VALIDATION OF TABLET MANUFACTURING PROCESS IN THE ETHIOPIAN PHARMACEUTICALS MANUFACTURING FACTORY (EPHARM)

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By

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TABLE OF CONTENTS **Page**

LIST OF TABLES **Page**

LIST OF FIGURES

SUMMARY

Process validation may be defined as a systematic approach to identifying, measuring, evaluating, documenting and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product. The approach is based on the principle that "quality is not tested into a product but rather is built into a product".

It is with this principle in mind that this work has been designed and conducted. The validation study was limited to the tablet manufacturing process in the Ethiopian Pharmaceuticals Manufacturing Factory (EPHARM). Three tablet products were selected, namely, Chloroquine phosphate 250 mg, Paracetamol 500 mg and Frusemide 40 mg for the study. Chloroquine phosphate, is a highly water-soluble salt with little or no compressibility problems. Paracetamol is moderately soluble in water with a high tendency to capping. Frusemide is practically insoluble in water which may pose problems in drug release.

In this study, the manufacturing facility and equipment, the raw material acquisition and testing procedures, the tablet manufacturing process, and the in-process control procedures were evaluated. Samples of the in-process materials and the finished products were taken and tested for compliance with quality specifications.

The results of the study suggest that the proportion of fines in granulations of some of the products was excessive (chloroquine phosphate). Measurements of angle of repose indicate that the granulation bulk density, flow and surface characteristics were generally good. One-

way analysis of variance (ANOVA) revealed that there was significant variation in the granulation moisture content of all of the products tested. Paracetamol tablets lacked the shiny smooth appearance expected of plain, compressed tablets. High hardness variation has been observed in some products (paracetamol, frusemide) but thickness was within the specification in all cases. Two batches of paracetamol capped and, hence, failed friability test specifications. The tablets complied with the official weight variation and content uniformity specifications, but the range need to be narrowed through the use of internal specifications. Tablets of all of the products tested disintegrated within the specified time. Dissolution rate was within the official requirements in all cases. Complete *in vitro* drug release (90% or more of label claim) was observed in all cases, but the optimum goal of achieving 90% drug release below 30 min was not attained particularly with frusemide and in some batches of paracetamol.

Standard operating procedure (SOP) was not strictly followed during some of the unit operations. The document (batch manufacturing record) was lacking the necessary details required of such a document. For example, mixing time and mixing intensity in mixers, drying time and temperature in dryers, machine speed, compression force etc. in tablet presses were not clearly stated. No in-process control activity was observed at the granulation stage and there were no quality specifications available for the granules. Machine cleaning and maintenance procedure and documentation was lacking. Personnel training was inadequate. Generally the GMP requirements in the area of facility and equipment, personnel, process validation, documentation, etc. are not fulfilled.

1. INTRODUCTION

1.1 General: Tablets

Drug substances are most frequently administered orally by means of solid dosage forms such as tablets. Solid oral dosage forms represent the preferred drug delivery system for the oral route because they deliver the drug accurately since each tablet represents one dosage unit; are easy to carry and are compact and easy to store; they lend themselves to rapid mass production and are the least expensive, and have inherently greater chemical stability, compared to liquid dosage forms (1).

In order for medicinal substances, with or without diluents, to be made into tablets with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, posses a number of physical characteristics. These characteristics include, the ability to flow freely, cohesiveness, and lubrication (2). Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets.

The basic mechanical unit in all tablet compression-equipment includes a lower punch that fits into a die from the bottom and an upper punch, having a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity. The tablet is formed by pressure applied on the punches and is subsequently ejected from the dies. The weight of the tablet is determined by the volume of the material that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in insuring uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not

posses cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be readily ejected from the punch faces, the material must have a degree of lubrication to minimize friction and to allow for the removal of the compressed tablet.

The method of preparation and the added ingredients are selected in order to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability and uniformity that are also influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets the formulator must also be cognizant of the effect that the ingredients and methods of preparation may have on the availability of the active ingredients and hence therapeutic efficacy of the dosage form (1).

The desired tablet qualities such as weight uniformity, content uniformity, hardness, friability, disintegration, dissolution and bioavailability are affected by the various formulation and processing variables. Therefore, process validation should be carried out to provide documented evidence that the product quality is consistently assured and that the quality parameters of both the in-process material and the end product are reproducible from batch-to-batch and from production-run to production-run and are within the set specifications. As required under the New Drug Application (NDA), this final step, for new drug products, is undertaken on the selected formulation after the process has been scaled up to full production batch size. Under the new concept of validation this responsibility is placed on the pharmacy development group, the pilot plant group, and

possibly the production department, to achieve the goals of validation as previously stated (3).

As stated above, in addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives. They may be classified according to the part they play in finished tablet. The first group contains those that which help to impart satisfactory compression characteristics to the formulation. These include diluents, binders, and lubricants. The second group of added substances, disintegrators, colors, in the case of chewable tablets, flavors, and sweetening agents helps to give additional desirable physical characteristics to the finished tablet (2).

Although the term "inert" has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability and the processes by which the dosage forms are prepared. Therefore, care must be taken in the selection and evaluation of additives and preparation methods to ensure that the physiological availability and therapeutic efficacy of the active ingredient will not be diminished.

Formulation ingredients

1.1.1 Diluents

Frequently the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size of compression. For example, compressed tablets of dexamethasone contain 0.75-mg steroid per tablet; hence it

is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, direct compressible starches and powdered sucrose. Diluents used as excipients for direct compression formulas are subjected to various processing to give them flowability and compressibility. They include microcrystalline cellulose, spray-dried lactose, and hydrolyzed starches (2).

In the selection of diluents for a given formulation compatibility of the diluents with the drug must be considered. For example, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline, have been shown to interfere with the drug's absorption from the gastrointestinal tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances, e.g., bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be adsorbed to the point where they are not completely available after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, results in tablets that discolor on aging (4).

1.1. 2 Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formation of granules of desired hardness and size. Materials commonly

used as binders include starch (paste and pregelatinized), gelatin, and sugars such as sucrose, dextrose, molasses and lactose; natural and synthetic gums include acacia, sodium alginate, carboxymethyl cellulose, methylcellulose, polyinylpyrollidone, and veegum. Other agents, which may be considered binders under certain circumstances, are polyethylenelycol, ethyl cellulose, water and alcohol

The quantity of binder used has considerable influence on the characteristics of compressed tablets. The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies. For instance, differences in binders used for compressed Tolbutamide tablet, resulted in differences in hypoglycemic effects observed clinically. Materials that have no cohesive qualities of their own will require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word; but because of their solvent action on some ingredients such as lactose and starch, they change the powdered material to granules and the residual moisture retained enables the materials to adhere together when compressed (5- 7).

1.1.3 Lubricants and glidants

Lubricants and glidants have a number of functions in tablet manufacture. They improve the rate of flow of the tablet granulation, prevent adhesion of the tablet material to the surface of the dies and punches, reduce inter-particle friction, and facilitate the ejection of the tablets from the die cavity. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, polyethylene glycols, waxes and hydrogenated vegetable oils. Most lubricants with the exception of talc are used in concentrations less

than 1% (8). When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection and excessive amounts can result in "water proofing" the tablets, resulting in poor tablet disintegration and dissolution of the drug substance.

Poorly flowing powders present many problems in the pharmaceutical industry and many efforts have been expended in finding ways to overcome poor fluidity. One method employed is the use of glidants, the term applied to dry agents that enhance the flow properties of powders as well as granular solids. Examples of substances employed as glidants include talc, starch and certain synthetic colloidal silicas such as cab-o-sil. In general, the colloidal silcas consist principally of silicon dioxide and are characterized by ultrafine particle size and low bulk density.

Glidants are fine particles which appear to coat the particles of the bulk powder and enhance flow properties by acting through one or more possible mechanisms which include:

a) Filling in irregularities and reducing surface roughness;

b) Physically separating the bulk particles, thereby reducing attractive forces;

c) Reducing electrostatic charges;

d) "Scavenging" moisture; and

e) Acting as "ball bearings" between the bulk particles.

There is usually an optimum concentration of glidant, often 1% or less, beyond which there is no further improvement in flow properties and possibly a deterioration of flow. The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression most tablets have tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant will effectively overcome this problem (2).

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be finely divided by passing it through a 100-mesh nylon cloth onto the granulation. In production this is called "bolting" the lubricant. After adding the lubricant the granulation is tumbled or mixed gently to coat the individual granules without breaking them down to finer particles. Prolonged blending of lubricant with a granulation can materially affect the hardness and the disintegration time for the resultant tablets. The quantity of lubricant varies, being as low as 0.1 % and in some case as high as 5 % (9).

In selecting a lubricant, proper attention must be given to its compatibility with the active ingredient. Perhaps the most investigated drug is acetylsalicylic acid. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate (10-15).

1.1.4 Disintegrants

A disintegrator is a substance, or a mixture of substances, added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been chemically classified as starches, clays, celluloses, algins, or gums (2).

The most popular disintegrators are corn and potato starches which have been well dried and powdered. Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in tablet is due to capillary action rather than swelling; the spherical shape of the starch grains increase the porosity of the tablet, thus promoting capillary action (16). Starch 5% is suggested but, if more rapid disintegration is desired, this amount may be increased to 10% or 15%. Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet is increased, this does not appear to be the case for tolbutamide tablets (17). In this instance, there appear to be a critical starch concentration for different granulations of the chemical. When their disintegration effect is desired, the starches are added to the powder blends in the dry state. Modified starches such as Primogel and Explotab have even higher disintegration capacity because of their much higher swelling power. Starch pastes, which are useful as binding agents, will generally not be effective as disintegrating agents.

In addition to the starches, a large variety of materials have been used and are reported to be effective as disintegrators. This group includes veegum HV, microcrystalline cellulose,

agar, bentonite, cellulose and wood products, cation-exchange resins, alginic acid, guar gum, citrus pulp, cross-linked microcrystalline cellulose (Ac-Di-Sol®), cross linked PVP and carboxymethyl cellulose. Sodium starch glycolate prepared from variety of starch sources such as "Enset" was also found to be an effective disintegrant (18). Sodium lauryl sulfate in combination with starch also has been demonstrated to be effective disintegrant. In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as being due to an increase in the rate of wetting (19).

The disintegrating agent is usually mixed with the active ingredient and diluents prior to granulation. In some cases it may be advantageous to divide the starch into two portions; one part is added to the powdered formula prior to granulation (internal disintegrant), and the remainder is mixed with the lubricant and added prior to compression (external disintegrant). Incorporated in this manner the starch serves a double purpose, the portion added to the lubricant rapidly breaks the tablet down to granules, and the starch mixed with the active ingredients disintegrates the granules down to smaller particles (20). Veegum has been shown to be more effective as disintegrator in sulfathiazole tablets when most of the quantity is added after granulation and only a small amount before granulation. Likewise, the montimorillonite clays were found to be good tablet disintegrants when added to prepared granulations as powder. They are much less effective as disintegrants when incorporated within the granules (21).

Factors other than the disintegrators can affect significantly the disintegration time of compressed tablets. The type and amount of binder used, tablet hardness, and the concentration of lubricant and mixing time during lubricant incorporation and the

granulation moisture content have been shown to influence the disintegration time. Thus when the formulator is faced with a problem concerning the disintegration and dissolution of compressed tablets, the answer may not lie in the selection and the quantity of the disintegrating agent alone (22,23).

1.2 Tablet characteristics

Compressed tablets may be characterized or described by a number of specifications. These include the diameter, size, shape, thickness, weight, hardness, and disintegration time. The diameter and shape depends on the die and the punches selected for the compression of the tablet. Generally, tablets are discoid in shape, although they can assume other forms. Their upper and lower surfaces may be flat, round, concave, or convex to various degrees. The tablets may be scored to facilitate breaking into halves, their top or lower surfaces embossed or engraved with symbols or letters for identification purposes.

The remaining specifications assure the manufacturer that the tablets do not vary from one production lot to another. In the case of new tablet formulations their therapeutic efficacy is demonstrated through clinical trials and it is the manufacturer's aim to reproduce the tablet with exact characteristics of the tablets that were used in the clinical evaluation of the dosage form. Therefore, from the control viewpoint, these specifications are important for reasons other than physical appearance.

1.2.1 Tablet thickness

At a constant compression load, tablet thickness varies with changes in the die fill and tablet weight, where as with a constant die fill, thickness varies with variations in compressive load. Three sets of factors influence tablet thickness and tablet thickness control. These are: the physical properties of the raw materials including crystal form and true and bulk densities; control of upper and lower punch lengths, which should be appropriately standardized; the granulation properties, including bulk density, particle size and particle size distribution (24,25).

Tablet thickness cannot be independently controlled, because it is related to tablet weight, which must also be closely adjusted and controlled, to compaction force, possibly to tablet friability, to tablet porosity, to drug release, and to bioavailability. Since we do not have the latitude to independently adjust tablet thickness, and as tablet thickness is often thought to be a specification of secondary importance to bioavailability, it is obvious that appropriate control of raw materials, machine operation and granulation properties is fundamental to the satisfactory control of the thickness specification in practice (25).

1.2.2 Tablet hardness

The resistance of the tablet to chipping, abrasion or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of a tablet is a function of many factors all working together. The three factors that were noted in the preceding section as being sources of variation in tablet thickness may also produce variations in tablet hardness. Hardness is a function of the applied pressure and is therefore a function of those factors which cause the force to vary. As additional pressure is applied

to make a tablet, the hardness values increase. This relationship holds up to a maximum value beyond which increases in pressure cause the tablet to laminate or cap, thus destroying the integrity of the tablet (1).

Factors that may alter tablet hardness in the course of a production run are substantial alterations in machine speed, a dirty worn camtrack, and changes in the particle size distribution of the granulation during the course of the run, which alters the weights of the fill in the dies. Dies having a light fill (large particles, low density) will produce a softer tablet than dies that receive a heavy fill (small particles, high-density. Lubricants can affect tablet hardness when used in too high a concentration or mixed for too long a period. The lubricants will coat the granulation particles and interfere with tablet bonding (26).

Hardness determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tablet machine. A hardness of about 5-kg is probably minimal for uncoated tablets, although some chewable tablets may be somewhat softer. If the tablet is too hard, it may not disintegrate in the required period of time, if it is too soft, it will not withstand the handling during packaging and shipping operations (1).

1.2.3 Tablet friability

Another approach to the measurement of tablet hardness is the use of friabilator. Rather than a measure of force required to crush a tablet, the friability measurement evaluates the ability of the tablet to withstand abrasion in packaging, handling and shipping. A number of tablets are weighed and placed in tumbling apparatus (e.g. Roche friabilator) where they

are exposed to rolling and repeated shocks resulting from free-falls within the apparatus. After a given number of rotations the tablets are weighed and the loss in weight indicates the ability of the tablets to withstand this type of wear.

1.2.4 Tablet weight

The volume fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill is adjusted to give the desired tablet weight. The weight of the tablet is the quantity of the granulation that contains the labeled amount of the therapeutic ingredient. After the tablet machine is in operation the weights of the tablets are checked routinely to insure that proper-weight tablets are being made. The USP has provided tolerances for the average weight of uncoated compressed tablets. Twenty tablets are weighed individually and the average weight calculated. The variation from the average weight in the weight of not more than two of the tablets must not differ by more than a given percentage of the mean weight. No tablet differs by more than double that percentage. Tablets that are coated are exempted from these requirements but must conform to the test for content uniformity if it is applicable (27,28).

The weight variation test is a satisfactory method of determining content uniformity of tablets, if: the tablet is all-drug (90% to 95%) or essentially all-active ingredient, or the uniformity of drug distribution of the granulation or powder from which the tablets are made is perfect (25).

For tablets such as aspirin tablets, which are usually 90% or more active ingredient, the ± 5% weight variation should come very close to defining true potency and content

uniformity (95 to 105% of label) if the average tablet weight is close to the theoretical average weight. The weight variation test is not sufficient to assure uniform potency of tablets of moderate to low-dose drugs, in which excipients make the bulk of the tablet weight (29).

The causes of weight variation can be separated into granulation problems and mechanical problems. The actual weight of tablet is determined by the geometry of the die and the position of the lower punch in the die as dictated by the weight adjustment cam. If every thing is working well mechanically, the weight can be caused to vary by a poorly flowing granulation, which causes a spasmodic filling of the dies (30). The improper mixing of the glidant into the granulation can influence the weight variation by not allowing uniform flow. If the granulation particle size is too great for the die size, the dies will not be uniformly filled, causing weight variation. Granulations that have a wide particle size distribution can have a localized non-uniformity of density in the granulation. With the geometry being fixed, non-uniform densities will cause varying amount of granulation to fill the dies, causing variations in the resulting tablets' weights. A wide particle size distribution can also be produced when the granulation has not been thoroughly mixed or when the granulation has been stored in an area where vibrations were present to cause particle segregation which produced a wide particle size distribution. It has been found that for a uniform size granulation, as the particle shape became angular, the weight variation increased (31). Mechanical problems can cause weight variation with a good granulation. A set of lower punches of non-uniform length will cause weight variations, as will lower punches that are dirty enough to restrict their movement to their lowest point during die fill (30).

