepared by a precipitation method (using acetone) or in the presence of stabilizing agents (e.g. gelatin, chitosan, different types of cellulose ethers) followed by spray-drying of the formed dispersion. The dissolution rate is significantly enhanced (common drug: 4% after 20 min / microcrystals 93% after 20 min) due to the large surface. Micron-sized particle of glicazide was prepared by using a solvent change method. Glicazide (0.5 or 1 g) was dissolved in acetone and the stabilizing agent in water (as non-solvent). The non-solvent was poured rapidly into the drug solution under stirring at 26,000 rpm by an ultra-homogenizer, and the resultant was freeze-dried (Varshosaz *et al*., 2008). β-Lapachone [βLAP], a novel

antitumor drug, microcrystals also prepared by using a solvent change precipitation process in the development of tablets with adequate dissolution properties was also stated. The procedure was optimized in order to obtain stable and homogeneous particles with a small mean particle size (~ 3 μm) and a narrow particle size distribution (Cunha-Filho *et al*., 2008).

Crystal form

Both the saturation solubility and the dissolution rate may differ markedly between different crystal forms as a consequence of the different external surface areas or bonding within the crystal lattice of the same drug. Perhaps one of the more remarkable examples is riboflavin, which has three polymorphs varying in solubility from 60 to 1200 mg/L." The availability and biological activity (measured as inhibition of stress ulceration in rats) of several polymorphic, hydrate and salt forms of cimetidine, for example, have been shown to correlate well with the dissolution rates of the different crystal form. As a result, the crystal behavior of a new drug substance with poor solubility is usually investigated at a very early stage, prior to the design of a tablet or capsule. Amorphous forms are often preferred by pharmaceutical scientists as they have the lowest degree of intermolecular bonding and hence the highest dissolution rates (Haleblian, 1975; Aulton, 2002). With novobiocin, for example, the amorphous form dissolves rapidly and is well absorbed (in dogs), whereas the crystalline form dissolves 10 times more slowly and shows poor bioavailability (Gibaldi M. 1984). With this drug, both the raw drug material and the grinding process must be carefully controlled as milling induces reversion to a therapeutically inactive polymorph, a process which is accelerated by the presence of small amounts of other polymorphs in the raw drug materia1 (Kaneniwa and Otsuka, 1985., Otsuka and Kaneniwa, 1986). Other drugs, such as cephalexin (Kaneniwa *et al*., 1985) and steroid (The Boots Company. Private communication 1987) are known to change crystal form during compression on tableting, and the application of heat and liquid during the granulation and drying stages of tablet manufacture provide an obvious area where careful control is required.

On the positive side, crystal form may be deliberately modified by the addition of small amounts of other substances such as surfactants or polymers during

crystallization, which are then incorporated into the crystal structure (Haleblian, 1975). This approach is sometimes termed 'crystal poisoning' and it may offer the opportunity to produce 'designer' crystals with optimal dissolution rates. Fast dissolving forms of drugs such as chlorthalidone and lorazepam (Choui *et al*., 1976; Shawky and Meshia, 1988) have been reported recently by this method.

During the manufacturing of the drug product, the drug substance can be exposed to a variety of physical stresses. A granulation step before a tablet is compacted may include a liquid that is removed in drying, but nevertheless may alter the crystalline form of the active. Awareness of the physical conditions of each step in manufacturing provides a rationale to support the selection of in-process or release controls, such as hardness and dissolution (DeCamp, 1999).

CPM, Highly soluble drugs, even if they have multiple polymorphs, are less likely to vary in their properties *in vivo*.

The use of drug salts or buffers in tablet and capsule formulations is one approach used to enhance dissolution of weak acid/base drugs under adverse conditions of pH. Sodium salts of weak acid drugs or hydrochlorides of weakly basic drugs will usually dissolve more rapidly at all pHs in comparison with the parent free acid or base (Gibaldi, 1984). Buffering agents (e.g. acetates, citrates) may be included in a formulation to provide favourable local pH environments and enhance drug dissolution rates in a similar manner and in view of the above are more useful for already established drugs (Doherty and York, 1989a).

