STUDIES ON THE EFFECTS OF CYCLODEXTRIN POLYMER AS A TABLETING AID ON SOME SELECTED ANALGECICS

by

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DEDICATION

THIS DISSERTATION IS RESPECTFULLY
DEDICATED TO MY MOTHER AND
MY BROTHER MOHSIN ALI
“WITH THE NAME OF GOD THE MOST BENEFICIENT, THE MOST MERCIFUL”
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AIMS AND OBJECTS OF STUDY

The rate of absorption and physiological availability of drugs administered orally in solid form is function of their rate of dissolution in gastrointestinal fluids. Certain formulation and processing factors such as the binder used and its concentration, the disintegrator used and the granulation method affect the disintegration time and dissolution rate of drug contained in tablets. Since it has been found that generally identical tablet products made by different manufacturers exhibit significant differences in disintegration and dissolution rate of the active ingredient from the tablets.

The present work is to find out the possible utility of β-cyclodextrin as a tablet disintegrant in wet granulations of poorly water-soluble drugs. The investigation is based on the study of the disintegration time and the rate of dissolution of paracetamol and mefenamic acid tablet formulations containing three different sets, and is intended to be carried out on the following lines.

1. Formulation of tablets using three different sets.

2. Evaluation of compressed tablets by official and unofficial control tests.

3. Assay of the active ingredient by official methods.
4. Study of the effects of β-cyclodextrin on the disintegration and dissolution rate of the tablets.

5. Comparison with the commercially available tablets of same strength.
ABSTRACT
ABSTRACT

The clinical effectiveness of tablets and other pharmaceutical dosage forms of drug depends on at least two factors: the medication must not only be present in labelled amount but also must be available to the body. The drug availability is usually determined by the rate of release of drug from the dosage form. Such processes as the disintegration and dissolution of the drug govern the release of the drug from the tablet.

In the present investigation, the effect of β-cyclodextrin on disintegration and the rate of dissolution of analgesic tablets (paracetamol and mefenamic acid) has been studied. The tablets were tested for the uniformity of weight, thickness and diameter, content of active ingredients, hardness, friability, disintegration time and rate of dissolution of drug. Three different sets were used for each drug.

The best results were achieved from the formulation No. 3 of both paracetamol and mefenamic acid formulations. The results were then compared with the commercially available tablets of each drug.
خلاصہ

دووے کے طور پر استعمال ہونے والے گلیولین اوردووری اوردووری اشکال کی تین اقسام ہیں کہ احصار روزوال پر تباہی کے مضر فیکٹر اور مزید متاثر کریں۔ میٹا بھی جوگزیا ہو گیا ہے۔ لیکن گلیولین کی برتری اوردووری اشکال میں سے دووے کے انار خارج کی شرح کے ذریعہ معلوم کی گئی ہے۔

سے دووے کا انار خارج داخل راکھے جا کے کم شروع بھی کریں ہوئے نہیں مخصوصہ ہے۔ موزوں دکھائی سے دووے کے کم شروع بھی کریں ہوئے نہیں مخصوصہ ہے۔


cyclodextrin

اور روشن اور مشکل کے قلم پر کیڈر کے گلیولین کے کام دکھائی دی جاتی ہے۔

مونو اور دووے کی کرائی اوردووری کا انار خارج کی شرح کے ذریعہ معلوم کی گئی ہے۔

یہہ نے کارکردگی اوردووری اوردووری اشکال میں سے مشکل کے لیے جائزہ آگیا ہے۔

کام دکھائی ہوئی اوردووری اشکال میں سے مشکل کے لیے جائزہ آگیا نہ ہوئے۔

یہہ نے کارکردگی اوردووری اشکال میں سے مشکل کے لیے جائزہ آگیا ہے۔
1. INTRODUCTION
INTRODUCTION

DRUG

A drug may be defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of diseases in human or in animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body (1).

ANALGESIC DRUGS AND ANTIPYRETICS

Analgesics are agents which relieve pain by acting centrally to elevate pain threshold without disturbing consciousness or altering other sensory modalities. Antipyretics are drugs which reduce elevated body temperature. Certain analgesics also possess anti rheumatic and anti inflammatory properties, such substances are used in the treatment of arthritis and other inflammatory conditions (2).
POORLY WATER SOLUBLE ANALGESICS

1. PARACETAMOL

Generic name

Acetaminophen (3), paracetamol and acetophenenum (4).

Chemical name

4-Hydroxy acetanilide, p-hydroxy-acetanilide, p-acetamidophenol, p-acetaminophenol, p-acetylene aminophenol, N-acetyl-p-aminophenol.

Formula

C₈H₉NO₂

Molecular weight

151.16

Preparation

p-nitrophenol is reduced and the resulting p-aminophenol is acetylated by heating with a mixture of acetic anhydride and glacial acetic acid. The crude product may be purified by recrystallization from an ethanol-water mixture.

Description

White, odorless, crystalline powder, possessing slight bitter taste, melts at about 170°C, pH (saturated solution) 5.3 to 6.5, Pka 9.51.

Solubility

1 g in 70 ml of water, 20 ml of boiling water, 10 ml of alcohol, 50 ml of chloroform, 40 ml of glycerine, slightly soluble in ether (2).
The solubility of paracetamol in distilled water has been described by several authors.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Solubility (mg/ml)</th>
<th>References</th>
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<tr>
<td>20°C</td>
<td>About 11.3</td>
<td>5, 6, 13</td>
</tr>
<tr>
<td>25°C</td>
<td>About 14.4</td>
<td>8, 14</td>
</tr>
<tr>
<td></td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.85</td>
<td>15</td>
</tr>
<tr>
<td>37°C</td>
<td>About 19</td>
<td>16</td>
</tr>
<tr>
<td>100°C</td>
<td>About 20</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>About 52</td>
<td>5, 12, 13, 18</td>
</tr>
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</table>

In pH 6.0 buffer solution at 37°C its solubility has been recorded (19) as 23.8 mg/ml.

**STABILITY OF PARACETAMOL**

**Stability to light**

Paracetamol is slightly light sensitive in solution (13) and may degrade by mechanism involving predissociation of N-C bond in the case of acetanilide (7, 9).

**Stability to heat**

Dry pure paracetamol is very stable at temperature upto at least 45°C.

**Stability to oxidation**

Paracetamol is relatively stable to aerial oxidation and it has been used as an antioxidant for carotene in mineral oil solution (10), a heat stabilizer and short stopping agent for synthetic rubber latexes.
METHOD OF ANALYSIS

The BP 1963 (11, 22) and US National Formulary (17) both adopted UV spectrophotometric procedures for the determination of paracetamol in paracetamol tablets.