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Generally, the following factors can cause weight variation: Poor granulation flow properties resulting in uneven die fill; a wide variation in granule particle size; difference in lower punch length; improper incorporation of glidant (granulation flow promoter); and tablet machines in mechanically poor condition or dirty (1).

1.2.5 Content uniformity

Official potency analytical methods generally require that a composite sample be taken of the tablets, ground up, mixed, and analyzed to produce an average potency value. In composite assays, individual discrepancies can be masked by the use of the blended sample. As shown in the preceding part, the use of weight can not be used as the potency indicator, except perhaps where the active ingredient is 90 to 95% of the total tablet weight. In tablets with smaller dosages, a good weight variation does not ensure good content uniformity, but a large weight variation precludes good content uniformity (25).

To ensure uniform potency for tablets of low-dose drugs, a content uniformity test is applied. In this test 30 tablets are randomly selected for the sample and at least 10 of them are assayed individually. Nine of the 10 tablets must not contain less than 85% or more than 115% of the labeled drug content. The tenth tablet must not contain less than 75% or more than 125% of label. If these conditions are not met, the remaining tablets of the 30 must be assayed individually, and none may fall outside the 85 to 115% range. In evaluating a particular lot of tablets, several samples of tablets should be taken from various parts of the production run to satisfy statistical procedures (32,33).

What appears to be a wide acceptance range (85% to 115%) for content uniformity can be difficult to achieve for low-dose tablet formulations. Three factors can directly contribute to content uniformity problems in tablets: non-uniform distribution of the drug substance throughout the powder mixture or granulation; segregation of the powder mixture or granulation during the various manufacturing processes; and tablet weight variation. The precision and variation of the assay used in the content uniformity test is also a factor that enters as a type of error in the determination of content uniformity.

The problem of non-uniform distribution in powder blends is due to lack of perfect physical mixture, i.e., uniform physical placement of the drug particles within the diluents and lack of statistical probability that all sections of the mix will contain a certain number of drug particles (25).

It is obvious that to achieve a reasonable content uniformity, there must be a large number of drug particles in every sample taken. If there are only three particles, on the average, of drug in a particular weight sample, an error of plus or minus one particle will constitute an error of 33% in the dose. If, on the other hand, there are an average of 100 particles of drug in every sample taken, an error of plus or minus one particle per sample is only an error of 1%. Increasing the number of particles, however, requires a reduction in drug particle size, which is some times negated because of the increased electrostatic effects and potential for segregation. The greatest potential for drug-diluent segregation in a tablet system occurs with powder or particulate mixtures intended for direct compression or with wet granulations in which drug migration is likely. In the first case, separation is promoted by vibration of the feed hopper or other parts of the machine, where differences in particle size and density of the drug and excipient will cause a consistent movement of the drug

throughout the bulk of the mixture. In such a situation, denser and smaller particles will sift through the bulk of the granulation and move downward, while lighter or larger particles will tend to float to the top of the bed. In the case of wet granulations, segregation is most likely to occur if the drug is very soluble in the granulating fluid and if a static drying method is used. As the granulating fluid (drug solvent) evaporates, the drug tends to be carried to the surface of the drying granulation. This migration destroys the homogeneous mix obtained prior to the drying step and reduces the chances of good content uniformity in the tablets, because the uniformity is now dependent on the mixing in the lubrication step (34).

In addition to the potency and content uniformity of solid pharmaceutical dosage forms, the pharmaceutical scientist should recognize a new concept, and that is the "effective drug content" of the product. This is not the amount of drug that is in the product and determined by assay. The effective drug content is the amount of drug in the product that is present in an absorbable or bioavailable form. Many controlled studies in humans indicate that the effective drug content of solid dosage forms is frequently not 100% of the assayable drug content of the product but may be as low as 50% or less of the labeled and assayed drug content. In addition, if certain manufacturing variables such as compressive load influence bioavailability, the effective drug content and effective drug content uniformity of a batch of tablets may be dependent upon both the actual drug content per tablet and the processing method and its variables employed to make that particular batch of product. The variation in effective drug content uniformity is undoubtedly much greater in certain cases than the chemical content uniformity indicates. To further complicate the matter, we now know that drugs which are subject to reduced effective drug content, and which may be further influenced by manufacturing methodology, are often critical in low-

dose drugs such as the anticoagulants. Obviously, extreme care in production control operations is required when manufacturing products of this type (35,36).

1.2.6 Tablet disintegration

It is generally recognized that the *in vitro* tablet disintegration test does not necessarily bear a relationship to *in vivo* action of solid dosage forms. To be absorbed, a drug substance must be in solution and the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. In the present disintegration test the particles are those, which will pass through a 10-mesh screen. In a comparison of disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster absorbed tablets had the longer disintegration times (37).

Regardless of the lack of significance as to *in vivo* action of the tablets, the test provides a means of control in assuring that a given tablet formula is the same as regards disintegration from one production batch to another. The disintegration test is used as a control to tablets intended to be administered by mouth, except where tablets are intended to be chewed before being swallowed or where tablets are designed to release drug substance over a period of time.

For compressed uncoated tablets, the testing fluid is usually water at 37^0 C, but in some cases the monographs direct that simulated gastric fluid TS (test solution) be used. For most uncoated tablets the disintegration time is 30 min when tested as directed in the

monographs. The conditions of the test are varied somewhat for coated tablets, buccal tablets, and sublingual tablets. For coated tablets up to 2 hrs may be required (28).

1.2.7 Tablet dissolution

Since a drug must normally be in solution before absorption can take place, orally administered tablets must have their drugs dissolved in the gastrointestinal tract before the absorption of the drugs can occur. Often, the rate of drug absorption is determined by the rate of drug dissolution from the tablet. Therefore, if it is important to quickly achieve peak blood levels for a drug (e.g., analgesic drugs), it will usually be important to obtain rapid drug dissolution from the tablet. For drugs that are absorbed high in the gastrointestinal tract (i.e., acidic drugs), which have a high dose and a low solubility, rapid dissolution may be especially important. The design of the tablet and the dissolution profile for such drugs may determine the total amount of drug absorbed as well as its rate of absorption. Thus, the rate of dissolution may be directly related to the efficacy of the tablet product as well as bioavailability differences between formulations. It is, therefore, important to evaluate whether a tablet releases its drug contents when placed into the environment of the gastrointestinal tract (38-40).

The most direct assessment of the drug's release would be *in vivo* bioavailability tests. However, there are several reasons that restrict the use of *in vivo* studies: length of time required, highly skilled personnel required especially for human studies, low precision of the measurements, inadequate discrimination between products, and a correlation with diseased state might have to be made with healthy human subjects or animals. The objectives of an *in vitro* dissolution test should be to show that: the release of the drug

from the tablet is as close to 100 % as possible, and the rate of the release is uniform batch to batch and is the same as the release rates from those batches proven to be bioavailable and clinically effective (25).

In a dissolution test, several requirements should be kept in mind. The dissolution test should be designed to be suitable for use with a wide range of drugs and dosage forms. The test should be able to meaningfully discriminate between formulations. There should be a reliable and reproducible assay for the drug being tested. The test should be simple to do, reproducible, and easily converted to an automatic system. Many different dissolution test apparatus have been reported in the literature. USP Apparatus 1 and 2 (basket and paddle, respectively) are the most commonly used (25).

Various parameters of the dissolution testing apparatus can affect the results. Water has been used as the preferred dissolution medium by some but is hardly the universal medium because of solubility restrictions and pH changes as the drug dissolves. In the latter case, the addition of appropriate buffers can solve the problem. The pH of the medium is important regarding the solubility and stability of some drugs and formulations. It is also important when trying to make the medium of dissolution reflect the medium at the site of absorption or above it in the gastrointestinal tract. For example, acidic drugs should be tested in an acidic medium, since for best absorption, they must dissolve in the stomach or upper small intestine. Dissolution testing of such drugs in a medium of pH 7.4, such as simulated intestinal fluid, would serve little purpose, since the acidic drugs would be nearly completely ionized and the absorption would be inhibited at that pH (40).

Equally important as running the dissolution test properly is proper interpretation of the resulting data. Dissolution results may be expressed in terms of the concentration of drug in the dissolution medium versus time; the amount of drug released from the dosage form versus time, or the amount of drug remaining unreleased from the dosage form versus time. Most commonly, the results are expressed in terms of the time required to release some percentage of the labeled amount of drug from the dosage form. For example, the USP specifies that 60% of the labeled amount of hydrochlorthiazide shall dissolve from hydrochlorthiazide tablets, USP, in not more than 30 min. Such expressions of dissolution and release characteristics suffer from the disadvantage that they do not account for the portion of the drug remaining unreleased. For example it is entirely possible that 60% of the labeled amount of hydrochlorthiazide could be released from a given tablet in 5 min. and also that 10% or more would never be released from the same tablet. Alternatively, it is possible for 60% to be released rapidly and for the remaining 40% to be released very slowly. Thus, the description of a dissolution process in terms of a single point in time is inherently risky. Such expressions are useful, however, for quality control purposes once the dissolution characteristics of a drug and dosage form are well understood. For tablet dosage form design purposes and for critical product comparisons, the time required for substantially complete (80 to 90%) release or amount released versus time profiles are the most desired data (38).

1.3 Tablet preparation

Final tablet characteristics, such as dissolution rates, disintegration time, porosity, friability, capping tendency, and hardness, are fundamental physicochemical properties of interest to the development pharmacist. Tablets are made from granular particulate solids; therefore, granulation characteristics are of interest as they can affect all of the

aforementioned performance characteristics of the final tablet, and others. The quality of tablets, once formulated, is as a general rule primarily dictated by the quality of the physicochemical properties of the granulation from which they are made. There are many formulation and process variables involved in the granulation step, and all of these can affect the characteristics of granulations produced.

The granulation characteristics that are probably of most immediate interest to development pharmacists and therefore the most universally measured are those of bulk density, some assessment of flow, particle size distribution, and some assessment of successful compaction into tablets. These basic granulation characteristics measurements have been used to develop and monitor the manufacture of the many successful pharmaceutical tablet products (2).

Many factors can affect granule structure, with the type of granulation equipment employed and amount of water used to granulate being most important (25). The structure of granules produced by spray drying are far different than those produced through an oscillating granulator, and in general, granulation equipment influence granule structure. Granules produced by spray drying are approximately spherical in shape, posses a narrow size distribution, and are often hollow. Therefore, spray-dried granulations are usually free-flowing, posses low bulk density, and dissolve rapidly. It has been shown that (2) the flow and compresional qualities of mannitol can be greatly improved by granulating this material by a spray congealing process. Fonner et al have shown that granules produced in a V-blender are more spherical and less dense than those produced in an oscillating granulator (1,25).

There are three general methods of tablet preparation: the wet-granulation method; the dry-granulation method, and direct compression.

1.3.1 Wet granulation method

The wet granulation method involves dampening or wet massing the tablet powder mixture with a liquid-adhesive granulating agent, that may be followed by wet screening or granulation to agglomerate the powder. The individual steps in the classical wet granulation process of tablet preparation include: weighing, milling, sieving, dry mixing, wet massing, granulation, drying, sizing, lubrication, and compression.

The greatest disadvantage of this process is the problem of reproducing a granulation from one lot to the next. Factors such as the chemical variation between lots of polymeric binding agents, differences in solvation of the polymers or gums in the granulating agent; moisture content, particle size, and other variables in the powders being granulated; amount of granulating agent added and rate of addition; wet-massing mixing time; rate of feeding the wetted powder to the granulating machine; and other variables can influence a range of properties of the resultant granulation. These granulation properties include particle size and particle size distribution, granule density and hardness, granule shape, granulation bulk density, compressibility and even drug content uniformity and bioavailability (1,2).

1.3.2 Dry granulation method

This method is also known as double "compression" or "slugging". Typically the process involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty

rotary tablet press. The slugged tablet is crude because of the poor compression properties of most powders. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillating granulator, and the resultant granules are lubricated and recompressed. The steps in the operation are basically the following, after weighing of the ingredients: mixing, compression (slugging), grinding (slug reduction or granulation), mixing (relubrication), and recompression. No wet binder or moisture is involved in any of the steps. The primary area of application of the method is accordingly the tableting of hydrolyzable or water-sensitive drugs. A less frequent application is the densification of a flocculant, low-density powder to permit compaction of a dose into a single tablet of reasonable size (25).

The slugging or double compression method requires fewer steps than wet granulation and avoids the time and handling required for a drying step. Dry binders such as spray dried or powdered acacia or microcrystalline cellulose may be added to the drug powder to permit the formation of a cohesive slug. It is usually necessary to add one or more lubricant materials to the powder to be slugged to reduce powder adhesion to the punches and to facilitate ejection of intact slugs from the dies. The result is that a typical tablet prepared by double compression contains lubricant throughout the tablet matrix and not simply at granule boundaries as in a wet granulated tablet. Because the double compression tableting process usually requires two lubrication steps, with most lubricants being water repellent, and tends to produce high density, hard tablets, drug dissolution and release are frequently retarded and drug bioavailability may be reduced (2).

The double compression method also has the disadvantage of being a slow production operation. The rate-limiting factor in double compression is the formation of the slugs

themselves. Very large heavy-duty rotary machines are used for slugging, to prepare slugs 1 to 2 inches in diameter and to produce the heavy compressive punch loads required (25).

1.3.3 The direct compression method

Direct compression is a method of tablet making in which:

a) crystalline drugs with intermediate to large doses are directly compressed without a prior granulation step, or

b) powdered drug is combined with a pre granulated or coarse particulate diluent and the mixture is directly compressed (25).

The great advantages of direct compression are the simplicity of the process, avoidance of the granulation step, avoidance of moisture and drying steps, minimal material handling, rapidity of the total process, and optimum possible bioavailability of drug from resulting tablet.

The process has no major disadvantages, but it has distinct limitations:

a) only a few crystalline drugs lend themselves to direct compression, e.g., sodium chloride, asprin or methenamine, and

b) when powdered drug is combined with pregranulated diluent, the drug content of the finished tablet often cannot exceed 20% to 25% of total weight without losing compressibility and tablet cohesion (39).

At the other extreme, potent drugs with doses below 10 to 25 mg may separate from the coarser diluent granulation in the hopper or feed frame, producing a nonuniform mixture

and lack of uniformity of content in the resultant tablets. When the drug has a low dose, a small particle size must be used to achieve uniformity of tablet content. The difference in particle size and density between the drug and the diluent may lead to stratification and separation of drug and diluent.

1.4 Process validation

After clinically effective formulations are obtained, variations among dosage units of a given batch, as well as batch-to-batch differences, are reduced to a minimum through proper in-process controls and good manufacturing practices. Process validation, which is part of the current good manufacturing practice (CGMP) principles, should be carried out as appropriate to minimize and control the stated variations among dosage units.

According to the FDA, process validation is defined as "establishing documented evidence which provides a high degree of assurance that a specific process, such as manufacturing of pharmaceutical dosage forms, will consistently produce a product meeting its predetermined specifications and quality characteristics"(41).

Assurance of product quality is derived from careful attention to a number of factors, including selection of quality components and materials, adequate product and process design, and statistical control of the process through in-process and end product testing.

The Current Good Manufacturing Practice (CGMP) guidelines requires (42):

a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of the manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include but are not limited to, the following where appropriate: a) tablet or capsule weight variation; b) disintegration time; c) adequacy of mixing to assure uniformity and homogeneity; d) dissolution time and rate; and e) clarity, completeness, or pH of solutions.

b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

The first four items listed in (a) are directly related to the manufacture and validation of solid dosage forms. Items "a" and "c" are normally associated with variability in the manufacturing process, while items "b" and "d" are usually influenced by the selection of the ingredients in the product formulation. With respect to content uniformity and unit potency control, adequacy of mixing to assure uniformity and homogeneity is considered a

high priority concern. Thus it is through careful design and validation of both the process and its control systems that a high degree of confidence can be established that all individual manufactured units of a given batch or succession of batches that meet specifications will be achieved.

Conventional quality control procedures for finished product testing encompass three basic steps (3):

a) establishment of specifications and performance characteristics;

b) selection of appropriate methodology, equipment, and instrumentation to ensure that testing of the product meets specifications; and

c) testing of the final product, using validated analytical and testing methods to ensure that finished product meets specifications.

With the emergence of the pharmaceutical process validation concept, the following four additional steps have been added:

d) qualification and validation of the processing facility and its equipment;

e) qualification and validation of the manufacturing process through appropriate means;

f) auditing, monitoring, sampling, or challenging the key steps in the process for conformance to in-process and final product specifications;

g) re-qualification and revalidation when there is a significant change in either the product or its manufacturing process. Thus, process validation encompasses a wider concept than the conventional quality control principles in assuring the quality of pharmaceutical products.

In general, process validation may be defined as the total activity, which shows that "the process will do what it is purported to do".

1.4.1 Why process validation?

An important concept in process validation is the axiom that "quality is not tested into a product but rather is built into a product". This is an important concept, since it serves to support the underline definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting and reevaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product. Furthermore, there are several reasons which necessitate pharmaceutical process validation documentation (43).