Dispersion approaches

A wide variety of approaches based on drug : adjunct combinations have been utilized. The drug is usually dispersed either on the surface, or within, a 'carrier' excipient and the most successful approaches to date have either (i) reduced drug particle size (ideally to a molecular level in a highly soluble adjunct) or (ii) increased the saturation solubility of drug in the gastrointestinal fluids. They have been produced by mixing, solvent deposition, spray-drying or by milling the drug substance with the carrier. As an example of this approach, nifedipine, when roll-mixed with polyvinyl pyrrolidone (PVP) and polyethylene glycol 1500 as carriers, has been shown to have a dissolution rate 400 times greater than drug solid alone (Nozawa *et al*., 1986). The co-melting of drugs with highly soluble substances (e.g.

sorbitol, urea, polyethylene glycols) may result in solid solutions, eutectic mixtures or solid dispersions with enhanced dissolution characteristic (Goldberg *et al*., 1966; Choui and Reigelman, 1969; Jachowitz, 1987). In certain cases, for example frusemide : PVP solid dispersions, it has been shown that improved dissolution is the result of a retardation of drug crystallization, which results in a higher proportion of the more soluble amorphous form being present. At pH 4, crystalline frusemide is only sparingly soluble, but drug in a solid dispersion has a markedly enhanced dissolution which results in a more rapid onset of in-vivo effect (Doherty and York, 1989 b). This approach is becoming increasingly popular with the advent of production-scale equipment to fill co-melted or thixotropic drug : polymer mixtures into conventional gelatin capsule (Walker *et al*., 1980). Dispersion formulations based on semi-solid surfactants, such as Vitamin E TPGS and Gelucire 44/14 (Yuksel *et al*, 2003; Soliman and Khan, 2005) have the potential to facilitate dissolution and inhibit precipitation in the GI tract as a result of their solubilizing properties, but typically have much lower melting points and a greater degree of molecular mobility in the solid state than polymers. It was found that the use of a swellable clay such as Veegum® and other magnesium aluminium silicates within the granulate of an acyclovir tablet formulation provides a tablet which has good dispersibility in water to provide a dispersion which can be drunk by a patient (Elzbieta, 1997).

Solubilizing and complexing agents

Hydrophobic drugs that do not wet easily tend to entrain gas films on their surfaces and reduce the surface area available for dissolution (Nail and Hem, 1982). The inclusion of small amounts of surface active agents (e.g. sodium lauryl sulphate) may often solve such wetting problems in tablets.

The solvent-diffusion method was used to prepare griseofulvin particles with hydrophilic surfactants (Brij 76/Tween 80 surfactant blends) with a particle size of 2.18 ± 0.12 μm and in-vivo studies were conducted in rats (Wong *et al*, 2006a). The dissolution rate and absolute oral bioavailability of the spray dried griseofulvin/Poloxamer 407 particles were significantly increased compared to the control (Wong *et al*, 2006b).

In theory, surfactants may be utilized for their solubility-enhancing properties through micellular solubilization (Gander *et al*, 1985). The addition of SLS to formulations containing sugar glass-based solid dispersions is a suitable technology to improve the dissolution behavior of poorly soluble drugs. But in practice, the toxicity of the relatively high concentrations of surfactant required often makes this approach undesirable (Melia and Devis, 1989). And studies in surfactant solution may provide further indirect evidence of aggregate formation.

Cyclodextrins (CD or β-CD) offer considerably to investigate their dissolution-enhancing properties. These non-toxic cyclic polysaccharides and their derivatives form water-soluble inclusion complexes with a wide variety of drugs, and can spectacularly increase the saturation solubility and dissolution rates of poorly soluble drug (Lin and Yang, 1986; Pitha *et al*, 1986; Tokumura *et al*. 1986; Celebi N. 1989). The dissolution rate of warfarin, for example, is increased 1200-fold when complexed with β-CD. The complex products are sometimes too stable to be useful, and may decrease the availability of the drug for absorption (Melia and Devis, 1989). It was found that β-CD and its combinations with spray dried lactose produced tablets having very good mechanical properties and higher dissolution rate. The uniformity of weight and thickness were good (coefficient of variation less than 2%) for all formulations containing up to 60% β-CD (M. H. ElShaboury, 1990).