PHARMACOKINETICS

Absorption and fate

Absorption of paracetamol after oral administration is rapid. Peak plasma levels are reached in 70 to 160 minutes. The therapeutic half life is approximately 3 hrs. Approximately 2% is excreted unchanged in the urine. The glucuronide and sulfate conjugates are nontoxic and account for about 95% of the drug. A much smaller amount, estimated to be 3%, is oxidized via the hepatic cytochrome P-450 system to a chemically reactive intermediate which combines with liver glutathione to form a non toxic substance. However, after massive single doses of paracetamol, the supply of liver glutathione is exhausted and the excess reactive arylating intermediate covalently binds to a vital hepatocellular macro molecules, leading to necrosis. Hepatic necrosis and death have been observed following over dosage. Hepatic damages is likely if an adult takes more than 10 g in a single dose or if 2 year old child takes more than 3 g. Treatment of over-dosage is largely supportive, no specific therapy is available.
Adverse effects

It rarely induces untoward effects and is usually well tolerated by aspirin sensitive patients. Rarely, a sensitivity reaction may occur; in this case, the drug should be stopped. Although large doses have been reported to potentiate anti-coagulants, small doses have no effect on prothrombin time.

Uses

A metabolite of phenacetin and acetanilide used as analgesic and antipyretic. It is effective in a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain of headache, dysmenorrhea, and neuralgias. Paracetamol is particularly useful as an analgesic, antipyretic in patients sensitive to aspirin and who experience other untowards reactions to aspirin.

Dose

- Usual adult, oral 300 mg to 1 g 3 or 4 times a day.
- Usual pediatric, oral, 175 mg/sq. meter of body surface 4 times a day; or 60 mg 3 or 4 times a day for children under one year of age.
- 60 to 120 mg 3 or 4 times a day for children 1 to 2 years of age.
- 120 mg 3 or 4 times a day for children 3 to 5 years of age.
- 150 to 325 mg 3 or 4 times a day for children 6 to 12 years of age.

Precaution

Do not give to children under 6 years of age or use more than 10 days unless directed by a physician (24).
2. MEFENAMIC ACID

Common name

N-(2,3-xylyl) anthranilic acid (21, 26).

Chemical name

2-[2,3-dimethyle phenyl amino] benzoic acid.

Formula

$C_{15}H_{18}NO_2$

Molecular weight

241.3 (2, 25)

Synthesis

O-chloro benzoic acid is condensed with 2,3-xylidine with the aid of potassium carbonate and the resulting potassium salt is treated with mineral acid to liberate the desired acid (2, 23).

Description

White to off white, crystalline powder, odorless, very little initiate taste, but a bitter after taste, melts between 227 and 232 (23).

Stability

Mefenamic acid darkens on prolonged exposure to light, non hygroscopic, and is stable up to 45°C, decarboxylates at temperature above its melting points (at 300°C, 100°C decarboxylated in 3 minutes) (23) stored in well closed container (2, 23).
Solubility

1 g in 220 ml of alcohol, insoluble in water, sparingly soluble in chloroform or ether (2, 23).

Loss of weight on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight 1 g is used (2).

Sulphated ash

Not more than 0.1% (20).

METHOD OF ANALYSIS

Identification

(A) The infra-red absorption spectrum is concordant with reference spectrum of mefenamic acid

(B) Dissolve 25 mg in 15 ml of chloroform and examine under UV light 254 nm, the solution exhibit a strong greenish yellow florescence. Carefully add 0.5ml of trichloro-acetic acid drop wise and examine under UV light 254 nm. The solution does not exhibit florescence (2).

Light absorption

Absorption of a 0.002% W/V solution in a mixture of 1 volume of 1M HCl and 99 volumes of methanol at the maximum at 279 nm 0.69 to 0.74 and the maximum at 350 nm 0.56 to 0.60 (2).
Assay

Dissolved 0.6 g in 100 ml of warm absolute ethanol previously neutralized to phenol red solution and titrate it with 0.1M NaOH VS using phenol red solution as indicator. Each ml of 0.1M NaOH VS is equivalent to 0.02413g of C_{15}H_{15}N_{0.5}

PHARMACOKINETICS

Absorption and fate

Mefenamic acid is absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2-4 hours after ingestion. The half-life is reported to be 2 hours.

Mefenamic acid is extensively bound to plasma protein. Approximately 50% of the dose may be recovered in the urine within 48 hours, mainly as conjugated metabolite (23). Mefenamic acid given to nursing mothers was found in breast milk in small quantities (28).

Adverse effect

The common adverse effects occurring by mefenamic acid are gastrointestinal disturbance (29,32). Peptic ulceration and gastrointestinal bleeding have also been reported. The common adverse effects occurring by the mefenamic acid are headache, drowsiness, dizziness, nervousness and visual disturbance (23). There may be hypersensitivity reaction including skin rashes and urticaria (33, 35) and occasionally allergic glomerulonephritis (36, 38), asthma may be
precipitated (27). Haematological effects have also been reported which include haemolytic anaemia, agranulocytosis, pancytopenia, thrombocytopenia or thrombocytopenic purpura and bone-marrow aplasia (30, 31). Therapy should be discontinued if diarrhoea or skin rash occur.

USES AND ADMINISTRATION

Uses

Mefenamic acid has analgesic, anti-inflammatory (2) and antipyretic properties. It is an inhibitor of prostaglandin synthetase (23, 24). It is used for the relief of mild to moderate pain including headache, dental pain, postoperative and post partum pain and dysmenorrhoea (34, 39). It is also used in rheumatic disorders such as osteoarthritis and rheumatoid arthritis (40, 37). Mefenamic acid may also be used in menorrhagia (2, 41).

Dose

The usual dose by mouth is 500g three times daily (24). A suggested dose for children with Still's disease is 25mg per kg body weight daily in divided dose. Mefenamic acid has also been given to children as antipyretic (23). Treatment with mefenamic acid should not be continued for longer than seven days (24).
Precautions

Mefenamic acid is contra-indicated in patient with peptic ulceration or inflammatory bowel disease. It should be used with caution in patient with impaired renal or liver function (23, 35). It may enhance the effect of the coumarin anticoagulants. Mefenamic acid has a marked tendency to induce toxic-clonic (grand mal) convulsion in over dosage, some sources have suggested that it should be avoided in epileptic subjects (23).
PHARMACEUTICAL DOSAGE FORM

In addition to providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for the following and other reasons.

1. For the protection of a drug substance from the destructive influence of atmospheric oxygen or moisture (e.g. coated tablet, sealed ampules).

2. For the protection of a drug substance from the destructive influence of gastric acid after oral administration (e.g. enteric coated tablet).

3. To conceal the bitter, salty or obnoxious taste or odor of a drug substance (e.g. capsules coated tablets, flavoured syrup).

4. To provide liquid preparation of substances that are either insoluble or unstable in the desired vehicle (e.g. suspension).