First, process validation documentation is a requirement by the drug regulatory authorities such as the FDA, as the "Good Housekeeping Seal of Approval", which shows that the manufacturing process is under the state of control. In the United States, a drug not produced in accordance with the CGMP, may be considered adulterated. As required under a new drug application (NDA), this final step is undertaken on the selected formulation after the process has been scaled up to full production batch size. Second, process validation should result in more technically and economically sound products and their manufacturing processes by avoiding or minimizing product recall and reprocessing activities. Third, the need to validate products will provide a great impetus to the optimization of product design and processing in the future, since the data base required for validation will often be largely adequate (if not totally, in some cases) for the necessary modeling and optimization.

1.4.2. Organizing for validation

Process validation work in the pharmaceutical industry is organized using one of the following structures: the consultant, the task force concept, or the dedicated group (64). Consultants are individuals or a group of persons hired by a company on a contractual basis. Consultants can be considered individuals who are immediately able to review processes and present protocols for validation. They are in a position to apply experience gained in other companies and fields to problems that individuals within the hiring company may not have anticipated. This also has the advantage of efficiency, because the company hiring the consultant will not need to go through the potentially time consuming and arduous task of recruiting individuals with highly specialized talents. Additionally, the workers associated with the consultant are not necessarily permanent members of the hiring company. This aspect is economically advantageous, since they will work on specific projects under contractual agreements with firm costs and completion dates. On the other hand, whereas the consultant who is hired has the necessary expertise, the training and experience of the team members associated with the consulting firm may be unacceptable.

The task force concept refers to the organizational approach in which the personnel assigned to the validation effort are individuals from various divisions within the company. When validation work is to be performed, the personnel meet as a committee consisting of members from each of the production, engineering, quality assurance, and research and development departments.

The major advantages of this approach are (3):

a) the task force members bring experience from a range of departments to apply to a related topic. When the job is complete, they can return full time to their previous functions. In this way, the need to hire full time professionals dedicated solely to validation work is avoided; and

b) the membership of the task force can change, depending on the work to be tackled. This is important if, for example, parenterals and solid dosage form products are to be investigated by the same task force. Generally, the requirements for sterile product validation are significantly different from those for nonsterile products.

The dedicated group describes a set of people whose principal task is that of validation. The validation department may exist as a subgroup within another larger department but it would normally be autonomous. The advantage of this type of organization is that the employs in such a group are totally dedicated to and responsible for the validation effort (44).

1.4.3 Process validation options

The guidelines on general principles of process validation mention three options. These are prospective process validation (also called pre-market validation), retrospective process validation, and revalidation. In actuality, there are four possible options (45).

A. Prospective process validation

In prospective process validation, an experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put into commercial use. Most validation efforts require some degree of prospective experimentations to generate validation support data. This particular type of process validation is normally carried out in connection with the introduction of new drug products and their manufacturing processes. The objective of prospective validation is to prove or to demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. The formalized process validation program should never be undertaken unless and until the following operations and procedures have been completed satisfactorily:

a) The facilities and equipment in which the process validation is to be conducted meet CGMP requirements (completion of installation qualification);

b) The operators and supervising personnel, who will be "running" the validation batch(es), have an understanding of the process and its requirements;

c) The design, selection, and optimization of the formula have been completed;

d) The qualification trials using (10x size) pilot-laboratory batches have been completed, in which the critical processing steps and process variables have been identified, and the provisional operational control limits for each critical test parameter have been provided;

e) Detailed technical information on the product and the manufacturing process have been provided, including documented evidence of product stability; and

f) Finally, at least one qualification trial of a pilot-production (100x size) batch has been made and shows, upon scale-up, that there were no significant deviations from the expected performance of the process (46).

In practice, usually two or three pilot-production (100x size) batches are prepared for validation purposes. This approach to validation is normally undertaken whenever a new formula, process and/or facility must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production (47).

B. Retrospective process validation

The retrospective validation option is chosen for established products whose manufacturing processes are considered stable (e.g., long-history state-of-control operation) and when, on the basis of economic considerations alone and resource limitations, prospective qualification and validation experimentation cannot be justified. Prior to undertaking retrospective validation, wherein the numerical in-process and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities, and subsystems used in connection with the manufacturing process must be qualified and validated in conformance with CGMP requirements (3).

Using data-based computer systems or manual methods, retrospective validation may be conducted in the following manner:

a) Gathering the numerical values from the completed batch record and include assay values, end-product test results, and in-process data;

b) Organizing these data in a chronological sequence, according to batch manufacturing data using a spreadsheet format;

c) Including data from at least the last 20-30 manufactured batches for analysis;

d) Trimming the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information;

e) Subjecting the resultant data to statistical analysis and evaluation;

f) Drawing conclusions as to the state of control of the manufacturing process based upon the analysis retrospective validation data; and

g) Issuing a report of the findings (documented evidence).

C. Concurrent validation

In-process monitoring of critical processing steps and end-product testing of current production can provide documented evidence to show that the manufacturing process is in a state of control. Such validation documentation can be provided from the test parameter and data sources disclosed in the section on retrospective validation.

Concurrent validation is defined as "establishing documented evidence that a process does what it purports to do based on information generated during actual implementation of the process". The protocol consists of a series of validated in-process tests to monitor the process and product release testing to assure compliance with the product's specifications. The protocol requires the kind of intensive testing that is normally associated with optimization and development. It can be considered a quality assurance tool if the activities are carried out in this fashion (3,47).

D. Revalidation

Conditions requiring revalidation study and documentation are listed as follows:

a) change in a critical component (usually refers to raw materials);

b) change or replacement in a critical piece of modular (capital) equipment;

c) change in a facility and/or plant (usually location or site);

d) significant (usually order of magnitude) increases or decreases in batch size; and

e) sequential batches that fail to meet product and process specifications.

Revalidation remains an important validation option and should be considered whenever the continued state of control and reliable performance of the manufacturing process are in doubt (47).

1.5 Validation of solid dosage forms

Validation may be defined as "a systematic approach to identifying, measuring, evaluating, documenting, and reevaluating a series of critical steps in the manufacturing process that require control to assure a reproducible final product". Four key elements were enumerated as forming the basis of prospective process validation (44):

a) definition of the desirable attributes of the drug product or components thereof, as well as those characteristics that are not desired;

b) establishment of limitations or constraints for those attributes;

c) determination of the controls or testing parameters that will be measured or tested; and

d) initiation of studies to establish control or boundary limits for those key attributes that influence the product, process, quality, and performance.

These criteria represent a logical progression of activities encompassing the development of a pharmaceutical product. The validation process begins with proper characterization, specification and control of raw materials, without which the foundation will be weak and will not support the evolving product when it is challenged during the formal validation of pilot and production batches.

1.5.1 Validation of raw materials

The validation process of a solid dosage form begins with a validation of the raw materials, both active ingredients and excipients (44). Variation in raw materials is one of the major causes of product variation or deviation from specification. The active ingredient may represent the most uncontrollable component in the complex product/process validation scheme. Characteristics such as drug morphology, particle size, surface area, color and other physical/chemical characteristics are important in assessing drug availability and reproducibility of subsequent manufacturing processes. For example, a water-insoluble drug, in order to achieve rapid dissolution and *in vivo* availability, is usually milled or micronized to achieve the desired particle size range. The particle size is usually inversely interrelated to surface area and, therefore, large surface area is created during particle reduction process. Particle size is directly interrelated to several key processing variables. Several of the most significant are flow, blend uniformity, granulation solution/binder uptake, compressibility and lubricant efficiency. In order to achieve a uniform blend of active ingredient with other formula components, either for subsequent wet granulation or direct compression processing, it is critical that active ingredient be compatible with other ingredients in terms of particle size, density and shape in order to permit a random distribution of ingredients within the blend prior to compression. If the milling or micronizing process is not controlled and properly validated

so as to achieve a reproducible particle size distribution, irregularities in blend distribution will result in content uniformity problems of the final dosage form (46).

This concept of particle control and the validation thereof is also important for excipients used in solid oral dosage forms. Variations in raw materials constitute one of the major sources of problems encountered during manufacturing. Variations in materials occur among different suppliers of the same product depending on the method of transportation chosen, the exposure of materials to undesirable conditions (heat, humidity, oxygen, light), the reliability of the supplier, and the individual supplier's conformance to regulatory requirements in terms of facilities, personnel, operating procedures and controls. In addition to the important physical characteristics of particle size, surface area, etc., mentioned above, the manufacturer should check the supplier's assay procedures as part of its own validation program. Other chemical characteristics such as water content, residue on ignition, and heavy metals should also be checked (45).

The steps involved in the validation of a raw materials or excipients follow those cited in the CGMPs and involve formal written documentation of those procedures and methods used as indicated below:

a) Each raw material should be validated by performing checks on several batches, preferably three, from the primary supplier as well as the alternate supplier. The batches chosen should be selected to represent the range of acceptable specifications, both high and low;

b) Depending on the acceptability of the raw material to aging, physical, chemical, or microbiological stability should be assessed. This is especially true for liquid or

semisolid ingredients where interaction with the container or permeability of the container to air and moisture could have a detrimental effect on the raw material;

c) Once the samples of raw materials have been selected as having fallen into an established, acceptable range of specifications and stability, it should be used to manufacture a batch of final dosage form. It may be appropriate to manufacture several lots of final product with raw material at high and low ends of the specification limit. Such testing would be especially useful when it is known that the product may be sensitive to small changes in the characteristics of the excipients or active ingredient; and

d) The final step of raw-material validation should involve an on-site inspection of the supplier to review the vendor's manufacturing operations and control procedures. The reliability of each vendor and how well each conforms to regulatory requirements must also be determined (44).

1.5.2 Control of process variables in the validation of solid dosage forms

Process validation can also be considered, as a means of challenging a process during development to determine which variables must be controlled to ensure the consistent production of an intermediate or final product. It also provides the means for an ongoing quality audit of the process during the marketing phase of the product to insure its compliance with the specifications.

The activity starts when the pharmaceutical development department begins its work. Pertinent data or information is collected during the pr-eformulation stage, and additional inputs are generated during formulation development and evaluation, process

development, and during full-scale manufacture. The information gathered in all four stages is evaluated to determine which parameters in the process can be used as possible tools to show that the product is under proper control. Once this is done, some other major steps taken in the development of a validation program are as follow (3):

a) obtaining test data to determine the numerical range of each parameter- e.g., assessing the tablet hardness over a series of batches that achieves an acceptable friability, disintegration, and dissolution;

b) establishing specification limits from the test data derived for a given parameter - based on the data collected, using statistical techniques to determine the extremes of acceptable hardness (high and low) that would provide 95% assurance that the friability, disintegration and dissolution specifications would be met (upper and lower control/release limits);

c) determining how well the specification limit indicates that the process is under control-challenge the process by producing product at the extremes of the specification limit to ensure all product specifications are met; and

d) certifying the equipment that is used in obtaining the data and controlling the process-ensuring that equipment operating conditions, e.g., speed of rotation, temperature, power utilization, are within specification limits under variations of product load.

Once this has been done, one can proceed to actual product testing utilizing these parameters and their specifications to validate that the process will produce acceptable product. Each product may have its own idiosyncrasies requiring special tests, but generally the tests that would be required for all solid dosage forms in process validation are as follows:

a) Moisture (total volatile) content as "dry" granulation - Has granulation solvent been removed to a sufficient extent during the drying operation (usually less than 1% moisture)?

b) Content uniformity of the blend and the final dosage form- across the blend or batch profile sampling at various points. Does the content uniformity comply with compendial standards (± 15% of labeled amount) or other internal standards? Is there demixing during the tablet manufacturing operation, e.g., segregation during flow of granulation from a storage bin?

c) Hardness- the relationship between tablet hardness, thickness, friability and release characteristics must be clearly defined.

d) Disintegration and dissolution- important to ensure proper drug release characteristics (in vitro availability) and batch-to-batch uniformity.

e) Friability- an important characteristic to interrelate to the extent tablet will chip, crack, or "dust" during the packaging operations.

f) Weight variation- throughout the batch sampling. Normally attempt to achieve weight variation of less than 5% from the average. If this is not achieved, problems related to poor granulation flow and equipment problems may be suspect.

g) Granulation particle size distribution- an extremely important parameter that affects tablet compressibility, hardness, thickness, disintegration, dissolution, weight variation, and content uniformity. This parameter should be monitored throughout the tablet validation process (46).

These key test parameters are the yardsticks by which the major processing variables in solid dosage forms are evaluated. These variables include mixing time and speed of

rotation (rpm) in blenders and granulators; solvent addition rates in granulators; time, temperature, and air flow conditions in dryers and coaters; screen size and feed rate in mills; tablet machine speed and compression force in tablet presses; and machine speed and fill volume in encapsulators. Process validation testing is generally done on the first three batches of product made in production size equipment. Therefore, revalidation testing is only done when a "significant" change has occurred. A significant change is one that will alter the in-process or final formula specification established during the validation program or a change in formula, process, or equipment (3).

1.6 Method of process validation employed and tablet products chosen in this investigation

Of the four options of process validation methods (prospective, concurrent, retrospective and revalidation) described above, concurrent process validation method was employed in this study. Three tablet products, chloroquine phosphate, paracetamol and frusemide, were selected for the validation work. These three products were selected because they have different physical, chemical and processing properties. The solubility and bioavailability characteristics of these drugs are shown in Table 1.1.

As could be seen from the table, choroquine phosphate is very soluble, paracetamol slightly soluble, and frusemide practically insoluble in aqueous medium. They also differ in their bioavailability characteristics. Paracetamol is very susceptible to capping (48-50), whereas this processing problem was not reported for the other two. Furthermore, frusemide is a low dose drug (the proportion of active ingredient is less than 50 % of the

total tablet weight) which can pose homogeneity problems during mixing with the other tableting additives resulting in variations in content uniformity.

Table 1.1: Physical characteristics and GI absorption profile of the drugs selected for validation study (2).

Drug	**Powder morphology**	**Aqueous solubility**	**Absorption characteristics**
Chloroquine phosphate	White or almost white powder, hygroscopic. Exists in two morphologic forms one melting at about 195^0 and the other at about 215^0.	Freely soluble in water.	Rapidly and almost completely absorbed from the GIT.
Paracetamol	A white crystalline powder.	Sparingly soluble in water, (1:70), soluble 1 in 20 of boiling water.	Rapidly and almost completely absorbed from the GIT.
Frusemide	A white or yellow crystalline powder.	Practically insoluble in water.	Fairly rapidly absorbed.

1.7 Objectives of the present work

1.7.1 General objective

To validate tablet manufacturing process in the Ethiopian Pharmaceuticals Manufacturing Enterprise (EPHARM), using concurrent process validation method.

This study was necessitated by the fact that similar process validation study, designed and conducted scientifically, and documented has never been undertaken, at least during the

last 20 or so years, of the company's existence. Furthermore, even if both the formulation and the process might have been validated initially, there might have been major changes in the manufacturing process, such as changes in the manufacturing equipment, changes in the raw materials (the active ingredients or the other additives) etc. during latter years, which would necessitate revalidation but there is no documented evidence in the factory to that effect.

1.7.2 Specific Objectives

I. To evaluate if all systems, subsystems, and unit operations of the tablet manufacturing process in EPHARM perform as intended, reproducibly and/or consistently, using concurrent process validation technique and through testing of certain parameters of process outputs (intermediates, bulk products, finished products, etc.), and by comparing the results of the test parameters with the set specifications, if available, and compendial specifications or specifications generally accepted by most of the pharmaceutical manufacturing companies through measuring or testing of the following quality specifications (parameters) on appropriate samples:

   a) Granule particle size and size distribution;

   b) Granule flow characteristics (repose angle);

   c) Granule moisture content and bulk density;

   d) Tablet hardness, thickness and friability;

   e) Tablet weight variation;

   f) Tablet dissolution rate;

   g) Tablet content uniformity and average potency;

II. To evaluate the adequacy of the facility and equipment, with regard to the CGMP, used in the tablet manufacturing process.

III. To evaluate the standard operating procedure (SOP), with regard to clarity and detail, and see whether the SOP is strictly followed or not and make recommendations, if necessary, for improvement and further study.

2. EXPERIMENTAL

2.1 Materials and methods

2.1.1 Materials

Materials used in the products studied in this investigation were chloroquine phosphate, supplied by Shanghai Medicines & Health products, China; paracetamol by Tiangin, China; and frusemide by IPCA, India. Starch, lactose (anhydrous), gelatin, magnesium stearate, talc, colloidal silicone dioxide, PVP, and glycerin were all of BP/Ph.Eur. grade. All were imported and quality approval (certificate of analysis) has been submitted by both the suppliers and EPHARM Quality Control Department. Analytical grade chemicals were used in the preparation of buffers and reagents. Reference standards used in the calibration curves were USP grade standards.