The study of liquisolid tablets demonstrated significantly higher drug release rates compared to tablets prepared by direct compression method (Spireas and Sadu, 1998; Javadsadeh *et al.*, 2007). This was due to an increase in wetting properties and surface of drug available for dissolution (Javadsadeh *et al.*, 2005).

1.4.8 Improvement of dissolution characteristic of diazepam

This review is summarization of the use carriers and the methods for enhancing diazepam solubility or increase the availability surface area for dissolution.

Inclusion complexes of 13 benzodiazepines with 3 cyclodextrins (α-, β-, γ-CyDs) in aqueous solution and in the solid phase were studied. The rapid dissolving form of diazepam-γ-CyD complex was found to significantly increase the serum levels of drug after oral administration to rabbits (Uekama *et al*, 1983).

Diazepam-β-cyclodextrin and diazepam-lactose products were prepared by spray-drying (Bootsma *et al,* 1989). These Complexations played only a minor role in dissolution rate enhancement. Absorption experiments in human volunteers showed also an increased absorption of diazepam by β-cyclodextrin complexation.

β-cyclodetrin (β-CD) was evaluated as a direct compression vehicle either singly or in blends with spray-dried lactose (sp.d.l) for preparing tablets containing either phenobarbitone, diazepam, prednisolone or spironolactone (ElShaboury, 1990). In each drug formulation, the dissolution rate was progressively increased with the increase in β-CD concentration up to a certain limit after which the dissolution rate was not significantly changed or only slightly decreased. The dissolution rate of the selected drugs was improved by about 6–10-fold compared to that of tablets prepared by wet granulation or those containing 100% sp.d.l.

The *in vitro* dissolution behavior of the kneaded mixture of three drugs (diclofenac acid, diazepam, and prednisolone) with casein hydrolysates A (mean peptide length 3.3) and B (mean peptide length 17.4) were significantly improved compared to the drugs alone (Imai *et al*, 1998).

Higher dissolution rates of diazepam were noted with tablets containing the drug in polyethylene glycol solid dispersion compared to these containing a physical mixture of the drug granulated with polyethylene glycol or to directly compressed tablets. The dissolution of the drug becomes pH independent when it is present as a solid dispersion, which may be advantageous for the bioavailability (Kinget R, 1989). The preparation method and diazepam-polyethylene glycol 6000 ratio influence the dissolution rate of the drug. It is observed that faster release characteristics were obtained with solid dispersions prepared by the fusion method and by increasing the carrier percentage. The increase in dissolution rate can be considered to result from crystal size reduction and the solubilizing effect of polyethylene glycol 6000 (Rabasco *et al*, 1991). Addition of PEG 6000 improves the dissolution rate of both diazepam and temazepam. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface of drug crystals after dissolution of the polymer. Formulation of solid dispersions were prepared by the solvent method (CH_2Cl_2), the fusion method with fast cooling (CO_2) or the fusion method with slow cooling (rT).

They did not further improve the dissolution rate compared with physical mixtures. X-ray spectra show that both drugs are in a highly crystalline state in the solid dispersions, while no significant changes in the lattice spacing of PEG6000 indicate the absence of solid solution formation. IR spectra show the absence of a hydrogen bonding interaction between the benzodiazepines and PEG6000. Furthermore, it was concluded that the reduction of the mean drug particle size by preparing solid dispersions with PEG6000 is limited and that the influence of the polymorphic behavior of PEG6000 (as observed by DSC) on the dissolution was negligible (Verheyen *et al*., 2002). Another time, the dissolution of diazepam, oxazepam and nitrazepam from its solid dispersions increased in the presence of PEG 6000 (Cwiertnia, 2006).