5. To provide liquid dosage form of substances soluble in the desired vehicle (e.g. solution).

6. To provide extended drug action through controlled released mechanism (e.g. various controlled release tablets, capsules and suspensions).
7. To provide optimal drug action from topical administration sites (e.g. ointments, creams, transdermal patches, ophthalmic, ear and nasal preparations).

8. To provide for the insertion of a drug into one of the body's orifices (e.g. rectal or vaginal suppositories).

9. To provide for the placement of drugs directly into the bloodstream or into body tissues (e.g. injection).

10. To provide for the optimal drug action through inhalation therapy (e.g. inhalants and inhalation aerosols).

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Drugs can be prepared for administration by every conceivable route, and appropriate pharmaceutical preparation formulated to insure maximum therapeutic response (1).
TABLETS

Drugs substances most frequently are administered orally in the form of solid dosage form such as tablets and capsules (2).

Tablets are solid dosage forms of medicinal substances usually prepared with the aid of suitable pharmaceutical adjuncts. Different tablets may vary in size, shape, weight, hardness, thickness and disintegration characteristics and in other aspects, depending upon the intended use of the tablets and their method of manufacture.

Tablets are prepared primarily by compression. Limited no. of tablets are prepared by molding (1).

TYPES OF TABLETS

The various tablets types and their abbreviations are listed below:

1. Compressed Tablets (C.T)
2. Multiple Compressed Tablets (M.C.T)
3. Sugar Coated Tablets (S.C.T)
4. Film Coated Tablets (F.C.T)
5. Enteric-Coated Tablets (E.C.T)
6. Controlled-Release Tablets
7. Tablets for solution.
8. Effervescent Tablets.
9. Buccal or sublingual Tablets
10. Molded Tablets or Tablet Triturate (T.T)
11. Dispensing Tablets
12. Hypodermic Tablets
13. Chewable Tablets

ADVANTAGES OF TABLETS

Compressed tablets have many advantages over alternative dosage forms. These are,

1. Convenience
2. Accuracy of dosage
3. Uniformity of effect
4. Stability
5. Ease of dispensing

ESSENTIALS OF GOOD TABLETS

1. Accuracy of the dose
2. Homogeneity of distribution of active ingredients
3. Absence of incompatibility
4. Stability during storage
5. Ease of disintegration
6. Pleasing appearance
TABLET INGREDIENTS

In addition to the active or therapeutic ingredients tablets contain a number of inert materials. The later are known as additive or excipients.

The term excipient is of Latin origin and refers to all materials except the medicament. Therefore, an excipient is an inert substance used to give a preparation a suitable shape (1, 2).

Excipients may be classified according to the part they play in the finished tablets. The first group contains those which help to impart satisfactory processing and compression characteristics to the formulation. These includes:

- Diluents
- Binder and
- Glidants and lubricants

The second group of added substances helps to give additional desirable physical characteristics to the finished tablets included in this group are:

- Disintegrants
- Colors
- Flavours
- Sweetening agents
DILUENTS

In order to make the tablet in a suitable size for compression an inert substance is added to increase the bulk. Diluents are used for this purpose.

The following are examples of diluents:

Lactose, sucrose, sodium chloride, solids starch, kaolin, and other purified clays, calcium carbonate, calcium sulphate, dicalcium phosphate etc.

When drug substances have low water, solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct compression formulas.

BINDERS

Agents used to impart cohesive qualities to the powdered materials are referred to as binder’s granulators. They impart cohesiveness to the tablets formulation which insures tablets remaining intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size.

Materials commonly used as binder are gelatin, starch, sugar as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic
gums, which have been used, include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, carboxymethyl cellulose, polyvinyl pyrrolidone.

Other agents, which may be considered binders under certain circumstances, are polyethylene glycol, ethyl cellulose, waxes, water and alcohol. Water, alcohol and acetone or mixtures thereof, are not binders in their own right. They act by means of their solvent effect upon ingredient e.g. sucrose in a tablet formula (1, 43).

The quantity of binder used has considerable influence on the characteristic of the compressed tablets. The use of too much binder or too strong binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies.

Binders are used both as a solution and in a dry form depending on the other ingredients in the formulation and the method of preparation.

The direct compression methods for preparing tablets requires a material that is not only free flowing but also have sufficient cohesiveness to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose and polyvinyl pyrrolidone.
LUBRICANTS

Lubricants have a number of functions in tablet manufacture. They prevent adhesiveness of tablet materials to the surfaces of the die and punches, reduce inter particle friction, facilitate the ejection of the tablet from the die cavity and improve the rate of flow of the tablet granules.

Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil and polyethylene glycol (PEG). Most lubricants with the exception of talc are used in concentration less than 1% when used alone; talc may require concentration as high as 5%.

Lubricants are in most cases hydrophobic materials. Poor selection or excessive amount can result in “water proofing” the tablets, resulting in poor tablet disintegration and/or delayed dissolution of drug substance.

GLIDANTS:

A glidant is a suitable substance, which improves the flow characteristics of a powder mixture. These materials always are added in the dry state just prior to compression (i.e. during the lubrication step). Colloidal silicon dioxide [cab-o-sil (cabot); Quso (Phila quartz)] is the most commonly used glidant and generally is used in low concentration
of 1% or less. Talc (asbestos-free) also is used and may serve the dual purpose as lubricant glidant.

**DISINTEGRANTS**

A disintegrant is a substance, or a mixture of substance added to a tablet to facilitate its breakup to disintegration after administration.

Materials serving as disintegrants have been classified chemically as starches, clays, cellulose, gums and cross-linked polymers.

The oldest and still the most popular disintegrants 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. Starch 5% is suggested, but if more rapid disintegration is desired, this amount may be increased to 10-15 %. In addition to the starches a large variety of materials have been used and are reported to be effective as disintegrants. This group includes vegum HV methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, guar gum, citrus pulp and carboxymethyl cellulose. Sodium lauryl sulphate in combination with starch has been demonstrated to be an effective disintegrant.

**SUPER DISINTEGRANTS**

A new group of materials known as "super disintegrant" have gained in popularity as disintegration agents. The names comes from the
low levels (2 to 4 %) at which they are completely effective. Croscarmelose, crospovidone and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer and cross-linked starch respectively.

The development of these disintegrants fostered new theories about the various mechanism by which disintegrants work. Sodium starch glycolate swells seven to twelve folds in less than 30 seconds. Croscarmelose swells four to eight fold in less than 10sec. The disintegrating agent usually is mixed with the active ingredients and dilutes prior to granulation. In some cases it may be advantageous to divided the starch into two portions. One part is added to the powdered formula prior to granulation, and remainder is mixed with the lubricant and added prior to compression.