2.1.2 Methods

2.1.2.1 Tablet manufacturing method

All of the three products investigated, chloroquine phosphate, paracetamol, and frusemide were prepared by the wet granulation process. The formulations used are shown in Tables 2.1-2.3. The preblends, (part A, of the tables), were weighed and transferred to a high shear, high speed mixer granulator (Zancheta, Roto 300G), equipped with a sigma blade and a chopper. The preblends were mixed for three minutes in all cases. Then the adhesive solution, (part B of the tables), prepared in a steam jacketed pan, was added through a sucker sprayer and granulation continued for 10 min. in the case of chloroquine phosphate and frusemide and for 20 min. in the case of paracetamol with the chopper on. Then the wet mass was transferred

directly to the container of the drier and drying commenced in a fluid bed drier (AEROMATIC Type T 5).

Table 2.1: Chloroquine phosphate 250 mg, tablet formulation

Part	**Raw material**	**Amount used**
A	Chloroquine phosphate	100.00 kg
	Starch	20.00 kg
B	Distilled water	25 liters
	Starch (for paste)	3.00 kg
	Gelatin	2.00 kg
C	Dried starch	3 %
	Talc	1 %
	Magnesium stearate	1.5 %
	Aerosil	0.5 %

The drying process continued for unspecified time, which varied from one to one and half hours for each container load. The thermostat of the drier was set at 80^0 C. The "dry" granules were then screened using Fitz mill (the Fitzpatrick company, model DA06) by passing through mesh No. 12 in each case. The granules were then weighed and transferred to a double cone mixer, the disintegrant and the lubricants (part C) were weighed and transferred to the mixer and mixed with the granules for about 5 min (4 to 6 min). The granules were then compressed in rotary tablet presses of different capacity (16 to 32 punches). All the compression machines were Manesty models except one, Ronchi model.

Table 2.2: Paracetamol 500 mg, tablet formulation

Part	Raw material	Amount used
A	**Paracetamol**	**100.00 kg**
	Starch	14.00 kg
B	Distilled water	26 liters
	PVP	4.00 kg
C	Glycerin	200 cc.
	Dried starch	6%
	Aerosil	0.5%
	Magnesium Stearate	0.5%

Weight adjustment was done by weighing tablet samples until the desired weight was achieved by machine operators and then periodically (every 15 min.) by taking samples and using control charts by the QC in-process control section. The other in-process control parameters that were being monitored were tablet appearance (sticking, capping, etc.), disintegration time and friability characteristics. Dissolution, hardness and thickness were not being monitored. Granulation characteristics such as particle size distribution and moisture content were not being checked. No specification limit is available for these granulation parameters.

Table 2.3: Frusemide 40 mg, tablet formulation

Part	Raw material	Amount used
A	Frusemide	21.00 kg
	Starch	13.65 kg
B	Lactose	31.50 kg
	Distilled water	22.0 liters
	Starch (for paste)	4.18 kg
	Gelatin	1.425 kg
	Nipagin	13.062 gm
	Nipasol	13.062 gm
C	Magnesium stearate	0.684 kg
	Dried starch	1.724 kg

2.1.2.2 Process Validation Method

Granule particle size distribution

Sieve analysis was carried out on 50 gm. samples, taken at random from different parts the containers (plastic drums), of the "dry" granules using BS 410/1986 ENDECOTTS LTD. laboratory test sieves and OCTAGON 200 test sieve shaker at amplitude of 5 for 10 min. Weight fraction retained on each sieve was determined on an analytical balance (SCALTEC SBC 31). Arithmetic mean diameter of the granules was calculated and frequency and cumulative frequency plots of particle size distribution were constructed. The results are mean values of three determinations.

Moisture content

Granule moisture content (total volatiles) was determined on five-gram samples, taken at random from different parts the containers (plastic drums), using SARTORIOUS model 7393A moisture balance (220v) by exposing the sample for 10 min. The loss in weight value obtained in this way was converted to percent moisture content. Average of three determinations was taken for each sample.

Determination of angle of repose of granules

The fixed cone method was used in the determination of angle of repose. A glass funnel, the stem length of which was 4 cm and the internal diameter (i. d.) 6.5 mm., measured using caliper, was fixed at 2.5 cm. above a horizontal surface. The granules were introduced and the cones formed on a piece of arithmetic grid a paper. Cone diameter was measured in cm. and the results were average of three determinations. The angle of repose, θ, was calculated as:

$$\theta = \tan\text{-}1\ h/r \qquad (2.1)$$

Where h is height of the cone in cm.; and r, radius of the cone in cm.

Granule bulk density

100 g of granule (unless stated otherwise) was accurately weighed and transferred to a measuring cylinder (250 cc), the volume noted, and then tapped on a tapping machine (Tapped volumeter, Type SVM 20, ERWEKA, Germany) 500 times.

The bulk density of the granules, ρb, was calculated as:

$$\rho b = \text{weight of granule, gm/tapped volume of the granule, ml.} \qquad (2.2)$$

Percent compressibility (%C), was also calculated:

$$\%C = \frac{(\rho b - \rho u)}{\rho b} \times 100 \qquad (2.3)$$

Where ρb is tapped bulk density, and ρu, untapped bulk density.

Tablet hardness

Hardness (crushing strength) test was performed on 20 tablets randomly selected from each batch using ERWEKA Type TB 24 hardness tester. The measurement was in kilograms and the average value calculated.

Tablet thickness

Thickness test was performed on 20 tablets, randomly selected from the each batch. Thickness, in mm., was measured using micrometers (Griffin & George, London) to within ±1 mm.

Tablet friability

Friability test was performed on 20 tablets from each batch and the average value taken. The tablets were placed on a No 10 sieve, dusted using soft brush, weighed on an analytical

balance (SCALTEC SBC 31) to four significant figures. Then placed in ERWEKA (Germany) Type T friability tester (which complies with the USP 23 specifications), and revolved for 4 min. at 25 revolutions per min. (total of 100 revolutions). The tablets were then withdrawn, dusted in a similar manner as before on No 10 sieve, and re-weighed. The difference in weight was taken and the % loss in weight calculated.

Tablet disintegration time

Disintegration test was carried out on each of 6 tablets, selected at random from each batch. The medium was distilled water, equilibrated at 37 ± 2 ^{0}C, in an ERWEKA Type 2T3 disintegration test apparatus conforming to USP 23 specifications. Average disintegration time was calculated. The tablets were considered disintegrated when all the particles passed through sieve No 10.

Dissolution

Chloroquine phosphate

The dissolution rate was determined on three tablets of each batch in distilled water (1000 ml), in a paddle stirrer assembly (ERWEKA, Germany, Type DT6), which meets the USP 23 specifications. The stirrer speed was 100 rpm. The temperature of the assembly was maintained at 37 ± 0.5 ^{0}C by a thermostatically controlled water bath. At times 0, 5, 10, 15, 20, 30 and 40 min, 5 ml of the dissolution medium was withdrawn and replaced with 5 ml of fresh medium at the same temperature. The absorbance was measured at 343 nm using CECIL

CE 4400 spectrophotometer. The measurement was an average of three determinations and the amount of drug dissolved at each time interval was calculated from a calibration curve.

Paracetamol

The dissolution rate was determined on three tablets of each batch in pH 5.8 phosphate buffer (1000 ml), in a paddle stirrer assembly (ERWEKA, Germany, Type DT6), described above. The stirrer speed was 50 rpm. The temperature of the assembly was maintained at 37 ± 0.5 ^{0}C. At times 0, 5, 10, 15, 20, 30 and 40 min, 5 ml of the dissolution medium was withdrawn and replaced with 5 ml of fresh medium at the same temperature. The withdrawn samples were filtered, diluted with the phosphate buffer, and the absorbance measured at 243 nm using CECIL CE 4400 spectrophotometer. The measurement was an average of three determinations and the amount of drug dissolved at each time interval was calculated from a calibration curve.

Frusemide

The procedure, the medium and the equipment used was the same as for paracetamol except that the absorbance was measured at 274 nm.

Uniformity of dosage units' test

Weight variation

20 tablets from each sample, selected at random from each batch of the products selected, were weighed individually to within ±1 mg using analytical balance (SCALTEC SBC 31)

which was previously calibrated. Average weight, standard deviation and coefficient of variation were calculated.

Content uniformity

Content uniformity test was performed on each of 10 tablets, taken at random, from each of the 5 batches of frusemide. The tablets were powdered individually, transferred to a 100 ml volumetric flask; about 60 ml of 0.1N NaOH solution was added and shaken for 10 min. on a magnetic stirrer. Sufficient 0.1N NaOH solution was added to produce 100 ml, filtered and 5 ml of the filtrate was diluted to 250 ml with 0.1N NaOH solution. The absorbance of the resulting solution was measured spectrophotometrically at 271 nm using CECIL model CE 4400 spectrophotometer. The content of frusemide was calculated from a calibration curve.

3. RESULTS AND DISCUSSION

3. RESULTS AND DISCUSSION

3.1 Observations and comments on the manufacturing process

a) The granulation machine did not have electronic control mechanism for the determination of granulation end point. This decision was left for the operators, whose level of training and experience can vary. Neither did the machine have control mechanism for controlling the mixing speed and intensity. Since usually the granulation stage is one of the most critical steps in the manufacturing process of compressed tablets strict control mechanism should be instituted to get reproducible results in the quality of the process output (the granules).

b) Screening of the wet mass was omitted. The wet mass was transferred from the granulating machine to the container of the drier directly. Avoiding screening of the wet mass might be acceptable in some kind of mixer-granulators but the influence of this procedure on the characteristics of the granules such as particle size and size distribution, particle shape, etc. should be carefully evaluated.

c) The inlet air temperature, the outlet air temperature, and the air velocity gauges of the drier, (fluid bed drier, AEROMATIC Type T.5) were not functional. Several factors can be affected by the level of moisture of granules, such as flowability, tablet hardness and drug stability. Therefore, this stage of the manufacturing operation should be closely monitored and specified including machine operational qualification.

d) Similar problems could be observed at the granule milling or sizing stage. Variables such as the machine (Fitz mill) speed and rate of feeding granules to the machine were not properly controlled. Screen size used in the mill for all the three products was the same (mesh No 12). These factors which can influence the size and distribution of the particles need to be properly controlled.

e) Tablet presses lack electronic devices to monitor machine speed (rpm), tablet weight control, compression force control etc. Therefore, the tablet presses need to be upgraded to conform to the current good manufacturing practice (CGMP) requirements regarding machine installation qualification and operational qualification.

f) Machine cleaning and maintenance procedure and documentations thereof, were not available and there were no logbooks for the machines. This important to maintain the machines in good working condition and to avoid cross contamination and other processing problems.

g) Machine operators and other workers were not given on job training.. All of the professional staff has their first degrees only (in pharmacy). Given the complexity of the work they are involved in, this may not be sufficient unless backed by proper on job training or higher education.

The reason why these manufacturing problems were not solved or not properly controlled in EPHARM even though the company was in the drug manufacturing business for many years could be because of lack of well trained and experienced personnel in the area of CGMP principles in general and process validation in particular.

3.2 Granulation properties

3.2.1 Particle size and size distribution

Tablet manufacturing involves compressing crystalline or granular solids in a die between two punches under pressure, which is in the range of pounds per square inch. Powders resist compression into tablets because of entrapped air in the powder bed, and poor particle-particle adhesion during compression.

Furthermore, powders generally have poor flow properties, which can result in a wide variation in tablet weight, and other tableting properties. To overcome the compression and flow problems of tablets, granulations are prepared. Granulations are agglomerated powders in which the powder particles are bonded together by adhesive materials, pressure or both into occluded particles as large as 6 to 8 mesh and as small as 40 to 80 mesh (1).

Satisfactory granulation is the key step in tablet making. Reproducing from lot to lot of granulation properties such as particle size and size distribution; granule density and hardness; granule shape; granulation bulk density, compressibility, and even content uniformity and bioavailability are problems encountered in wet granulation.

There are several formulation and processing variables, which will contribute to variations in the granulation properties cited above. Some of these variables are chemical variations between polymeric binding agents; moisture content, particle size etc. of the powders being granulated; amount of granulating agent added and rate of addition; wet massing mixing time; rate of feeding the wetted mass to the granulating machine. Therefore, close monitoring of these variables through standardization of the processing methods is important to achieve uniform product specifications, which is a constant goal of a pharmaceutical industry.

An important requirement of tablet formulations is that the powder or granular material posses uniform and free flowing properties. The ability of particulate matter to flow into the dies in a reproducible manner results in uniform tablet weights and uniform doses of active ingredients as well as increased production rates. Particle size and size distribution

is an important parameter in the production of uniform tablets. Arambulo *et al* (51) found that as the granule size was decreased, the variation in the tablet weight decreased reaching a minimum weight variation at 400 - 800 μ granule diameter. Further reduction in granule size led to an increase in tablet weight variation. Particle size distribution, and other particulate properties, by affecting the internal flow and segregation of a granulation, can vary the composition of compressed tablets. Granule particle size also influences the in vivo drug dissolution release. It has been shown that 40 to 60 mesh granules of salicylic acid had much slower rate of dissolution than the 60 to 80 mesh particles (52).

The incidence of capping also increases with decreasing granule size. Forlano and Chapkin (53) reported that with tablets prepared with sodium bicarbonate/starch granules granulated with 10 % acacia, percent of capping increased as particle size decreased following 60 mesh. These investigators have shown that with sodium bicarbonate and lactose, the disintegration time decreased, binding of punches and dics increased, and percent of capping increased in the vicinity of 40 to 80 mesh. They have defined particles of this size range as "fines". Even though it is difficult to generalize, an excess of these particles and smaller ones (30 % w/w or more) can be detrimental to the compression of satisfactory tablets. The effect of powder particle size and size distribution on powder flow characteristics has also been investigated. Gold *et al* (54) have shown that in binary mixtures, a strong negative correlation existed between flow rates of granules and proportion of particles less than 100 mesh in size.

Granule size distribution is best determined by sieving procedures using standard test sieves and test sieve shakers. The size distribution of granules tested in this investigation is

shown in Figure 3.1-3.6. As could be seen from the frequency the cumulative frequency versus mean particle diameter plots, the particle size distribution is wide non-symmetrical and the proportion of "fines", particles ≤ 215 μm (mesh No. 60), is 34% - 77% for chloroquine phosphate, 20% - 30% for paracetamol, and 18% - 28% for frusemide. Thus, it can be seen that the proportion of "fines" is high (more than 30%) particularly in chloroquine phosphate granules.

Average particle size (arithmetic mean diameter) of batches of granules tested was calculated. Except for some batches of chloroquine phosphate, the average granule size is between 400 and 800 μm, the required size range as stated by Arambulo *et al* (51). But the particle size distribution, as could be seen from the bar graphs, is wide and non-symmetrical (skewed) in all of the granules investigated.

With regard to particle size distribution and proportion of fines, it can be seen that paracetamol and frusemide granules could be considered to be in a suitable size range theoretically, while those of chloroquine phosphate were not. But the level of fines in a granulation that can be tolerated without producing processing problems such as flow, weight variation, capping, and sticking in tablets, should be practically determined for each product.