The coground mixtures of diazepam with Pullulan as a water-soluble carrier were prepared to improve the in vitro dissolution rate of the poorly water-soluble drug diazepam (Choudhari and Sanghavi, 1993). The results indicated the prominent role of amorphization of crystalline drug in enhancing the in vitro dissolution rate.

Diazepam release from capsules was slightly increased on application of amylodextrin, either as a filler in a physical mixture or as a carrier for solid dispersion of the drug, as compared to the release from capsules containing drug only. The limited increase in drug dissolution is caused by the limited solubility of amylodextrin. Application of the soluble fraction of amylodextrin therefore showed faster drug release. (Wierik *et al*, 1993).

Incorporation of a small dose of an active principle (4% w/w diazepam) in tablets prepared from the fully hydrated β-lactose had a significant negative effect on their mechanical properties. This effect, together with the above-mentioned increase in the specific surface of the fully hydrated excipient, caused rapid dissolution of the diazepam from these tablets (Cal *et al*, 1996). Diazepam-compactrol interactive mixtures had initial dissolution rates similar to that of pure diazepam owing to the deposition of a continuous layer of diazepam on the disc surface from the interactive mixture. Linear Levich plots were produced at all drug loadings and the presence of compactrol in the disc slightly enhanced dissolution rates. Dissolution rates for diazepam-emcompress interactive mixtures were lower

than those of pure diazepam. The Levich plots for these systems were non-linear with increasing negative curvature as the diazepam loading decreased. The rate of dissolution of diazepam in the lactose interactive mixture was markedly higher than that of pure diazepam, but high diazepam loadings in the lactose mixtures inhibited diazepam dissolution. Rapid carrier dissolution caused surface retraction of the disc, enhancing the dissolution rate (Supabphol and Stewart, 1996). Dissolution of diazepam was concentration dependent and occurred rapidly, i.e., greater than 95% dissolved within 10 and 20 min for the 1 and 10% of diazepam in lactose interactive mixtures, respectively (Alway *et al*, 1996). The formulation of solid self-emulsifying pellets using the extrusion/spheronization technique were made from a mixture of diazepam, C18 partial glycerides, Solutol® HS15 and microcrystalline cellulose. It was capable of accelerating the release of the drug diazepam and achieving a diazepam concentration above its saturation solubility (Abdalla and Mäder, 2001). A higher dissolution rate was obtained with a lower diazepam concentration. Admixing lactose monohydrate which was melt agglomerated with polyethylene glycol (PEG) 3000 or Gelucire® 50/13 (mixture of glycerides and PEG esters of fatty acids) as meltable binders by the melt-in procedure resulted in similar dissolution rates as the pump-on procedure. Gelucire 50/13 resulted in faster dissolution rates compared to PEG 3000 (Seo *et al*, 2003).

Benzodiazepine-lactose interactive mixtures with higher benzodiazepine concentrations displayed transition profiles with higher levels of agglomeration. The presence of surfactant, i.e., micronized sodium lauryl sulfate and cetrimide up to 5% w/w in interactive mixtures dramatically decreased agglomeration. Sodium lauryl sulfate was more effective than cetrimide in dispersing agglomerates (Zhao and Stewart, 2003). Micronized diazepam, nitrazepam, oxazepam, and, for ternary mixtures, micronized sodium lauryl sulfate were mixed with lactose-povidone granules (250-355 microm). Increasing benzodiazepine and sodium lauryl sulphate concentrations in the lactose-povidone mixtures increased both dispersible and nondispersible agglomerate concentrations (Zhao and Stewart, 2004).