**COLOURING AGENT**

When a coloured tablet is desired, a certified food and drug colour is normally added by dissolving the dye in the binding solution, spraying the granules with a special solution of the dye, distributing the dye through the dry mix and then employing wet granulation or adding a triturate of the dye to starch or calcium sulphate. Such dye triturates are commercially available. A no. 40-mesh granulation or fixer is necessary to avoid mottled tablets.
FLAVOURING AGENTS

If flavoured tablets are desired, it is usually accomplished by spraying an alcoholic or ethereal solution of a volatile oil or other flavouring agents on the dry granules before the compression of the finished tablets. After spraying the granules are tumbled and some times stored in sealed containers to allow greater permeation of the flavour. Frequently fruit flavour are also incorporated into the original powder mix before granulation (1).
METHODS OF MANUFACTURE

The method used for preparing compressed tablets are:

- Wet granulation method
- Dry granulation method
- Direct compression

Each method has its advantages and disadvantages, specific applications and restriction. The choice of methods depends upon a number of factors, the most important being the properties and the dose of the drug. Other factors include the choice of available equipments and relevant practical and regulatory concern (44).

WET GRANULATION METHOD

Wet granulation is a widely employed method for the production of compressed tablets. The various steps involved in the wet granulation process have significant effect on the tableting properties of the resulting granulation. It is therefore, important to understand these process parameters in term of their impact on process design and selection of formulation components. Essentials to the wet granulation process are the following operation processes.

- Preparation of the powder mixture with screening and mixing.
- Addition of binder solution and mixing with powder to proper wetness.
- Drying the solid liquid blend.
- Milling the dry granulation to size.
- Addition of lubricant, glidant and/or other expipient prior to compression (44).

In granulation the first stage is the preparation of the granulation fluid. Most of these act more satisfactorily when freshly made and it is therefore, convenient to do this while the remaining ingredients are being mixed. It is often advantageous to incorporate the granulating fluid while hot since it is then mobile and penetrates the powder more readily. Commonly used solution include starch paste (10%), liquid glucose (50%), acacia mucilage (10%) and gelatin (5-10%). Each fluid has its own special features and it may some times be necessary to use a combination of two or more. The moist granules are spread uniformly and thinly on the tray (about \( \frac{1}{2} \) inch - 1 inch deep) and these are then transferred to the drying oven. The drying cycle will vary from one material to another by a typical requirement would be of the order of 8-12 hours at 60°C and by appropriate use of automatic time switches this can often be done over night. If there is any risk of contamination by atmospheric dust particles, trays containing white granules should be covered with papers before drying. The granules are then placed in clean, dry, covered container ready for compression (2).
ADVANTAGES OF WET GRANULATION

1. The cohesiveness and compressibility of powder is improved due to added binder which coats the individual powder particle, causing them to adhere to each other so they can be formed into agglomerates called granules. During the compaction process, granules are fractured, exposing fresh, clean powder surfaces and this also improves compressibility. Lower pressures are therefore needed to compress tablets resulting in improvements in tools life and machine wear.

2. High dosage during having poor flow or compressibility properties must be prepared by wet granulation to obtain suitable flow and cohesion for compression. In this case; the proportion of dry binder needed to produce a tablet by direct compression.

3. Good distribution and uniform contents for soluble low dosage drug and color additives is obtained, if these are in the binder solution of a wet granulation. This represent a distinct advantage over direct compression, when content uniformity of drug and uniform color dispersion can be a problem.

4. The wet granulation prevents segregation of components of a homogenous powder mix during processing, transferring and handling. In effect, the composition of each granules become fixed
and remains the same as/or very nearly of the powder mixture at the time of liquid – binder addition.

5. The dissolution rate of a hydrophobic drug may be improved by wet granulation with proper choice of solvent and binder
LIMITATION OF WET GRANULATION

The greatest disadvantage of wet granulation is its cost. It is an expensive process because of the labour, time, equipment, energy and space requirement. However, a number of improvements have been made in recent years to improve the wet granulation method and reduce its cost. These include:

1. A solid liquid twin – shell blender with a dispersion bar to add the binder solution to produce agglomerates, with a heated jacket and vacuums take off to facilitate and hasten drying. This unit, properly operated, can produce a complete granulation.

2. A fluidized bed dryer equipped with a spray head to add the binder and other component, granulating and drying simultaneously.

3. Mixtures such as Lodge and Diosna, which provide efficient and rapid solid – solid and solid liquid blending, reducing the time and material handling involved. Wet granulation of moisture sensitive drugs can usually be overcome by the use of anhydrous solvents with solvent soluble binders to form the wet mass to produce the granulation.

The use of soluble dyes in wet granulation often causes migration of the dyes during the drying cycle. This can be overcome by the use of insoluble lake dyes which do not migrate in either aqueous or solvent granulation.
An inherent limitation of wet granulation is that any incompatibility between formulation components will be aggravated by granulating solvents bringing them into close contact (2, 44).

**DRY GRANULATION METHOD**

In dry granulation method the granulation is formed by compacting large masses of the mixture and subsequently crushing and sizing these pieces into smaller granules. By this method, either the active ingredient or the diluent must have cohesive properties in order for the large masses to be formed. This method is especially applicable to the material that cannot be prepared by the wet granulation method due to their sensitivity to moisture or to the elevated temperature required for drying.

After weighing and mixing the ingredients the powder is slugged or compressed into large flat tablets or pellets of about 1 inch in diameter. It is possible to do this because the flow of powder into the slugging machines is facilitated by the large cavity and the tablet need not be of exact size and weight.

The slugs are broken up by hand or by a mill and passed through a screen of desired mesh for sizing. Lubricant is added in the usual manner and tablets are prepared by compression. Instead of slugging method, compaction mills may be used to increase the density of a powder by pressing it between high-pressure rollers.
DIRECT COMPRESSION

Some granular chemicals like potassium chloride, potassium iodide, ammonium chloride and methenamine possess free flowing as well as cohesive properties that enable them to be compressed directly in a tablet machine without need of either wet or dry granulation.

Today the use of spray-dried diluents rather than plane powdered diluents imparts to certain tablet formulations the required qualities for tablet production by direct compression, and many additional products may now be produced in this manner. In addition, the forced or induced feeders which have been developed permit the preparation of certain additional tablets by direct compression because the deaerating action of the feeder on light, bulky powder makes them more dense and permits them to flow evenly and completely into the die cavities under moderate pressure. This deaeration also eliminates air entrapment within the die as the tablets are compressed (1).
CHARACTERISTICS OF TABLETS

Compressed tablets may be characterized or described by a number of specifications. These include the diameter, size, shape, thickness, hardness, weight, disintegration time and dissolution characteristics.

DIAMETER SIZE AND SHAPE

The diameter, size and shape depend on die and the punches selected for the compression of the tablet. Generally tablets are discoid in shape, although they may be oval, oblong, round, cylindrical or triangular (2). The size of tablets produced depends not only on the weight of the fill but also on the diameter of the die and upon the pressure applied to the fill on compaction (1, 2).

TABLET WEIGHT

The amount of fill placed in the die of a tablet press will determine the weight of the resulting tablet. The volume of fill (granulation of the powder) permitted to enter the die must be adjusted with the first few tablets produced to yield tablets of desired weight.