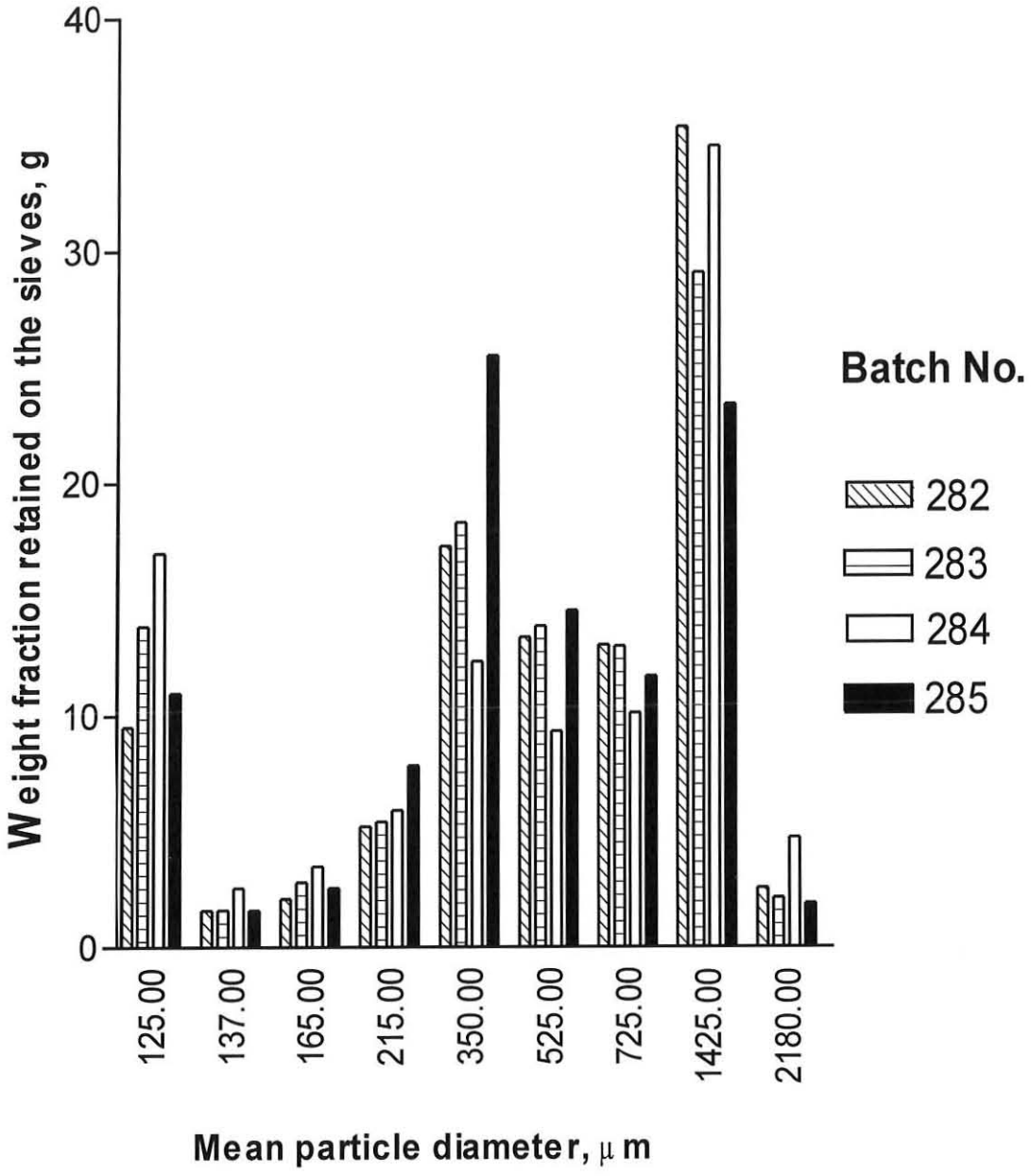

Figure 3.1: Frequency particle size distribution of chloroquine phosphate granules

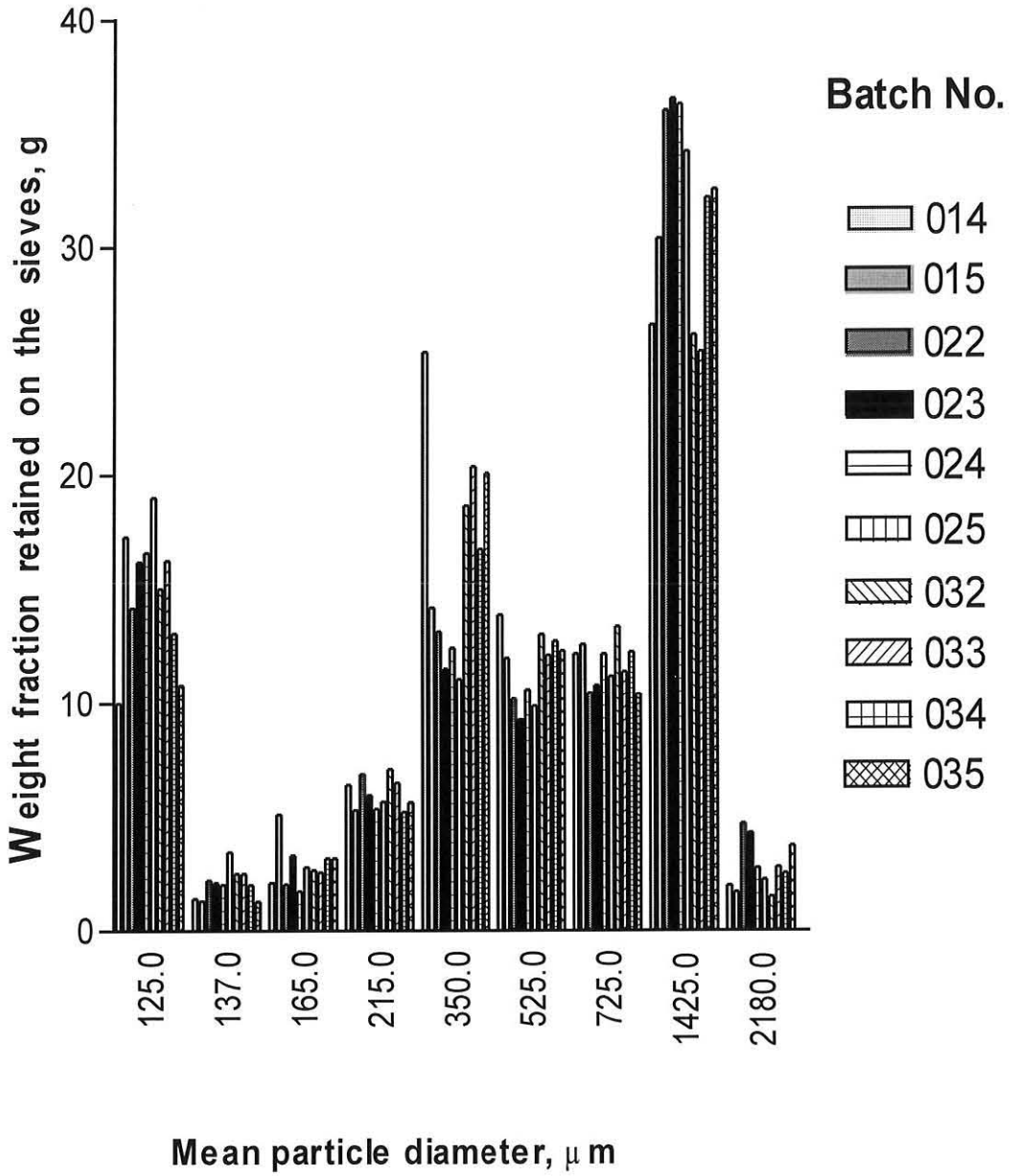

Figure 3.3: Frequency particle size distribution of paracetamol granules

Furthermore, inter-batch variation in granule size distribution was checked using statistical methods. When one way analysis of variance (one way ANOVA) test is applied to the sieve analysis data of different batches produced on different days, no statistically significant variation was observed at $p < 0.05$ for paracetamol and frusemide granules indicating good reproducibility of the granulation process. But significant variation was observed in the case of chloroquine phosphate granules.

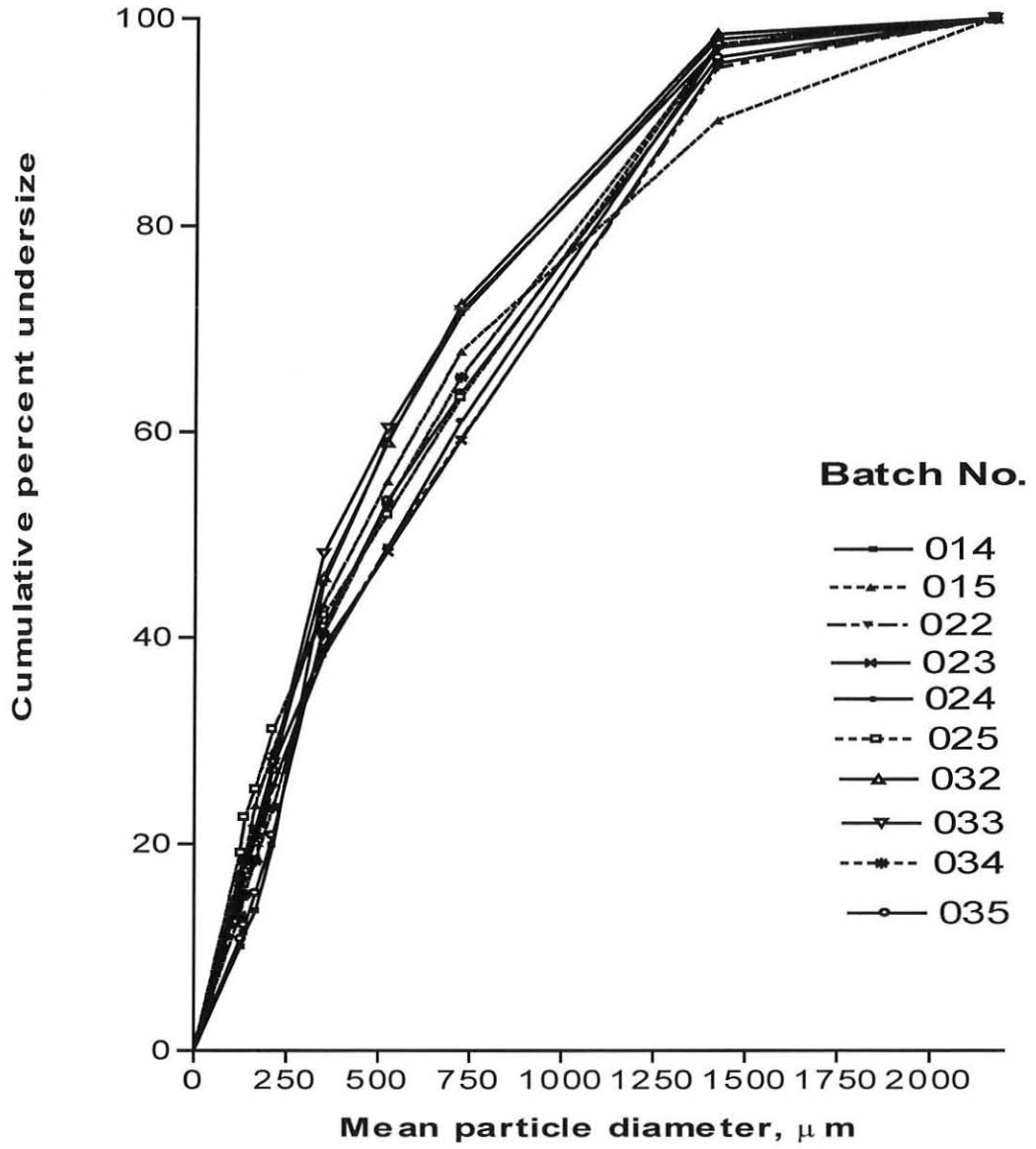

Figure 3.4: Cumulative frequency particle size distribution of paracetamol granules.

Generally, it might be concluded that the granulation process was not reproducible and good quality granules were not being produced at least for chloroquine phosphate. The optimization process must concentrate on the areas of granulation, drying and sieving processes to minimize the proportion of fines since each of this unit operations could have contributed individually or together to the excess proportion of fines observed. It should be remembered that the amount of what could be considered "fines" should be determined for each product and that up to 10 % fines are usually sought for good granulation flow.

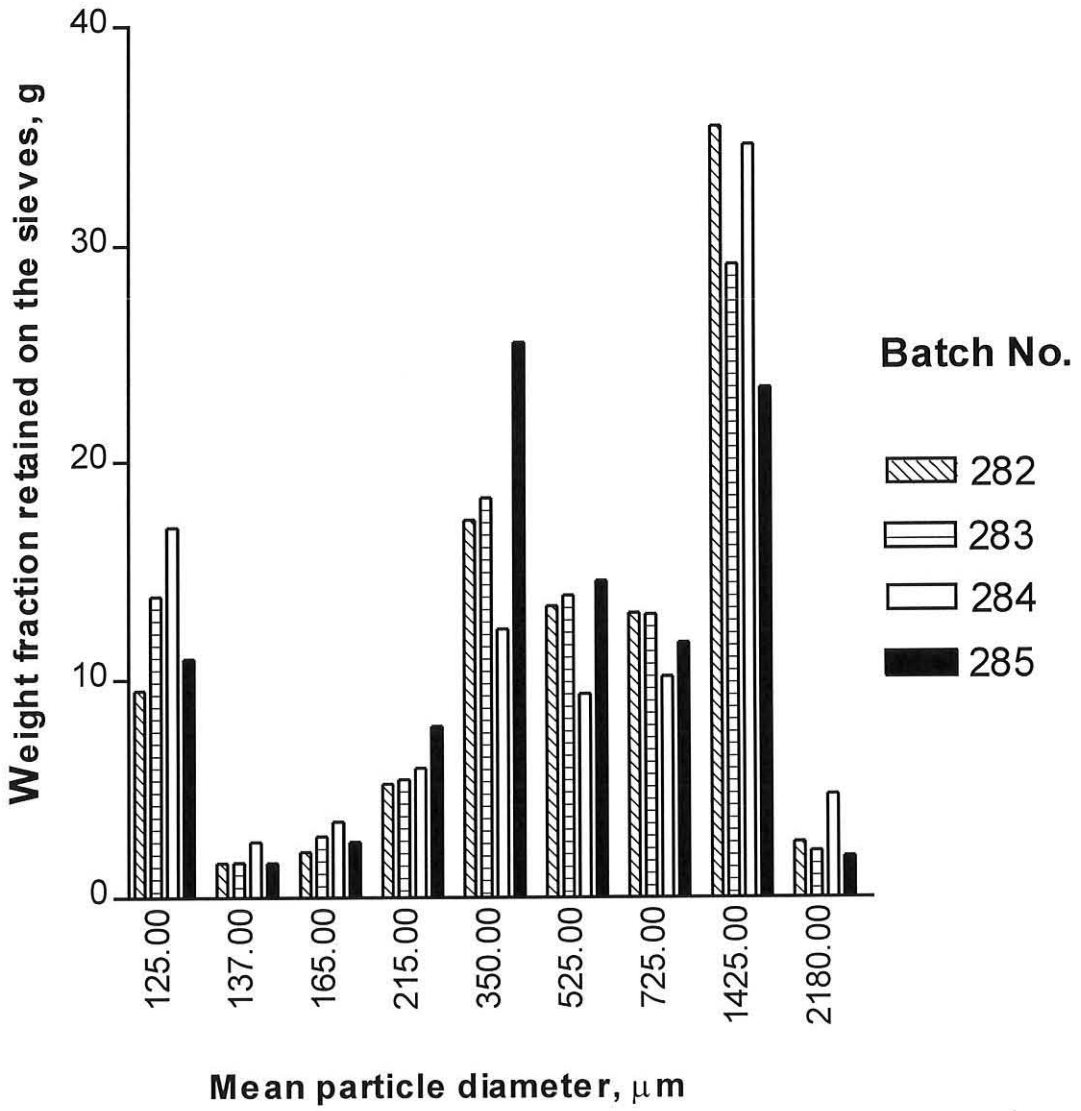

Figure 3.5: Frequency particle size distribution of frusemide granules

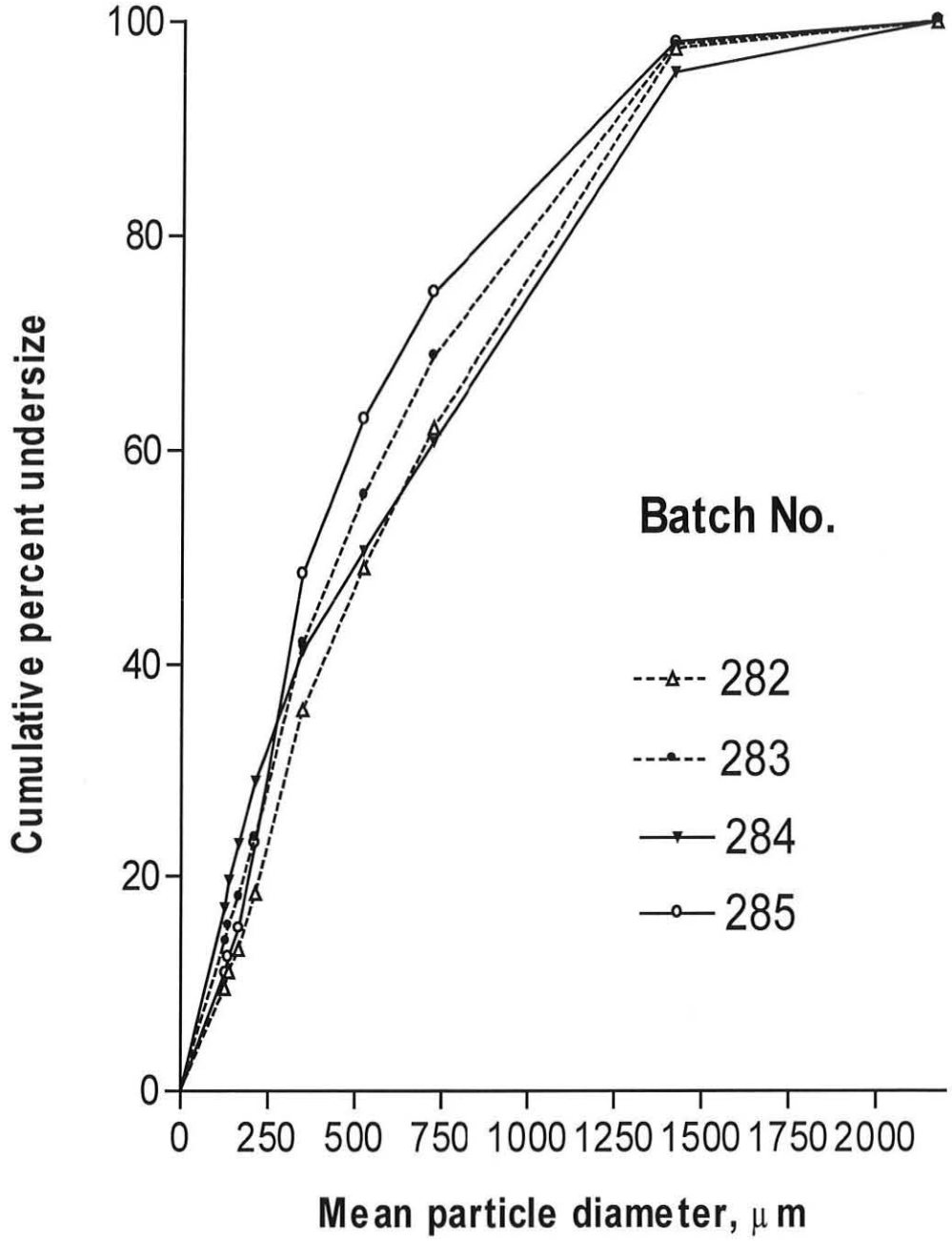

Figure 3.6: Cumulative frequency particle size distribution of frusemide granules.