Diazepam was incorporated in four different sugar glasses, i.e. sucrose, trehalose and two oligo-fructoses; inulinDP11 and inulinDP23 as carriers in the amorphous state by means of freeze drying using water and tertiary butyl alcohol as

solvents. None of the tablets disintegrated during dissolution. Dissolution of 80% of the lipophilic drug within 20 min was found when release profiles of diazepam and sugar coincided. For relatively fast dissolving carriers like sucrose or trehalose with high drug loads, dissolution profiles of diazepam and sugar did not coincide by diazepam dissolved much more slowly than the sugars (Drooge *et al*, 2004). To increase dissolution rate of diazepam, a surfactant, i.e., sodium lauryl sulphate (SLS), was incorporated in the sugar glass or physically mixed with it. The dissolution behavior of diazepam tablet prepared from solid dispersion in which SLS was incorporated was strongly improved. Surprisingly, the dissolution rate of tablet prepared from physical mixture of SLS and the solid dispersion was initially fast, but slowed down after about 10 min (Waard *et al*, 2008).

The solubilities of five poorly water-soluble drugs, i.e., diazepam, griseofulvin, progesterone, 17 β-estradiol, and testosterone, in the presence of nicotinamide were found to increase the solubilities in a nonlinear fashion as a function of nicotinamide concentration. The aromaticity (Pi-system) of the pyridine ring is an important factor in complexation because the aromatic amide (*N,N*-diethylnicotinamide) ligands were found to enhance the aqueous solubilities of the test drugs to a greater extent than the aliphatic amide (nipecotamide and *N,N*-dimethylacetamide) ligands (Rasool *et al* 2006).

1.4.9 Drug-Solution-Dropping Tablet (DSDT)

There are many factors associated with the processes to prepare conventional tablet effect on content uniformity, bioavailability, or stability which is mentioned before. For the example, segregation is particularly likely to occur in mixtures where the components differ markedly in size, with differences in shape and density which affect on uniformity. The size of the granulator and the mixing time can be major influences on the physical properties and dissolution rate of the resulting tablets (Armstrong, 2007; Ertel *et al*, 1990). The other problems, drug powders are often not easily compressible (Niazi, 2004a) or the incompatibility of drug and tablet excipients.

The following reviews were corresponding to the study of a novel preparation, drug solution dropping tablet (DSDT).

Buehler, 1978 showed how to overcome the incompatibility of the simethicone and the antacid. Simethicone is entrapped in solid, discrete particles of a matrix composition of glycerol and corn syrup solids to generate this shielding action.

Rider, 1980 claimed a tablet containing at least two separate and discrete volume portions one of which contains simethicone and the other of which contains antacid. The simethicone is physically combined with the other ingredients of the tablet in such a manner that the simethicone is available relatively immediately for anti-foaming action, and its availability does not depend upon the breakdown of a matrix.

Gole *et al*, 1996 claimed a method for preparing a solid, porous delivery matrix comprising a porous network of matrix material such as gelatin, mannitol, xanthan gum and glycine, additionally comprises a cyclodextrin, magnesium trisilicate or magnesium aluminum silicate, that disperses rapidly in water in less than about ten seconds. Examples of pharmaceutical agents that may be incorporated in the initial mixture are chlorpheniramine maleate, pseudo-ephedrine, and benzodiazepines such as diazepam, lorazepam and congeners thereof. However virtually any pharmaceutical agent may be used in connection with this invention, either adding in the mixture to be solidified or by post loading onto a preformed placebo delivery matrix or dosage form. These active agents may be loaded or dosed on the placebo as a solution, suspension, dispersion or emulsion of the agent in a carrier solvent immiscible with the placebo materials. Thus, the active agent will be substantially distributed throughout the placebo. The carrier solvent is the allowed to evaporate at normal pressure and normal or elevated temperatures, by passing a stream of air or nitrogen over the dosage form in a vacuum chamber under reduced pressure and normal or elevated temperatures. Alternatively, microwave assisted drying may be used. Alternatively, the dosage form may be placed in a vacuum chamber to remove the residual carrier solvent. The concentration of active agent in the final dosage form prepared by either method, i.e., post loading or conventional premixing, is related to the amount of active agent desired to be delivered in the processed dosage form. If post loading, this concentration is limited by the solubility of the active agent in the solvent, although dosage forms may be serially processed with multiple post loadings in order to increase the concentration to a desirable level. In addition, suspensions of

the active agent may be used to post load the placebo. Consequently, the concentration of active agent in the final matrix or dosage form may range from less than 0.01% to more than 300% of the weight of the dosage form.