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. A number of tablet hardness tester in use measure the degree of force (in kilograms, pounds, or in arbitrary units)
that is required to break a tablet. In the industry, a force of about 4 kg is considered to be the minimum permitted for a satisfactory tablet.

Hardness determination are made throughout the tablet runs to determine the pressure adjustments on the tableting machine. If tablet is too hard, it may not disintegrate in the required period of time or meet the dissolution specification, if it is too soft, it will not withstand the handling during subsequent processing such as coating or packaging and shipping operation (2, 74).

**TABLET THICKNESS**

The thickness desired in a tablet must be coordinated with the volume of fill issued to the die, the diameter of the die and the pressure applied to the fill by punches. In order to produce tablets of uniform thickness during production and between production for same formulation, care must be exercised to employ the same volume of fill and same pressure.

Tablets of same product which vary in size not only might alarm the patient but also might cause problem in packaging. Tablets are measured with the caliper during production to make certain of consistent thickness.

The thickness of a tablet is varied more by the size of the die and fill permitted than by pressure. Pressure adjustments are made primarily to control the softness or the hardness of the tablets.
UNIFORMITY OF DOSAGE FORMS

The dose uniformity of tablets can be determined by two different general approaches. Weight variation or drug content uniformity. The USP permits the latter approach in all cases and must be used for coated tablets. Weight uniformity can only be applied to uncoated tablets which contains 50 mg or more of a single active ingredients which in addition comprises 50% or more of the total weight of the tablet.

(A) Weight Variation

Most pharmacopoeias include a simple weight test on a specified number of tablets which are weighted individually and the arithmetic mean weight is calculated. Limitations on the number of test tablet that may lie out side certain limits are then specified. However, in the USP the results assay are used to convert these weights into active ingredient content.

(B) Content Uniformity

In order to ensure that every tablet contains the amount of drug substance intended, with little variation among tablets with in a batch, USP include the content uniformity test for certain tablets.

This USP test is designed to establish the homogeneity of the batch. 10 tablets are assayed individually, and the arithmetic mean and Relative Standard Deviation are calculated. USP criteria is met if the content uniformity lies with in 85% to 115% of the label claim and the
RSD is not greater than 6%. The same criteria is applied to result calculated from the weight variation described above. Provision is included in the compendium for additional testing if one or more units fail to meet the standards (2, 74).
TABLET DISINTEGRATION

Disintegration of tablets or solid dosage form may be defined as the act of disintegrating or state of being disintegrated i.e. the act of crumbling or gradual decay. In the case of a tablet it is the process of the whole tablet breaking up into small pieces or granules when in contact with some fluid.

Dissolution is the act of dissolving. Rate of dissolution is the rate of dissolving of the medicament from the intact dosage form on fragments of the disintegrated dosage form. In the case of a tablet, prepared in such a manner that it is intended to disintegrate. Disintegration occurs with the production of fragments, granules and aggregates of powder (42).

FACTORS AFFECTING TABLET DISINTEGRATION

Method of added disintegrants

Addition of the disintegrant to the powders before granulation, addition to the dried granules and addition to both powders and granules made several investigations to determine which procedure would be better. The result were different.

The addition of starches or colloidal silicon dioxide to granules was reported as more effective (45). The addition of starch before and after granulation was described as most effective; the addition of disintegrates before and after wet or dry granulation was stated to have no effect (46). No difference between the method of disintegrant addition or slugging was also mentioned.
EFFECT OF DISINTEGRANT CONCENTRATION

Malay et al. (47) found that pressure usually decreased as disintegrant concentration increased, to attempt to keep a constant radial hardness. Potatoes starch and alginic acid with organic or inorganic water-soluble drug needed slightly increased pressure. Tablet hardness was suggested as a predictor of disintegration time (48).

EFFECT OF MATERIAL AND PARTICULAR DISINTEGRANT

Shteingart et al. (49) reported that tablet with water insoluble drug disintegrated quickly with starch while those with water soluble drug did not disintegrate as well due to the diminished absorption capacity of starch.

In a statistical study, Holstin and Dekay (50) used sulfathiazole, sodium bicarbonate, and an aspirin mixture, gelatin-acacia solution, sucrose solution and starch paste as binder, and arrowroot, corn, potato, sweet potato, rice, sorghum, tapioca, and wheat starches, bentonite, and sodium alginate as disintegrants. They found that sulfathiazole had higher disintegration time than sodium bicarbonate, and the aspirin mixture had the lowest time.

Gelatin-acacia had the largest time, followed by sucrose solution, and starch paste gave the lowest break-up times. Bentonite produced much larger disintegration times than the starches.
EFFECT OF PHYSICAL PROPERTIES OF DRUG AND EXCIPIENTS

Chalabala and Malay (51) determined that disintegration was affected by the physical properties of the drug, excipient and by the process. They studied various drugs, filler binder, disintegrants and lubricants in different concentration. Potatoes, corn, rice and wheat starches has less effect on water-soluble tablet than on tablets of lyphobic drugs. Generally wood cellulose was reported best except for phenyl oxy methyle penicillin. Potato starches and amyllopectin also were effective. They claimed that a significant drug disintegrant interaction showed that there is no universal disintegrant and that each drug must be tested for on optimum disintegrants.

EFFECT OF BINDER

Kwan et al. (60) found that binders had a significant effect on disintegration. Starch paste gave the lowest disintegration time compared to gums. Binder effect may be due to rate of dissolution or dispersion of the binder.

As early as 1915, it was revealed that binders such as gelatin and glu might result in 2-3 hours disintegration (52). Among the many binder’s comparison described, aqueous binder was better than ethyl cellulose (53), ethyl cellulose was better than gelatin (54), gelatin solution was better than soluble starch (55), starch paste was better than gums (56, 57). Increase in molecular weight of polyvinyl pyrrolidone or polyvinyl alcohol above 50,000 increased binding capacity but
decreased disintegration rate (58), a vinyl polymer cause disintegration time to increase more rapidly with an increase in pressure than did starch paste (59), starch paste was better than polyvinyl pyrrolidone or acacia, aqueous acacia or methyl cellulose increase disintegration time, but an alcohol chloroform solution of methyl cellulose gave rapid disintegration, starch paste gave lower disintegration time than syrup, gelatin acacia, and ammonium calcium alginate.

In the present study five different disintegrants/binders, i.e., starch, gum, acacia, avicel, gelatin carboxymethyl cellulose and polyvinyl pyrrolidone. These disintegrants/binders have been used alone or in combination with others. The result of these disintegrants/binders on the disintegration time of ephedrine tablets has been summarized in following Table A.