3.2.2 Granule flow characteristics (angle of repose of granules)

Particle shape and size distribution are important factors in packing and flow. Particles of more regular shape (nearly spherical) led to lower angles of repose and higher bulk densities. In general these effects should result in better granule flow properties, hence smaller tablet weight variation and a more efficient compression/consolidation tableting sequence.

According to Pilpel (55), angle of repose, θ, is a measure of forces operating between particles. These forces are: a) frictional forces; b) surface tension forces due to the possible presence on the particles of adsorbed films of gas and/or moisture; c) mechanical forces caused by interlocking of particles of irregular shape; and d) electrostatic forces which arise from friction between particles. He has also shown that θ varies directly with the weight fraction of fines (< 150 μ) present in a coarse granulation. With fine powders (≤ 150 μm), the magnitude of frictional and van der Waals forces usually predominate (55). However, surface tension forces between particles can be significant where capillary condensation can occur (25,56-58). Thus, small liquid bridges can be formed between particles if moisture content is high or particles are exposed to high humidities (60% relative humidity). Surface tension forces resulting from absorbed films of gasses are generally quite small and not significant in comparison to other forces acting between particles. Although electrostatic forces of a magnitude greater than van der Waals forces are theoretically possible, the usual presence of even minute quantities of water are sufficient to minimize the effect of electrostatic forces. For larger particles (≥ 150 μm), such as granules produced by a wet granulation technique, frictional forces normally predominate over van der Waals forces (59). Thus when evaluating inter-particle forces of

granules, agglomerates or other large particles, cohesive or van der Waals are often assumed to be insignificant or equal to zero. The gravitational effect of large particles will normally overwhelm any effects due to van der Waals forces.

The effect of moisture on the angle of repose, θ, has been determined (60,61). It was reported that the angle of repose, θ, of starch powder increased with equilibrium moisture content at different relative humidities. This is attributed to the increase in the adhesive forces between the particles due to the presence of a moisture film on their surface. These workers have also observed that fine powders such as light magnesium oxide by coating the surface of particles can reduce θ and make particles free flowing. This is because the presence of powder coat increases the distance between particles and reduces the van der Waal's attractive forces between them. As a result, θ decreases and powder flow characteristics improves.

According to Craik and Miller (60), the angle of repose corresponds qualitatively to the flow properties of a powder. A high angle (e.g. 50^0 to 60^0) is obtained for powders, which form large aggregates and can be caused to flow only with difficulty; while a low angle (30^0 to 40^0) is obtained for powders which acquire a smooth surface and flow easily. He suggested that, since the method provides a reproducible numerical value, it is reasonable to adopt it as a measurement of the flow properties of powders.

Jones and Pilpel (57) have enumerated the applications of the principle of repose angle as follows:

a) Angle of repose, θ, can be successfully applied to control excessive moisture in powders and granulations.

b) Since the presence of fine particles in granulations produces changes in the value of θ, methods, which do not cause segregation of material, may be used as a control over excessive fines produced during handling.

c) Flowability: An increase in the static angle of repose, θ, reflects a decrease in flow rate. In general, if $\theta < 40^0$ a material will flow easily through orifices and from hoppers. When the angle exceeds 50^0, flow takes place with difficulty and aggregation, "rat holing" bridging may occur.

The use of angle of repose as a measure of powder flow property was criticized on the ground that:

a) No direct correlation could be found between angle of repose and flow;

b) The magnitude of the angle is dependent on the numerous methods by which it is measured and the condition of measurement.

Train (59), in a critical examination of four methods, {(i) fixed funnel free standing cone; (ii) fixed bed cone; (iii) tilting box; and (iv) revolving cylinder}, of determining angle of repose, θ, concluded that the type of method influenced the results but most methods of measurement would provide suitable data for comparison between samples during routine quality control tests.

As could be seen in the Table 3.1, the angle of repose, θ, values of granules measured in this study lie between 29^0 and 34.5^0. Since the angle of repose measured in this investigation for all of the samples of granules tested is less than 40^0, it can be said that the granules were free flowing. This is so probably because the granules were smooth and were of suitable shape (nearly spherical) which was observed during sieve analysis.

Table 3.1: Angle of repose (θ) values of granules

Chloroquine phosphate		Paracetamol		Frusemide	
Batch No.	θ	Batch No.	θ	Batch No.	θ
285	32.5^o	014	30.9^o	282	30.6^o
275	31.2^o	015	32.1^o	283	30.1^o
283	32.9^o	022	29.6^o	284	31.2^o
282	31.5^o	023	34.2^o	285	31.2^o
295	31.8^o	024	29.7^o	-	-
194	31.9^o	025	31.6^o	-	-
303	31.5^o	032	30.5^o	-	-
302	29.9^o	033	30.2^o	-	-
304	33.8^o	034	30.6^o	-	-

The strong negative correlation between the proportion of fines and powder flow characteristics reported by Gold *et al* (54) could not be found (r = 0.206) in this study when the proportion of fines (particles ≤ 137 μm) is compared with repose angle (see Table 3.2). As expected, there was positive correlation between repose angle and proportion of fines but the correlation was not strong enough to assume significance. Even though there were variations among the samples of granules tested, with regard to parameters such as moisture content, proportion of "fines" etc., these variations did not influence significantly the values of "θ" to such an extent as to make it rise to above 40^0 or

50^0, indicative of poor flow characteristics, at least in this investigation. But further study is suggested in this area in the future.

Table 3.2: Proportion of fines Versus angle of repose of paracetamol granules.

Batch No.	Percentage of fines (%) (mean particle diameter ≤ 137 μm)	Angle of repose (degree)
014	11.40	30.9
015	18.60	32.1
022	16.52	29.6
023	18.30	34.2
024	18.64	29.7
025	22.54	31.6
032	17.54	30.5
033	18.78	30.2
034	15.12	30.6

3.2.3 Granule moisture content

The presence of moisture can have a profound effect on the physical and chemical stability of pharmaceutical products. The presence of moisture encourages chemical reaction that may lead to loss of potency or to the formation of an insoluble reaction product on the drug surface, which may inhibit drug availability.

The stability of drugs such as aspirin, ascorbic acid and penicillin is adversely affected by the presence of moisture. The stability of pharmaceutical preparations containing paracetamol decreases rapidly with increase in their moisture content and temperature. When the moisture of these preparations is kept to the minimum possible level, their

stability is generally improved. It is, therefore, recommended that such preparations be kept in a dry atmosphere in order to increase their stability during storage. As stated above, high moisture content reduces the ease of flow of some powders, an effect very pronounced with soluble crystalline solids. Cohesion increases with increasing moisture content resulting in aggregate formation and caking with some powders such as starch, which makes the flow of such powders difficult. It is apparent from the above discussion, therefore, that the moisture content of pharmaceutical solids, including granulations, be narrowly controlled.

The moisture content of granules tested in this study is shown in Table 3.3. The average moisture content (%) varies from 1.5 to 2.76 for chloroquine phosphate, from 2.18 to 3.64 for paracetamol and from 1.16 to 4.14 for frusemide.

Table 3.3: Granule moisture content

Chloroquine phosphate		Paracetamol		Frusemide	
Batch No.	Moisture content (%)	Batch No.	Moisture content (%)	Batch No.	Moisture content (%)
285	1.95	014	2.8	282	3.3
275	2.0	015	3.2	283	1.4
283	2.1	022	3.6	284	4.1
282	1.8	023	2.4	285	1.2
295	1.5	024	3.5	-	-
294	2.5	025	2.4	-	-
203	2.7	032	2.7	-	-
302	1.8	033	2.9	-	-
304	1.9	034	2.2	-	-

The average moisture content in tablet granulations is usually kept at 1% or below although some products might need higher level of moisture for good compressibility. Since up to 4% moisture content may be tolerated in most of tablet granulations, the average moisture content of granules tested in this investigation does not appear excessive even though the effect of this level of moisture on the stability of the respective products has not been determined. However, the inter-batch variation with regard to moisture content seems to be significant. To see the statistical significance of this variation, the moisture content data has been subjected to a one-way analysis of variance (ANOVA) test and the variation was statistically significant at $p = 0.05$ indicating poor control of this important parameter. Therefore, further validation work needs to be done in this area also.

3.2.4 Granule bulk density

The term bulk density refers to a measure used to describe the packing of particles or granules. It depends largely on particle shape. As particles become more spherical in shape, bulk density is increased. As granule size increases, bulk density decreases. The smaller granules are able to close more intimate packing than larger granules.

An important measure that can be obtained from bulk density determinations is the percent compressibility in theory, the more compressible a bed of particles is the less flowable the powder or granulation will be. Carr defines a material having a C value of less than 20 to 21 % as being a free flowing material.

The bulk density and compressibility of granules tested in this investigation is shown in Table 3.4–3.6. As could be seen from the tables, chloroquine phosphate and frusemide

granules appear denser than paracetamol granules and all of the batches of granules tested have compressibility values less than 15% indicative of good flow characteristics.

Table 3.4: Bulk density and compressibility characteristics of chloroquine phosphate granules

Batch No.	Granule weight (g)	Untapped volume (ml)	Tapped volume (ml)	Untapped density (g/cm^3)	Tapped density (g/cm^3)	Compressibility (%)
275	168	250	232.6	0.672	0.722	7.44
282	179.3	250	226.6	0.717	0.791	10.32
283	177.1	250	227.3	0.708	0.779	10.03
284	176.8	250	231.3	0.707	0.764	8.06
285	165	250	231.3	0.660	0.713	8.03
293	164.5	250	226.6	0.658	0.726	10.33
294	74.3	150	149.6	0.495	0.497	0.404
295	74.8	110	95.6	0.680	0.782	15.00
302	172.9	250	236.6	0.692	0.731	5.64
303	169.7	250	232	0.679	0.731	7.66

This is in agreement with the findings of repose angle indicating that the granules were of suitable shape and surface characteristics.

Table 3.5: Bulk density and compressibility characteristics of paracetamol granules

Batch No.	Untapped volume (ml)	Tapped volume (ml)	Untapped density (g/cm^3)	Tapped density (g/cm^3)	Compressibility (%)
912014	176	159	0.568	0.629	10.73
912015	176	158	0.568	0.633	11.43
912022	173	163	0.578	0.613	6.14
912023	185	170	0.541	0.588	8.73
912024	173	165.5	0.578	0.604	4.54
912025	174	159	0.575	0.629	9.38
912032	177	160	0.565	0.625	10.62
912033	183	165	0.546	0.606	11.0
912034	183	168	0.546	0.595	9.02
912035	173	160	0.578	0.625	8.13

Table 3.6: Bulk density and compressibility characteristics of Frusemide granule

Batch No.	Untapped volume (ml)	Tapped volume (ml)	Untapped density (g/cm^3)	Tapped density (g/cm^3)	Compressibility (%)
911282	149	133	0.671	0.752	12.05
911283	141	137	0.709	0.730	2.95
911284	152	148	0.658	0.676	2.69
911285	152	144	0.658	0.694	5.54

3.3 Tablet quality parameters

3.3.1 Tablet weight variation

Among the essential qualities of a well-made tablet, uniformity of drug dosage is considered to be of prime importance. In compressed tablets, this is dependent upon a uniform distribution of the active ingredient throughout the tablet matrices (percent composition) and a constant tablet weight. The variation in weight can be determined and controlled by the official method (individual deviation from mean weight of 20 tablets), or better, a method based on standard deviation (1). A control chart is used as a tool for controlling the weight variation during production. Composition variation is not as easily determined. Studies carried out in several laboratories have indicated that this variation often is the larger of the two.

Factors contributing to variations in individual weight within a batch of tablets can be classified in to two (62):

i). Gross errors, not normally distributed, due to variations in the setting of the machine, mixing of batches, etc.

ii). Small errors, probably normally distributed, that result from irregular filling of the die due to the lack of a uniform free-flowing granulation, incomplete filling of the die due to internal flow and segregation in the hopper leading to depletion of fines in the latter stages of compression, and too large or too small granulation particle size.

To a large extent, excessive variations are controllable; however, small deviations can always be expected. In recognition of this, tolerances have been established by the pharmacopoeias for the protection of the patient against excessive disparity in drug dosage.

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The pharmacopoeia commissions, in setting standards for tablets, make the assumption that a perfect distribution within the tablets does exist and employ the criterion of uniformity of tablet weight as a control over uniformity of drug dosage. According to the specification for weight variation test, the quality of tablets in a given batch is measured by the percentage of defective tablets in the batch, a defective tablet being defined as one which differs in weight from the batch mean by more than a certain percentage of the batch mean. Since batch mean is not practical to obtain the measurement is based on sample mean even though the two may not coincide in general.

The mean weight and the ranges in weight of the batches of tablets tested in this investigation are given in Table 3.7 - 3.9. The compendial specification for uniformity of weight test is also given in Table 3.10. Based on this specification, all of the batches of tablets tested meet the tolerance limits for uniformity of weight. Chloroquine phosphate batch No 293 and frusemide tablets batch No 292 both had one defective tablet each in the sample of 20 tested. But, since two tablets are allowed according to the official requirement as far as the deviation from the mean weight is not more than twice the percentage deviation allowed, the batches can be considered acceptable The coefficient of variation (CV) for tablet weight is also shown in the tables. This is simply the standard deviation expressed as the percentage of the mean weight In statistical populations, which are approximately normally distributed, the standard deviation is considered the most efficient measure of variability. Thus the smaller the CV the smaller the deviations in individual tablet weights from the mean and, consequently, the better is the control over the compression process. As could be seen from the tables, frusemide tablets batch No 292 shows the largest CV (4.46), in comparison to the other batches. This could be expected since according to Rogers (62), a graph which relates coefficient of variation with mean

weight shows a rapid increase in the coefficient of variation for tablets weighing less than about 150 mg, i.e., small tablets show a greater amount of variation in relation to their weight than large tablets. However, it is desirable to limit the variation to ± 5% of the mean weight, if possible, whatever the average weight of the tablet may be and the CV to below 4.

Table 3.7: Weight variation test data of chloroquine phosphate tablets.

		Parameters		
Batch No.	Mean weight (mg)	Range (mg)	SD	CV
282	331.9	322.0- 355.0	6.31	1.90
283	338.2	329.0 - 360.0	8.92	2.64
285	335.2	328.0 - 354.0	7.05	2.10
292	335.1	325.0 - 351.0	6.37	1.90
293	335.2	325.0 - 353.0	5.18	1.54
294	331.1	322.0 - 350.0	6.86	2.07
295	336.8	324.0 - 347.0	5.56	1.65
302	332.6	318.0 – 343.0	5.06	1.52
303	335.5	326.0 - 352.0	5.60	1.79

SD = Standard deviation; CV = Coefficient of variation

Table 3.8: Official specification for tablet weight uniformity.

Compendium	Sample size	Mean tablet weight (mg)	Limit	Acceptance criterion
BP	20	≤ 130	m ± 0.10m	Not more than two (2/20) should deviate from the given limit.
		131-324	m ± 0.075m	
		> 324	m ± 0.05m	
USP	20	≤ 80	m ± 0.10m	
		81- 249	m ± 0.075m	
		> 250	m ± 0.05m	

Table 3.9: Weight variation test data of Paracetamol tablets.

	Parameter			
Batch No.	Mean weight (mg)	Range (mg)	SD	CV
014	630.9	614.4-640.5	8.35	1.32
015	644.0	626.3-662.5	10.9	1.69
022	636.8	615.6-671.8	13.3	2.09
023	648.7	642.5-673.5	10.6	1.63
024	639.9	627.7-650.5	9.4	1.47
025	640.0	610.1-660.4	13.7	2.14
032	637.6	613.4-679.1	13.8	2.16
033	632.8	605.7-647.7	9.62	1.52
034	651.6	642.7-673.3	10.29	1.58
035	636.9	623.4-658.6	7.71	1.21

SD = Standard deviation; CV = Coefficient of variation

Table 3.10: Weight variation test data of frusemide tablets.

	Parameters			
Batch No.	Mean weight (mg)	Range (mg)	SD	CV
282	140.2	136.5 – 147.0	2.65	1.89
283	140.2	139.1 - 147.4	3.51	2.48
284	143.2	134.3 - 150.6	2.40	1.68
285	142.5	138.1 - 146.3	3.42	2.40
292	144.7	125.7 - 152.6	6.45	4.46

SD = Standard deviation; CV = Coefficient of variation

The reason why tablet weight variation could not be observed in this study even though there was excess amount of fines in the some of the batches of the granules could be because:

a) The products can tolerate that amount of fines in the granules, or without showing granulation flow problems.

b) The tableting machine speed could have been so slow as to overcome the flow problem that could have been encountered, or

c) Frequent machine adjustment might have been done by the operators of the tablet compression machines.