The examples of post loading active agents on the placebo were shown in the following examples.

Example 1. Preparation of a pharmaceutical dosage form containing an active agent by post-loading a colored processed matrix.

A 100 ml drugs solution was prepared to soluble 3.75 g pseudoephedrine HCl, 0.25 g chlorpheniramine maleate, 1.25 g dextromethorphan, 0.50 g sodium saccharin, and 0.10 g of menthol in absolute ethanol. A colored placebo, cylindrical depression 18 mm diameter and 5 mm deep, was prepared by freeze-drying the solution of 20 g of gelatin (pharmaceutical grade), 30 g of mannitol and 0.1 ml of FD&C yellow #5 solution in 949.9 g of water that disintegrated rapidly, in 1 to 5 seconds. To this placebo was added 0.20 ml of the solution and the solvent was subsequently allowed to evaporate in a vacuum chamber for one hour. The resulting dry dosage form dissolves rapidly in water and also in the mouth. Each dosage unit weighed 62 mg and contained 7.5 mg of pseudoephedrine HCl, 0.5 mg of chlorpheniramine maleate and 2.5 mg of dextromethorphan HBr. Several doses of above three drugs were prepared with different flavor systems such as grape, punch, lemon-lime, raspberry and cherry. Each resulted in a unit dosage form that dissolved rapidly in 1 to 5 seconds when taken orally.

Example 2. Preparation of a pharmaceutical dosage form containing an active agent by post-loading a processed matrix.

A placebo sample was prepared similar to colored processed matrix in example 1 except FD&C yellow #5 solution with heating and constant stirring. To this placebo sample was added 0.2 ml of a solution prepared to contain 15.0 g meclizine HCl, 0.1 g menthol, 1.25 g aspartame, 0.1 ml raspberry flavor in sufficient 1:1 chloroform : isopropyl alcohol to yield 100 ml. The solvent was then allowed to evaporate in a vacuum chamber for about one hour. The resulting dosage unit contained 25 mg of meclizine. Several doses of meclizine HCl were prepared with different flavor systems such as grape, punch, lemon-lime, raspberry and cherry. Each

resulted in a dosage unit that weighed 83 mg and dissolved in 1 to 5 seconds when taken orally.

Lee *et al***,** 2001 provided pharmaceutical formulations which contained (1) an inert core of sugar, sugar and starch, or microcrystalline cellulose, (2) a drug emulsion (3) a protective coating and (4) an enteric coating. Optionally, a basic amino acid could be added to the drug emulsion layer or the protective coating.

The details of this invention were described as the following:

A. Formulation of the Pharmaceutical Granules

(1) Inert Core: 1097.6 g of sugar, sugar plus starch (in any combinations), or microcrystalline cellulose.

(2) Drug Emulsion: Omeprazole 147 g Poloxamer 188 98 g Arginine 78.4 g Purified Water 924 ml.

(3) Protective Coating: HPMC 78.4 g Triethyl Citrate 7.84 g Purified Water 784 ml.

(4) Enteric Coating Layer: Eudragit L30D 1437.33 g Triethyl Citrate 21.56 g Purified Water 478.8 ml.

B. Method of Preparing the Formulation

The inert core was either bought from companies selling core particles or prepared using the Glatt machine. The drug emulsion was prepared by mixing omeprazole, Poloxamer 188 as non-ionic surfactant, and arginine in purified water. The emulsion was then placed into the spray gun of the Glatt machine and sprayed onto the core particles while the machine was set in circulating condition. This would allow the drug to be evenly coated onto the core particles to form drug-coated spherical particles. The drug-coated particles were dried under warm air within the Glatt machine. Then, a protective coating solution was prepared by mixing hydroxypropyl methylcellulose as film former and triethyl citrate as plasticizer in purified water. This coating was then placed into the spray gun of the Glatt machine and sprayed onto the drug-coated particles while the machine was set in running condition. This coating was placed into the spray gun of the Glatt machine and sprayed onto the protective coating-covered particles to form the pharmaceutical granules before final drying of the granules to complete the process of making the enteric coating-covered granules.