**TABLE A**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Disintegrants</th>
<th>Binders</th>
<th>Disintegration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Starch</td>
<td>Starch</td>
<td>4 min</td>
</tr>
<tr>
<td>2</td>
<td>Starch</td>
<td>Polyvinyl pyrrolidone</td>
<td>3.5 min</td>
</tr>
<tr>
<td>3</td>
<td>Starch</td>
<td>Avicel</td>
<td>10 sec</td>
</tr>
<tr>
<td>4</td>
<td>Starch</td>
<td>Starch</td>
<td>40 sec</td>
</tr>
<tr>
<td>5</td>
<td>Avicel</td>
<td>Starch</td>
<td>5 min</td>
</tr>
<tr>
<td>6</td>
<td>Gelatin &amp; starch</td>
<td>Carboxymethyl Cellulose</td>
<td>2.14 min</td>
</tr>
<tr>
<td>7</td>
<td>Starch</td>
<td>Gum accacia</td>
<td>3.5 min</td>
</tr>
<tr>
<td>8</td>
<td>Starch</td>
<td>Polyvinyl Pyrrolidone</td>
<td>Min</td>
</tr>
</tbody>
</table>
The best result was achieved by the combination of starch as disintegrant and avicel as a binder. Next result was obtained by incorporating starch with carboxymethyl cellulose. The rate of disintegration of the tablet containing gelatin as disintegrant was very high (5 minutes). This is because of the gummy nature of the disintegrant which keeps the fragments of the tablet intact and the tablets do not crumble apart. This result with other disintegrant and binders used in other formulations were satisfactory.

EFFECT OF LUBRICANTS

Kawn et al. (60) also found that lubricants affected disintegration times of starch-lactose tablets. It was suggested that the lubricant effect might have been due to increasing the hydrophobicity of the materials. Talc affected disintegration time less than mineral oil, stearic acid and calcium stearate.

The effect of lubricant on the disintegration may be attributed to their water repellent nature (61) as well as the fact that they are added just prior to compression to coat the granules physically. In the present investigation we have used magnesium stearate and/or talc. The result are summarized in following Table B.
### TABLE B

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Lubricants</th>
<th>%age</th>
<th>Disintegrants</th>
<th>%age</th>
<th>Binders</th>
<th>%age</th>
<th>Disintegration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Magnesium stearate</td>
<td>2</td>
<td>Starch</td>
<td>7.2</td>
<td>Starch</td>
<td>30.9</td>
<td>4 min</td>
</tr>
<tr>
<td>2</td>
<td>Magnesium stearate</td>
<td>2</td>
<td>Starch</td>
<td>29.8</td>
<td>Polyvinylpyrrolidone</td>
<td>8.2</td>
<td>3.4 min</td>
</tr>
<tr>
<td>3</td>
<td>Magnesium stearate</td>
<td>2</td>
<td>Starch</td>
<td>36</td>
<td>Gum acacia</td>
<td>5.1</td>
<td>3.2 min</td>
</tr>
<tr>
<td>4</td>
<td>Magnesium stearate</td>
<td>2</td>
<td>Starch</td>
<td>28.8</td>
<td>Avicel</td>
<td>9</td>
<td>10 sec</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium stearate</td>
<td>2</td>
<td>Avicel</td>
<td>25.7</td>
<td>Starch</td>
<td>15.4</td>
<td>40 sec</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium stearate + talcium</td>
<td>2&amp;2</td>
<td>Gelatin and</td>
<td>2&amp;41</td>
<td>Starch</td>
<td>8.2</td>
<td>5 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Starch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Magnesium stearate + talcium</td>
<td>2&amp;3</td>
<td>Starch</td>
<td>30.9</td>
<td>Carboxymethyl cellulose</td>
<td>4.1</td>
<td>2.14 min</td>
</tr>
<tr>
<td>8</td>
<td>Talcum</td>
<td>4</td>
<td>Starch</td>
<td>30.9</td>
<td>Polyvinylpyrrolidone</td>
<td>5.1</td>
<td>4.45 min</td>
</tr>
</tbody>
</table>

### EFFECTS OF HARDNESS.

Table C shows different disintegration time with respect to hardness.

### TABLE C

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Hardness in kg</th>
<th>Disintegration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.31</td>
<td>4 min</td>
</tr>
<tr>
<td>2</td>
<td>6.82</td>
<td>3.5 min</td>
</tr>
<tr>
<td>3</td>
<td>7.6</td>
<td>3.2 min</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>10 sec</td>
</tr>
<tr>
<td>5</td>
<td>8.91</td>
<td>5 min</td>
</tr>
<tr>
<td>6</td>
<td>6.7</td>
<td>2.14 min</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>4.45 min</td>
</tr>
</tbody>
</table>
REASONS FOR MEASURING DISINTEGRATION TIME AND RATE OF DISSOLUTION

- For research purposes to elucidate the mechanisms involved in the process and to determine the relative importance of the various variables involved in the processes.

- For development purposes to guide the pharmaceutical formulation in the preparation of optimum dosage forms of drugs for clinical trial.

- For control purposes to guide the pharmaceutical product in essentially uniform form batch to batch.

- For predictive purposes so that one may estimate rate of absorption in vivo and / or availability of drug for absorption in man from measurement of disintegration time and / or rates of dissolution in vitro. Such prediction requires careful correlation of in vitro and in vivo results (42).
TABLET DISSOLUTION

Dissolution is the process by which solid solutes of only fair solubility characteristics enter into solution. It is a qualitative tool, which can provide valuable information about the biological availability of a drug as well as batch consistency. Another area of difficulty is the fact that the accuracy and precision of the testing procedure is dependent to large extent on the strict observance of so many subtle parameter and detailed operational controls.

In spite of these shortcomings, dissolution is considered today as one of the most important quality control test performed on pharmaceutical dosage forms.

The earliest reference to dissolution is probably an article by Noyes and Whitney in 1897 (62), about “The rate of solution of solid substances in Their Own Solution”. The authors suggested that the rate of dissolution of solid substances is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. Noyes and Whitney developed the mathematical relationship that co-relates the dissolution rate to the solubility gradients of the solid. Their equation is still the basic formula upon which most of the modern mathematical treatments of dissolution phenomenon revolve.
Other studies, especially those reported by Nelson (63), Levy (64) and Hayes, confirmed beyond doubt, the significant effect of the dissolution behavior of drug on their pharmacological activities. Because of the novelty and importance of these findings, dissolution testing began to emerge as a dominant topic within both the pharmaceuticals academia and the drug industry. In the late 60s, biopharmaceutics were established as an important discipline in the pharmaceutical sciences and dissolution testing become a mandatory USP requirement for several dosage forms.

THEORITICAL CONCEPTS FOR THE RELEASE OF A DRUG FROM DOSAGE FORMS

In determining the dissolution rate of drugs from solid dosage forms under standardized conditions, one has to consider several physico-chemical process. These include wetting characteristics of the solid dosage forms, penetration ability of the dissolution medium into the dosage forms, the swelling process, disintegration and deaggregation.