3.3.2 Tablet content uniformity

Variations in percent composition are associated with the problems of mixing. In the production of tablets, a perfect mixture represented by a random distribution of particles can never be attained. Proper equipment and sufficient time of mixing are certainly important considerations, but the mixing process is also affected by the size, shape, proportion and density of the particles and by various surface- active forces. Even if a fairly uniform particle distribution has been achieved, this condition is unstable and is easily disturbed by vibration or bumping. In the preparation of uniform granulations, the solubility of the drug in the granulating solvent, and the conditions of drying also play important roles.

Train (59) has predicted that, although the official specifications may be met under the conditions of the assay (based on the composite mean of 20 tablets), the dosage variation can be over twice the official limits in a few cases, over four times the official assay limits in most cases, and eight or more times the official limits with one or two formulations. This is especially true if the active ingredient in less than half the tablet weight and is

added as a powder or a batch of concentrated granules which are mixed with other granular materials.

If a drug is uniformly distributed through out a batch of tablets, then the potency of each individual tablet will be directly proportional to its weight. Thus knowing the mean weight and mean potency of a batch, one may calculate the theoretical potencies for each tablet. In general, variations in the potency of individual tablets may result from (62):

(a) Incomplete mixing in the granulation from which the tablets were compressed;

(b) A disruption, during compression, of the degree of mixing established in the granulation; and

(c) Variations in individual tablet weights.

The pharmacopoeias employ the uniformity of weight test as a control over variability in potencies. The USP, states that "weight variation requirements may be applied where the product to be tested contains 50 mg or more of an active ingredient comprising 50 % or more, by weight, of the dosage form unit". If the product contains less than 50-mg active ingredient comprising less than 50%, by weight, content uniformity test is indicated. It is based on this criterion that frusemide selected for content uniformity test in this investigation. The content uniformity and assay result of frusemide tablets is shown in Table 3.11.

Table 3.11: Content uniformity and assay results of frusemide tablets.

Batch No.	Content Uniformity			Assay*
	Range (%)	Mean (%)	CV	
282	94.4 – 105.6	99.4	4.37	97.6
283	93.0 – 102.6	99.9	2.98	99.8
284	95.3 – 103.4	100.6	2.52	99.6
285	91.4 – 98.7	95.2	2.33	101.3
292	96.3 – 109.1	102.2	3.51	102.6

Range of content uniformity (%) values of 10 individual dosage units; Mean (%) of 10 content uniformity values; CV = Coefficient of variation.

*Assay represents composite assay (%) on 20 powdered tablets.

Based on the official requirements of ± 15 % of the mean potency of the sample of 10 individual units, all of the batches tested meet the tolerance limits. But if the tolerance were limited to 95 to 105 % (± 5%) of label claim as is stated in the potency requirement of the official compendia, only one of the five batches tested would comply with the requirement. Even though official specification for content uniformity test is set at ± 15% of label claim, manufacturers set their own internal specification and try to achieve a variation of not more than ± 5%. This is important to make sure that no batch of tablets or dosage unit will be out of the official specification requirement for content uniformity before the expiration date of the batch is reached. As could be seen from the table, this narrower specification limit was not attained with most of the batches of frusemide tablets tested.

The content uniformity test data has been subjected to a one-sample t-test to see whether there is statistically significant difference between the sample mean and the population

mean (labeled claim). As could be seen from Table 3.12, one of the five batches (Batch No. 285) tested shows statistically significant variation from the population mean (100 % label claim) at 5 % probability.

Tablets 3.12: Statistical analysis (one-sample t-test) on content uniformity test data of frusemide tablets (n=10, P=0.05)

Batch No.	Mean (%) strength	SD	$t_{observed}$	$t_{tabulated}$
282	99.41	4.34	0.43	2.62
283	99.94	2.98	0.06	2.62
284	100.6	2.54	0.75	2.62
285	95.48	2.22	6.4	2.62
292	102.2	3.59	2.62	2.62

Note also that the population mean (100%) is not included in the confidence interval of tablet Batch No. 285. This means that the process needs to be revalidated to achieve a product of better quality with regard to content uniformity of individual units.

3.3.3 Tablet Hardness

The resistance of tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. If the tablet is too soft it will not withstand the handling during packaging and shipping operations and if too hard it may not disintegrate in the required period of time. Hardness of 4 kg is considered minimum for a satisfactory tablet (4).

As could be seen from Tables 3.13- 3.15, frusemide tablets tend to be soft (around 4 kg or less). If 5 - 8 kg is taken as an acceptable range, as is the case with several tablet manufacturers, paracetamol appears to be hard far out of that range on the positive side (8.8 - 12.6).

Table 3.13: Hardness, thickness and friability test profiles of chloroquine phosphate tablets.

	Parameter				
	Hardness		Thickness		Friability
Batch No.	Mean	SD	Mean	SD	%
282	4.8	0.6	3.92	0.15	0.23
283	5.3	0.5	3.80	0.02	0.16
285	4.0	1.0	3.81	0.53	0.23
292	4.2	0.5	3.90	0.11	0.31
293	6.7	0.9	3.80	0.05	0.20
294	4.7	1.3	3.80	0.05	0.24
295	5.06	0.7	3.88	0.06	0.21
302	4.5	0.9	3.90	0.16	0.26
303	5.2	0.5	3.81	0.03	0.26
304	6.17	0.7	3.77	0.03	0.18

Mean of 20 tablets; SD = Standard deviation; Hardness, kg; thickness, mm

The influence of hardness on dissolution was checked by comparing mean hardness (kg) of a batch with dissolution ($t_{50\%}$). No correlation could be found (r = 0.249) for paracetamol. This could be because of the large proportion of starch in the formula (about 20 %, see Tables 1.2 - 1.4) leading to rapid disintegration and dissolution times.

Table 3.14: Hardness, thickness and friability test profiles of paracetamol tablets.

	Parameter				
	Hardness		Thickness		Friability
Batch No.	Mean	SD	Mean	SD	%
014	11.30	1.78	5.65	0.11	0.42
015	9.98	1.50	5.68	0.08	0.47
022	9.26	2.04	5.58	0.10	-
023	7.90	1.24	5.86	0.05	0.92
024	8.98	1.58	5.67	0.04	0.61
025	12.60	1.93	5.70	0.09	0.52
032	12.10	1.44	5.58	0.10	0.37
033	12.40	1.29	5.54	0.03	0.42
034	11.00	2.05	5.80	0.16	0.53
035	8.85	1.93	5.88	0.12	-

Mean of 20 tablets; SD = Standard deviation.

Table 3.15: Hardness, thickness and friability test profiles of frusemide tablets.

	Parameter				
	Hardness		Thickness		Friability
Batch No.	Mean	SD	Mean	SD	%
283	5.18	1.29	3.58	0.04	0.26
284	3.91	0.85	3.74	0.18	0.42
285	4,54	0.89	3.66	0.13	0.30
292	3.98	0.90	3.63	0.04	0.30
282	4.35	1.28	3.67	0.14	0.35

X = Mean of 20 tablets; SD = standard deviation

In general, it can be concluded that this parameter is not properly controlled in EPHARM since the result of this observation, at least for paracetamol, has shown that it was out of the generally accepted specification limit.

3.3.4 Tablet thickness

Tablet thickness is usually carefully controlled from production run to production run. Not only is it important in reproducing tablets identical in appearance but also to ensure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no longer may be contained in the volume of a given size container. Tablet thickness also becomes an important characteristic in counting tablets using filling equipment, which utilize the uniform thickness of the tablets as a counting mechanism.

As stated in the introduction part of this report, thickness can vary with variation in weight of the tablets due to improper filling of the dies that can also be manifested by variations in hardness. This effect can take place at high speed of rotary tablet presses. As the speed increases the die fill decreases, the tablet weight diminishes and the compressional force being generated decreases. The apparent thickness and density of the tablets also decreases. It can also vary with no change in weight due to the difference in the density of the granulation and the pressure applied to the tablets. Regulation of the thickness control of the compression machine is the usual method of controlling the thickness and hardness of tablets.

A thickness variation of ± 5 % is allowed by manufacturers. As is seen in the Tables 3.13 - 3.15, if the average thickness (± SD) is considered as 5%, it appears that the thickness variation is within this unofficial tolerance limit.

3.3.5 Tablet friability

Friability test data for the tablets tested in this investigation is also given in the Tables 3.13 - 3.15. Unofficial requirement for friability is that tablets tested according to the USP procedure should not loose more than 0.8 to 1 % of their weights. Manufacturers limit this specification to below o.5 % of tablet weight.

Out of the tablets tested in this investigation, chloroquine phosphate and frusemide tablets comply with the unofficial friability test requirement. However, two batches of paracetamol showed capping and friability was not calculated for these batches. Furthermore, one batch had more than 0,8 % friability value. This means that this parameter is not properly under control for paracetamol, but friability for the other two products is within the acceptable specification range. Therefore, process and/or product revalidation seems to be important for paracetamol.

3.3.6 Tablet disintegration

Rapid disintegration is usually sought for orally administered solid dosage forms (chewable tablets excluded). This is because the active ingredient must be released from the tablet matrix (or capsule shell) as efficiently as possible to allow for its rapid dissolution.

It is now recognized that, in general, there is poor correlation between *in vitro* and *in vivo* drug action (37). But regardless of the lack of significance, disintegration test provides a means of control in assuring that a given tablet formula is the same as regards disintegration from one production batch to another. The official requirement in the USP disintegration test apparatus is that uncoated tablets should disintegrate in less than 30 min. As could be seen from the Table 3.16, all of the batches tested in this study comply with official requirement, in all cases disintegration was complete (all particles pass through mesh No 10) in less than 10 min. time. This could be expected since in all cases the proportion of starch in the formulation is high. It is well documented that as the starch concentration increases disintegration time decreases.

3.3.7 Tablet dissolution

The most direct assessment of drug's release from various tablet formulations or products is accomplished through *in vivo* bioavailability measurements. The use of *in vivo* studies is restricted, however, for several reasons: the length of time needed to plan, conduct and interpret the study; the highly skilled personnel required for human studies; the low precision and high variability typical of the measurements; the high cost of the studies; the use of human subjects for "non essential" research; and the necessary assumption that a perfect correlation exists between diseased patients and the healthy human subjects used in the test (1). Consequently, *in vitro* dissolution tests have been extensively studied, developed and used as an indirect measurement of drug availability, especially in preliminary assessments of formulation factors and manufacturing methods that are likely to influence bioavailability. As with any *in vitro* test, it is critically important that the dissolution test be correlated with *in vivo* bioavailability tests.

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Table 3.16: Tablet disintegration test data

Disintegration time (min.)								
Chloroquine phosphate			**Paracetamol**			**Frusemide**		
Batch No.	Mean	Range	Batch No.	Mean	Range	Batch No.	Mean	Range
293	6.5	6-7	014	1	1-2	282	3	2-4
275	4.2	3-5	015	1	1-2	283	3.7	2-6
294	4.8	4-5	022	1.8	1-2	284	7.2	7-8
282	3.5	3-4	023	1	1-2	285	7.7	7-9
284	4.7	4-6	024	1	1-2	292	7.2	6-8
292	6.5	6-8	025	1.8	1-2	-	-	-
295	5.7	4-8	032	1.7	1-2	-	-	-
283	5.2	5-6	033	1	1-2	-	-	-
285	5.2	5-6	034	1	1-2	-	-	-

Levy (37) showed that there is a good correlation between *in vitro* dissolution data and *in vivo* bioavailability of aspirin products. In that study he has concluded that:

a) There is a positive correlation between dissolution and urinary excretion rate of aspirin tablets;

b) Disintegration time had no relation, whatsoever, to biological availability since the faster absorbed products had the longer disintegration time.

This has been explained on the basis of the fact that the rate of release of drug from primary particles (dissolution) is essential for absorption to take place and disintegration does not necessarily mean that the drug has dissolved.

Similar correlations have been observed for many drugs. Often the rate of drug absorption is determined by the rate of drug dissolution from the dosage form. This is particularly important for the drugs absorbed high in the gastrointestinal tract (e.g. acidic drugs), which have a large dose and low equilibrium solubility. Thus, the importance of dissolution testing as the major *in vitro* test of tablet characteristics is obvious.

The dissolution data obtained in a given test may involve factors related to:

a) The drug dissolution rate (intrinsic),

b) The drug particle size (distribution), and

c) The disintegration rate of the dosage form.

Formulation and processing factors also affect both the disintegration and dissolution rate of tablets. Chalmers and Helworthy (63) have shown that wet mixing time in wet granulation process has influenced the properties of oxytetracycline dihydrate tablet formulations. According to them, increased time of wet mixing produced larger, stronger and denser granules, which compressed into tablets with longer disintegration and dissolution times. These workers have reported that the increase in wet mixing time from 5 to 15 min. increased the disintegration time by a factor of 21 and the dissolution $t_{50\%}$ time by a factor of 11 in the case of oxytetracycline tablets granulated with PVP solution. This is because the longer mixing time the better would be the expected distribution of PVP in the powder bed and the dried film of PVP in the tablet structure retards disintegration and dissolution.

Binder concentration also affected disintegration and dissolution times. Due to a heavier coating of the powder particles with PVP solution, the higher viscosity of this solution slowed both the rate at which the invading water reached the surface of the powder particles and the rate of diffusion away from the surface of the drug particle.

The effect of the type of the binder used on dissolution rate has also been noted. Solvang (64) have shown that Phenobarbital tablets prepared with gelatin as granulating agent were found to dissolve much faster in human gastric juice than tablets prepared with carboxymethyl cellulose sodium or PEG 6000 as binders, probably because gelatin makes the originally hydrophobic surface of the drug particles hydrophilic whereas sodium carboxymethyl cellulose at the pH of the dissolution medium is converted to the less hydrophilic free acid and PEG 6000 forms a complex of reduced solubility with Phenobarbital.

Disintegration and dissolution rates may also be affected by the type and concentration of the disintegrant as well as the fillers (diluents) used. For an "insoluble" drug indomethacin, the dissolution rate decreased with increase in the ratio of dicalciumphosphate dihydrate to microcrystalline cellulose (65). In general, higher levels of starch result in more rapid disintegration times.

According to Banker (1) the two objectives in the development of in vitro dissolution test are to show:

a) That the release of the drug from the tablet is as close as possible to 100 %, and

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

Several methods of treatment of data obtained from a dissolution test exist but the method routinely used by industrial pharmacists is the concentration versus time plot. Values for $t_{50\%}$, and the percentage dissolved in 30 min. are used as guides. The value for $t_{50\%}$ is the length of time required for 50 % of the drug to go into solution. A value for $t_{90\%}$ of 30 min. is often considered satisfactory and is an excellent goal since a common dissolution tolerance in USP/NF is not less than 75 % dissolved in 45 min (1).

The dissolution profile of tablets tested in this investigation is shown in figure 3.7 - 3.9. The $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ values are also shown in Tables 3.17-3.19. The dissolution rate constants (k), indicated in this later tables, were calculated from the slope of Wagner's plot (log of % undissolved versus time plot) which showed first order reaction rate after curve fitting. The 50 %, 75% and 90% dissolution times were calculated by using the constants in the first order reaction equations. The values obtained were compared with those obtained from % dissolved versus time plots and were found to be similar for all practical purposes.

As could be seen, in the case of chloroquine phosphate tablets the $t_{90\%}$ is less than 10 min. for all of the batches tested. But in the case of frusemide and paracetamol there are batches whose $t_{90\%}$ is more than 30 min. For frusemide 2 batches out of 5 tested had $t_{90\%}$ of more than 30 min, 56 min in one case.

Even though the dissolution profile of these tablets complies with the official dissolution test requirement, some kind of optimization needs to be done to bring the $t_{90\%}$ down to below 30 min. particularly with regard to frusemide and paracetamol tablets.