Lee and Lee, 2002 describes a blank tablet includes an absorbent, a disintegrant, a lubricant, and a diluent and/or a binder. An active ingredient in liquid form is introduced into the blank tablet to produce a pharmaceutical composition. The examples of tablet composition of this invention were shown in the following:

Tablet composition in example 1:

Active ingredients: Dimethylpolysiloxane	40	mg
Blank tablet:		
Silicon dioxide	4	mg
Microcrystalline cellulose	304	mg
Sodium starch Glycolate	8	mg
Talc	4	mg
Total	360	mg

Tablet composition in example 2:

Active ingredients: Dimethylpolysiloxane	50	mg
Blank tablet:		
Silicon dioxide	4	mg
Lactose	294	mg
Sodium starch Glycolate	8	mg
Magnesium stearate	4	mg
Total	360	mg

Tablet composition in example 3:

Active ingredients: Dimethylpolysiloxane	80	mg
Blank tablet:		
Silicon dioxide	8	mg
Microcrystalline cellulose	244	mg
Glucose	244	mg
Calcium carboxymethyl cellulose	16	mg
Magnesium stearate	8	mg
Total	600	mg

Tablet composition in example 4:

Active ingredients: Dimethylpolysiloxane	80	mg
Blank tablet:		
Silicon dioxide	8.0	mg
Microcrystalline cellulose	390.4	mg
Glucose	97.6	mg
Calcium carboxymethyl cellulose	16.0	mg
Magnesium stearate	8.0	mg
Total	600.0	mg

Tablet composition in example 5:

Active ingredients: Dimethylpolysiloxane	80	mg
Blank tablet:		
Silicon dioxide	8.0	mg
Microcrystalline cellulose	97.6	mg
Glucose	360.4	mg
Calcium carboxymethyl cellulose	16.0	mg
Magnesium stearate	8.0	mg
Total	600.0	mg

The blank tablet was prepared by direct compression method and formed into tablets by a high speed tablet press. The blank tablet was immersed into dimethylpolysiloxane until the blank tablet absorbed the dimethylpolysiloxane to the specified amount, i.e., 40 mg. Whenever required, any excess active ingredient was removed by centrifugation.

Heil *et al*, 2006 developed a quick-release tablet formulation with >99.19% pure fludara (high-purity fludara for treating cancer) as an active ingredient in a defined composition of residual contaminants. Selected is such a quick-release tablet formulation that comprises 10 mg of the active ingredient fludara at a purity of >99.19%, together with 74.75 mg of lactose monohydrate, 0.75 mg of colloidal silicon dioxide, 60.00 mg of microcrystallinecellulose (avicel), 3.00 mg of

crosscaramellose-Na (sodium carboxymethyl cellulose) and 1.5-2.00 mg of magnesium stearate.

HOLM *et al*, 2006 invented the novel technique of controlled agglomeration by which it was possible to load a particulate material with a relatively high amount of oil or an oily-like material. The technique was based on a process that involves spraying of a carrier composition containing the oil or oily-like material onto a particulate material. The process involves heating of the carrier composition and maintaining the temperature of the carrier composition during spraying in order to avoid clotting of the spray nozzle etc. Furthermore, a novel tablet product was provided that in an easy, flexible and reproducible manner could be loaded with a relatively high amount of a pharmaceutically acceptable liquid formulation e.g. carrying a therapeutically, prophylactically and/or diagnostically active substance. The novel loadable tablet product might be produced in large-scale batches and stored until use and each batch or sub-batch may be loaded with the same or different pharmaceutically acceptable liquid formulations and/or active substances. A loadable tablet according to this invention had a porosity of 30% v/v or more.

In the final formulation of Shanbhag et al., 2008, the compound may be molecularly dispersed in the excipient matrix, or may be dispersed as fine nanocrystalline or amorphous particles which form during solvent evaporation or cooling of the melt.