Carstensen (65) explained that the wetting of the dosage solid surface controls the liquid access to the solid surface and, many times, is the limiting factor in the dissolution process. The speed of wetting is directly dependent upon the surface tension at the interface (interfacial tension) and upon the contact angle $\theta$, between the solid surface and the liquid. Generally, a contact angle of more than 90° indicate poor wettability. Incorporation of a surfactant, either in the formulation or in
the dissolution medium, lowers the contact angle or enhances dissolution.

**CO-RELATION BETWEEN DISINTEGRATION AND DISSOLUTION**

In general, disintegration has proved to be a poor indicator of bioavailability because of the turbulent agitation maintained during the test. Several other factors such as solubility, particle size, and crystalline structure, among others, have been found to affect seriously the dissolution of the drug substance but have no relevance to disintegration.

**FACTORS AFFECTING THE RATE OF DISSOLUTION**

Factors that affect the dissolution rate of drug forms can be classified under three main categories as delineated below;

**(a) FACTORS RELATING TO THE PHYSICO-CHEMICAL PROPERTIES OF THE DRUG**

The physico-chemical properties of the drug substance play a prime role in controlling its dissolution from the dosage form. Solubility of the drug is the major factor, which determines its dissolution rate.

Other factors that affect dissolution rates include:

- Particle size
- Crystalline state, such as polymorphism and state of hydration
- Solvation
- Complexation
- Surfactants
- Density
- Viscosity
- Wettability
- Adsorption characteristics of drugs.

**EFFECT OF PARTICLE SIZE ON DISSOLUTION RATE**

There is a direct relation between the surface area of the drug and its dissolution rate. Since the surface area increases with decreasing particle size, higher dissolution rates may be achieved through reduction of the particle size. This effect has been highlighted by the superior dissolution rate observed after micronization of certain sparingly soluble drugs as opposed to the regularly milled form. Micronization increases the surface area exposed to the dissolution medium and, hence, improves the rate of dissolution. Physical properties of the drug particles other than size also affects indirectly the effective surface area by modifying the shear rate of the fresh solvent that comes in contact with the solid. These properties include the particle shape and the density (66, 67).

**EFFECTS OF CRYSTALLINE STATE OF THE DRUG ON DISSOLUTION RATE**

The solid phase characteristics of drugs, such as amorphicity, crystallinity, state of hydration and polymorphic structure has been
shown to have significant influence on the dissolution rate. Mullins and Macek showed that the amorphous form of norvobiocin has a crystalline form. Blood level studies confirmed such finding where administration of the amorphous form yielded about 3-4 times the concentration compared to the administration of the crystalline form. Similar differences were demonstrated for griseoflavrin, Phenobarbital, cortisone acetate, and chloramphenicol (68, 69)

**EFFECTS OF PHYSICAL PROPERTIES**

Physical properties such as density, viscosity and wettability contribute to the general dissolution problems of flocculation, flotation and agglomeration.

**EFFECTS OF ADSORPTION CHARACTERISTICS**

Adsorption characteristics of the drug have also been found to have significant effect on the dissolution of certain drugs.

**[b] FACTORS RELATING TO THE SOLID DOSAGE FORM**

The effect of various formulation and manufacturing processing factors on the rate of dissolution and bioavailability of the active ingredients from tablets and capsules have been well documented by several investigators since the early sixties. The following discussion of earlier and current finding can certainly serve as a guideline for the pharmaceutical scientists especially during the initial stages of the formulation design and product development.
EFFECT OF FORMULATION FACTORS ON TABLET DISSOLUTION RATE

It has been shown that the dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts during the manufacturing process of solid dosage forms.

Diluents and Disintegrants

Levy (70) in 1963, studied the effect of starch, the most commonly used diluent, on the rate of dissolution of salicylic acid tablets manufactured by dry double compression process. Increasing the starch contents from 5 to 20% resulted in a dramatic increase in the dissolution rate. Later, however, Finholt (71) suggested that the hydrophobic drug crystals acquire a surface layer of fine starch particle that impart a hydrophilic property to the granular formulation and thereby increase the effective surface area and hence the dissolution rate.

Binders and Granulating Agents

Difference in binders used for tolbutamide tablets resulted in variable dissolution characteristics and difference in the hypoglycemic effects observed clinically. Wet granulation, in general has been shown to improve dissolution rate of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules. Solvang and Finholt (72) showed that Phenobarbital tablets granulated with gelatin solution dissolved much faster in human gastric juice than those
prepared with sodium carboxymethyl cellulose or polyethylene glycol 6000 as a binder. They suggested that gelatin impart hydrophilic characteristics to the hydrophobic drug surface, whereas polyethylene glycol forms a complex with poor solubility sodium carboxymethyl cellulose is converted to its less soluble acid form in low pH gastric juice (73).

**Lubricants**

Levy and Leonard (74) investigated the effects of different types of lubricants on the dissolution rate of salicylic acid tablets. They found that magnesium stearate, a hydrophobic lubricant, tends to retard the dissolution rate of salicylic acid tablet, while a water soluble surface-active lubricant, sodium lauryl sulfate, enhanced the dissolution rate significantly.

(e) **EFFECTS OF THE PROCESSING FACTORS ON DISSOLUTION RATES OF TABLETS**

The many processing factors used in tablet manufacturing greatly influence the dissolution rates of the active ingredients. The method of granulation, the size, density moisture contents and age of granules, as well as the compression force utilized in the tabletting process, all contribute to the dissolution rate characteristics of the final product.

**Method of Granulation**
Studies have shown that the granulation process, in general enhances the dissolution rate of poorly soluble drugs. The use of fillers and diluents, such as starch, spray-dried lactose and microcrystalline cellulose, tend to increase the hydrophilicity of the active ingredients and improve their dissolution characteristics. In this regard, the wet granulation procedure was traditionally considered as a superior method compared to the dry or double compression procedure. With the advent of newer tableting machines and materials, however, it became more evident that the careful formulation and proper mixing sequence and time of adding the several ingredients are the main criteria that affect the dissolution characteristics of the tablets and not the method of granulation (75).

Effects of Compression Force on Dissolution Rate

In his early studies of the physics of tablet compression, Higuchi (2) pointed to the great influence of the compressional force employed in the tableting process on the apparent density, porosity, hardness, disintegration time, and average primary particle size of compressed tablets. There is always a competing relationship between the enhancing effect due to the increase in surface area through crushing effect and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness, consequently, a decrease in solvent penetrability. The high compression also may inhibit the wettability of the tablet due to the formation of a firmer and more effective sealing
layer by the lubricant under the high pressure and temperature that usually accompanies a strong compressive force (71, 76).

**EFFECTS OF TEST PARAMETERS ON DISSOLUTION RATE**

**Agitation**

The relationship between intensity of agitation and the rate of dissolution varies considerably according to the type of agitation used, the degree of laminar and turbulent flow in the system, the shape and design of stirrer, and the physico-chemical properties of the solid (77, 78).