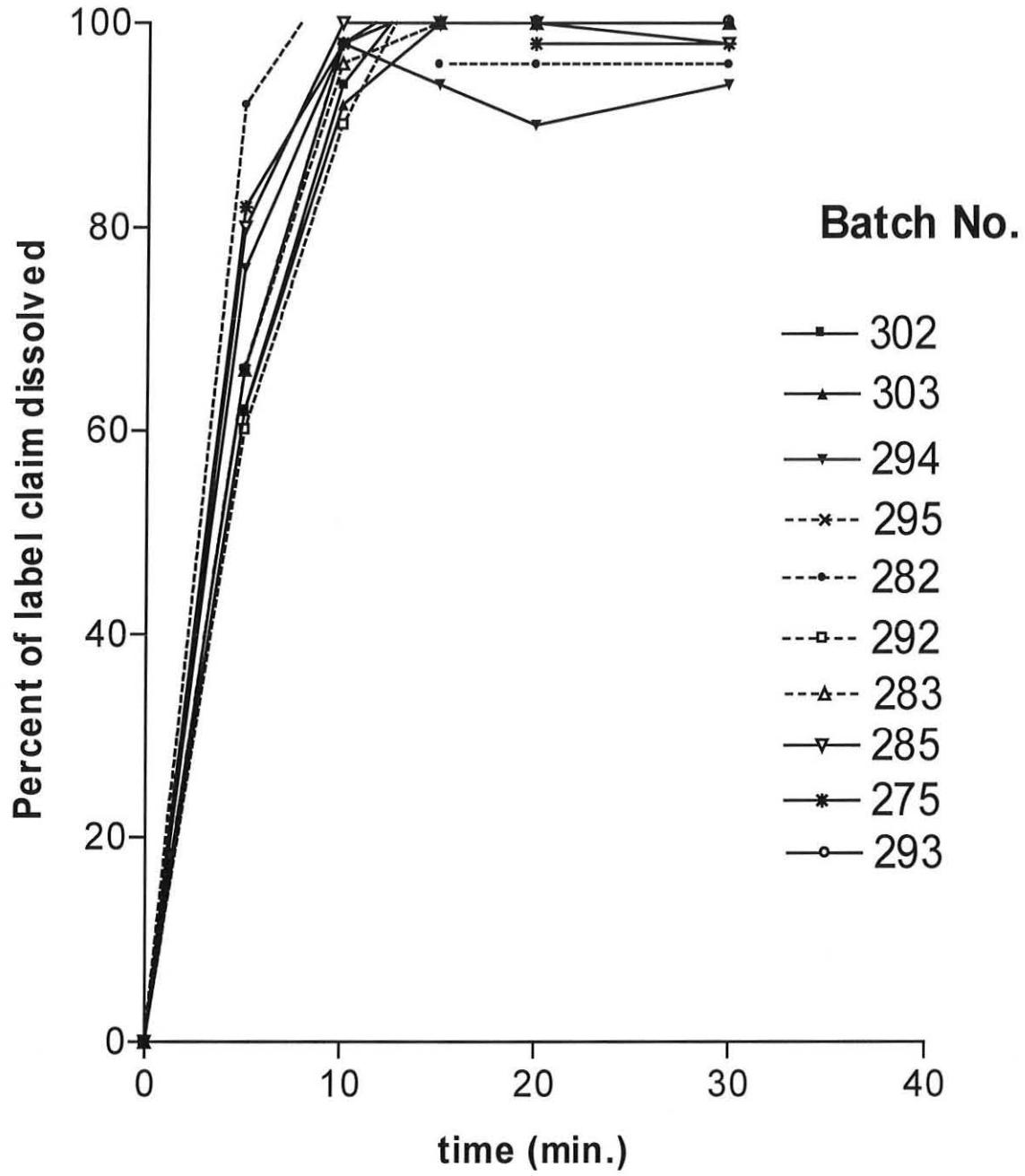

Figure 3.7: Dissolution profile of chloroquine phosphate tablets.

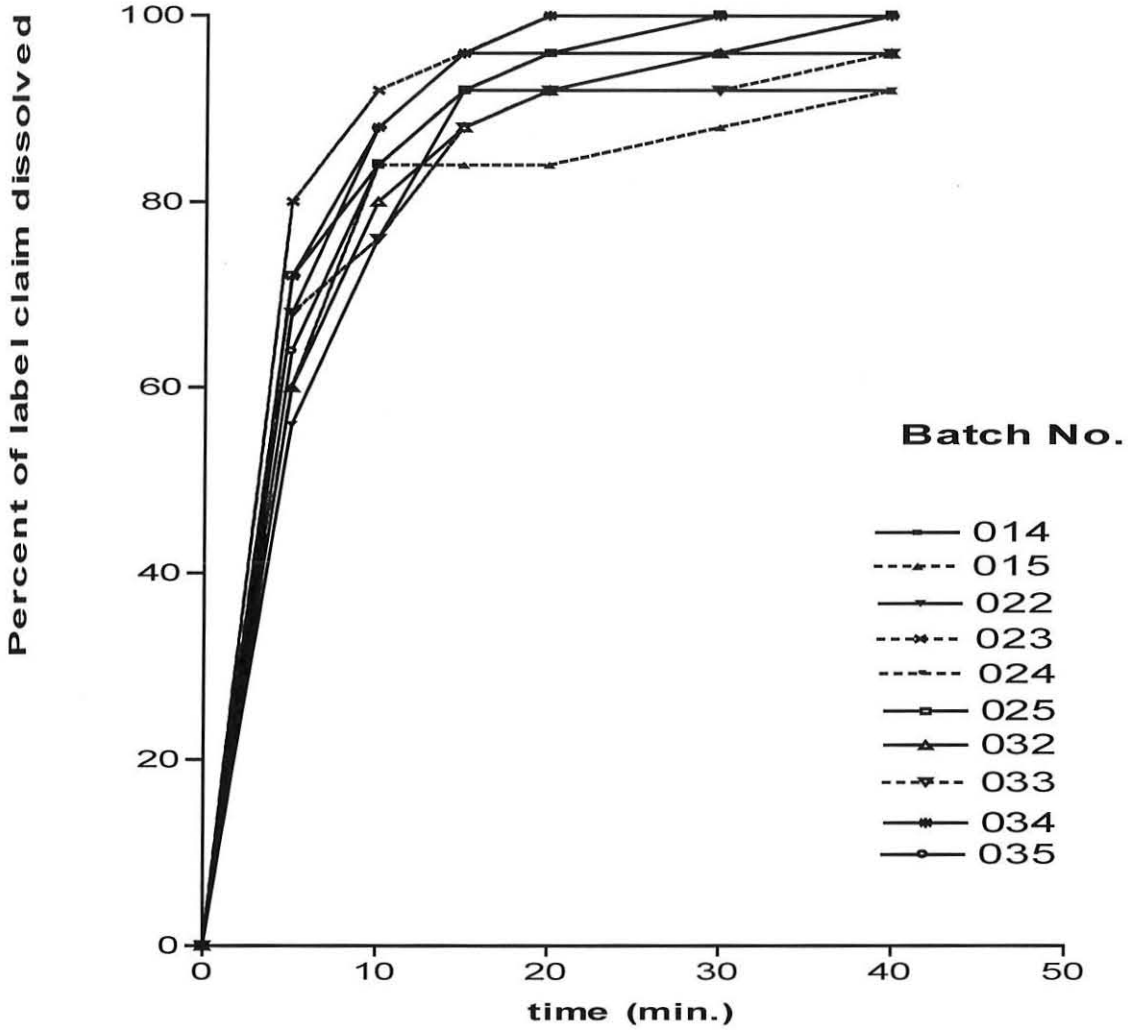

Figure 3.8: Dissolution profile of paracetamol tablets.

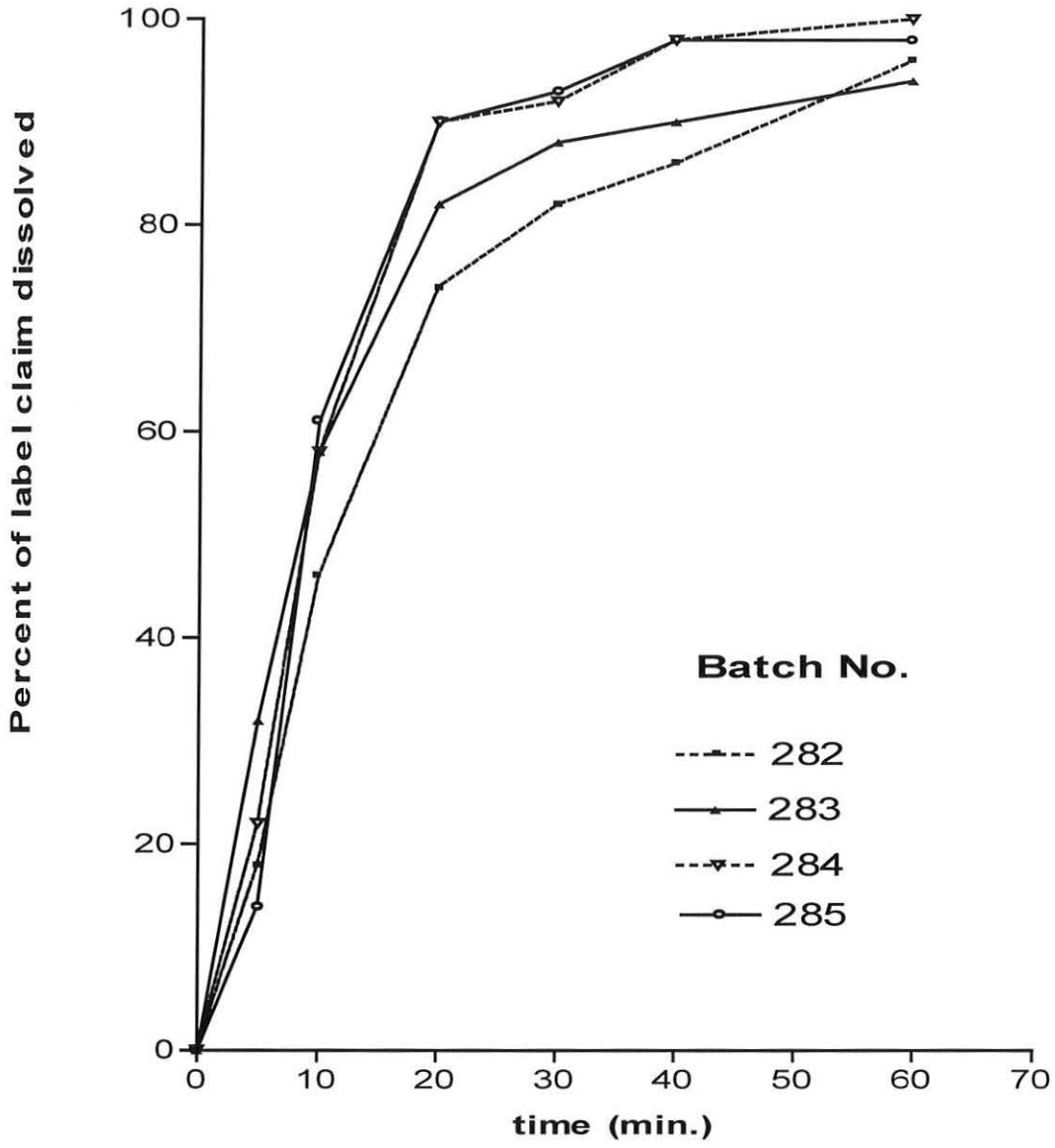

Figure 3.9: Dissolution profile of frusemide tablets.

Table 3.17: Release rate constant (k) and percentage of drug release from chloroquine phosphate tablets.

Batch No.	k	$t_{50\%}$	$t_{75\%}$	$t_{90\%}$
302	0.281	2.5	4.9	8.2
303	0.253	2.7	5.5	9.1
294	0.389	1.8	3.6	5.9
295	0.391	1.8	3.5	5.9
282	0.507	1.4	2.7	4.5
292	0.230	3.0	6.0	10.0
283	0.320	2.2	4.3	7.2
285	0.320	2.2	4.3	7.2

Table 3.18: Release rate constant (k) and percentage of drug release from paracetamol tablets.

Batch No.	K	$t_{50\%}$	$t_{75\%}$	$t_{90\%}$
014	0.0739	9.4	18.8	31.2
015	0.0729	9.5	19.0	31.6
022	0.088	7.9	15.8	26.2
023	0.212	3.3	6.5	10.9
024	0.112	6.2	12.4	20.6
025	0.154	4.5	9.0	15.0
032	0.105	6.6	13.2	21.9
033	0.071	9.8	19.5	32.4
034	0.210	3.3	6.6	11.0
035	0.111	6.2	12.5	20.7

The tablet dissolution test data has also been subjected to a one-way analysis of variance ANOVA) test to see whether there is statistically significant batch-to-batch variation in the dissolution profile or not. The batch-to-batch variation was not statistically significant at p = 0.05.

As can be seen from these figures, the dissolution profile of the tablets tested may be summarized as follows:

a) With chloroquine phosphate and paracetamol tablets 90% drug dissolution could be achieved in less than 30 min. which is an ideal goal to be targeted during formula and process development.

Table 3.19: Release rate constant (k) and percentage of drug release from frusemide tablets.

Batch No.	k	$t_{50\%}$	$t_{75\%}$	$t_{90\%}$
282	0.05	13.2	26.4	43.9
283	0.04	16.9	33.8	56.2
284	0.09	7.1	14.2	23.6
285	0.09	7.0	14.0	23.3
292	0.08	7.9	15.6	25.9

b) With frusemide, 90% drug dissolution could be achieved only at about 60 min. with one batch and at about 40 min. with the rest. Even though this may be expected for this

drug given its very low aqueous solubility some kind of formula and/or process optimization needs to be undertaken for this product to improve the dissolution rate.

c) Complete drug release (90% dissolution) could be achieved and compendial specifications complied with in all of the three products tested with regard to dissolution.

d) No statistically significant batch-to-batch variation in dissolution rate was observed in all cases.

4. CONCLUSION

The moisture content variation of the "dry" granules showed significant variation when the data for moisture content was subjected to statistical test procedures. This means that the drying process was not properly controlled. The proportion of "fines", particles of sizes less than 250 μ, seems to be excessive for chloroquine phosphate tablets. Even though this might have advantage with regard to drug dissolution rate, it can possibly cause processing problems such as sticking, capping, and flow problems that can result in tablet weight variations. Flow characteristics of all of the granules, shown by angle of repose and compressibility index values, were generally good.

Two batches of paracetamol tablets failed friability (capping) test requirement. Hardness variations were observed with paracetamol and frusemide tablets. All of the tablets tested comply with official (USP) specifications regarding uniformity of weight, disintegration and dissolution; complete (90%) drug release was achieved in all cases. Content uniformity of frusemide tablets was within the official (± 15%) specification limit, but narrower (± 5%) internal specification limit might be needed to assure product efficacy throughout its shelf life.

Facility, Equipment and Control procedures:

1. There was space problem for proper arrangement of equipment and materials in the manufacturing area.
2. Tablet manufacturing involves powder processing which can result in excessive contamination of the surrounding air with dust particles and serious cross

contamination problems. The air exhaust system (dust suckers) in EPHARM were not very efficient.

3. Some of the manufacturing equipment lack the necessary electronic control mechanisms. For example: (a) the granulator lacks electronic control mechanisms for monitoring mixing time and mixing intensity and, possibly, for granulation end point determination. (b) the inlet air temperature, outlet air temperature and air velocity gauges of the drier were not functional.

4. All of the compression machines did not have the qualities of the modern instrumented equipment. For example, they did not have electronic control mechanisms for compression force, ejection force, or for in-process control of tablet weight.

5. Documentation was insufficient. There were no logbooks and procedures for machine cleaning and maintenance. The batch manufacturing record did not contain detail Standard Operating Procedure (SOP) guidelines for each unit operations and the master formula record, which possibly contains detail operating instructions, was not accessible to the operators/supervisors. Therefore, there was no SOP to be strictly followed during processing.

6. In-process follow up was not being carried out for control of granule particle size / size distribution and granule moisture content. These are parameters which can easily lend themselves to in-process control like tablet weight variation, hardness, thickness or disintegration, etc..

7. Training of personnel, with respect to the general principles of CGMP or with respect to the particular job they were assigned to was insufficient or not effective. Advanced academic training for professional personnel to cope with the complex pharmaceutical manufacturing processes was lacking. As a result, there were not sufficient number of

personnel with the necessary advanced training and experience in the factory including in the key departments such as production, the QC, and R&D.

8. Assurance of product quality and implementation of the CGMP principles needs commitment of both the management and the workers. More needs to be done particularly on the part of the management to assure quality of products.

Generally, it can be said that the tablet manufacturing process in the Ethiopian Pharmaceuticals Manufacturing Factory is not validated and the entire spectrum of the GMP requirements are not fulfilled.

Finally, it is my firm belief that the data from this investigation can be used as a base line to improve product quality in EPHARM and would like to remind the company's management to capitalize on it for validation of other products and dosage forms not included in this investigation.

5. RECOMENDATIONS

1. Optimization of the granulation and drying processes should be carried out for all of the three products tested.
2. Homogeneity of mixing should be assured for frusemide and similar potent, low dose tablet products.
3. Similar process validation study needs to be carried out for tablet products and other dosage forms (injectables, capsules, oral solutions, topical preparations, etc) not included in this investigation.

4. As could be observed in this study, not only process validation but other validation requirements such as facility and equipment validation, raw materials validation, personnel validation, control validation, cleaning validation, documentation validation, etc. were not adequate in the company. This work which requires considerable resources but very important for the viability of the factory needs the attention of the management and the commitment of all involved. CGMP committee composed of senior staff or the use of consultants might be considered for the implementation of the validation principles. Consultants can be very useful since they usually come up with new ideas and experiences not available in the factory. The use of consultants can also be cost effective.

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DECLARATION

I, the undersigned, declare that this thesis is my original work and has not been presented for a degree in any other university.

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