Other factors that affect the correlation between agitation and dissolution rate include the density of the solid phase, the size and characteristics of the solid, the stirrer, the dissolution vessel and the heat of solution of the solute.

**Temperature**

Since drug solubility is temperature dependent, its careful control during the dissolution process is very important and should be maintained within 0.5°C. Generally a temperature of 37°C is always maintained during dissolution determination. The effect of temperature variations of the dissolution medium depends mainly on the temperature/solubility curves of the drug and excipients in the formulation (79).
DISSOLUTION MEDIUM

The selection of the proper fluid for dissolution testing depends largely on the solubility of the drug as well as mere economics and practical reasons.

pH of the Dissolution Medium

Great emphasis and effort was first placed on simulating in vivo conditions. Especially pH, surface tension, viscosity, and sink condition. Most of the early studies were conducted in 0.1N HCl or buffered solutions with a pH close to that of the gastric juice (pH-1.2). The acidic solution tends to disintegrate the tablet slightly faster than water and there by it may enhance the dissolution rate by increasing the effective surface area.

Surface Tension of the Dissolution Medium

Surface tension has been shown to have a significant effect on the dissolution rate of drugs and their release rate from solid dosage forms. Surfactants and wetting agents lower the contact angle and thereby improve the penetration process of the matrix by the dissolution medium. A measurable enhancement in the dissolution rate of salicylic acid from an inert matrix was reported by Singh et al. when the contact angle \( \theta \) was lower from 92\(^\circ\) (water) to 31\(^\circ\) (using 0.01% dioctyl sodium sulfo succinate) (80). The same findings were obtained in benzocaine studies when polysorbate 80 was used as the surface-active agent (81). Other studies conducted on conventional tablet formulation and
capsules also showed significant enhancements in the dissolution rate of poorly soluble drugs when surfactants were added to the dissolution medium, even at a level below the critical micelle concentration, probably by reducing the interfacial tension (82).

Finhold and Solvang (71) composed the dissolution behavior of phenacetin and phenobarbital tablets in human gastric juice to that in dilute HCl with and without various amount of polysorbate 80 in the dissolution medium. The data showed that both pH and surface tension have significant influences on the dissolution kinetics of the drugs studies.

**Viscosity of the Medium**

In the case of diffusion-controlled dissolution process, it would be expected that the dissolution rate decrease with an increase in viscosity. In the case of inter-facial controlled dissolution processes however, viscosity should have very little effect. Braun and Parott showed that the dissolution rate of benzoic acid is inversely proportional to the viscosity of the dissolution medium utilizing various concentrations of sucrose and methylcellulose solutions (83).
EFFECTS OF β-CYCLODEXTRIN ON BIOPHARMACEUTICAL PROPERTIES OF DRUGS

Starch is most commonly used tablets disintegrant, though its advantages have been recognized for a long time. A large concentration of starch is necessary to achieve proper disintegration of a tablet, but the use of high concentration results in soft tablets because of the weak cohesive and adhesive properties of starch (84). Many attempts have been made to find new disintegrating agents that would improve the disintegration and dissolution behavior without adversely affecting the tablet matrix (85).

Cyclodextrin polymer a newly discovered disintegrant (86) seems to meet this requirement as demonstrated by Eva Fenyveri (86) by the binding properties of this material together with its accelerating effect on disintegration and dissolution. Cyclodextrins (α-cyclodextrin, β-cyclodextrin γ-cyclodextrin) are produced by the enzymatic degradation of starch and have been used as carrier for drug delivery system (87,88).

α-, β and γ-cyclodextrins are composed of six, seven and eight d-glucopyranose units respectively. Isolation of β-cyclodextrin was carried out by Villiers in 1891 (89), of α and β-cyclodextrin was carried out by Schardinger in 1903 (90) and of γ-cyclodextrin was carried out by Freudenberg in 1935 (90) and X-ray molecular weight determination was carried out by French (92, 93).
α-Cyclodextrin having molecular formula C_{36}H_{60}O_{30} and chemical name cyclohexa-amyllose have hexagonal plates or blades-shaped needles. β-Cyclodextrin having chemical formula C_{42}H_{70}O_{35} and chemical name cyclohepta-amyllose have parallelogram shaped crystals and γ-cyclodextrin having molecular formula C_{48}H_{80}O_{40} and chemical name cycloocta-amyllose having square plates or rectangular rods (94).

Martini used dehydrated β-cyclodextrin as a pharmaceutical expipient and evaluated for improving bio-pharmaceutical properties of drugs (95). Seiki et al. compared the moisture adsorption properties of α, β, γ-cyclodextrins and branched α-cyclodextrin and found that branched cyclodextrin have less interaction with water (96). Similarly Eniko et al. (97) compared the membrane diffusion of α, β and γ-dimethyl β-cyclodextrin and methyl-β-cyclodextrins and found that different cyclodextrins exert their influence on pharmaceutical diffusion in different ways depending upon ratio of cyclodextrin and the mode of preparation of product.

Munoz-Ruiz et al. (98) showed through a study that particle size distribution and particle shape uniformity is found in β-cyclodextrin as compared to α, γ-cyclodextrins which shows big differences.

Valero Margarita et al. (99) showed that β-cyclodextrin was more hydrophobic than α- and γ-cyclodextrin when inclusion complex of NSAIDs were made with cyclodextrins. In another study, it was found
that all cyclodextrins are highly prone to plastic deformation. Hp-β and β-cyclodextrins were especially prone to last elastic recovery with increasing punch velocities (100).

Pande, Girish Shridhar characterized β-cyclodextrin for direct compression in tableting. Abdul Rahman et al. (101, 102) found that amorphous state of DM β-cyclodextrin can be transferred into crystalline by heating the ground mixture of flunitrazepan with DM β-cyclodextrin.

Tasic et al. (103) studied the compression behaviour of paracetamol tablets with β-cyclodextrin and found that β-cyclodextrin has positive influence on paracetamol characteristics.

Ikeda et al. (104) modified cyclodextrins and compared their binding abilities with unmodified ones and found that binding ability was stronger for modified cyclodextrins.

Cyclodextrins have hydrophobic cavities, form inclusion compounds with organic substances, salts and halogens in the solid state in aqueous solution (105, 106). Cyclodextrin as well as their derivatives have ability of encapsulating in their cavities a wide variety of molecules conferring in their cavities a wide variety of molecules conferring on them new physico-chemical characteristics (107).

Cyclodextrins can deliver drugs because they trap complex hydrophobic molecules in their hydrophobic cavity. The outside of the
doughnut being hydrophilic makes the molecules as a whole partially soluble in water. Thus a hydrophilic or otherwise insoluble drug can be made orally active and absorbed from the gut rather having to be injected (108).

Cyclodextins form inclusion complex with some drugs such as ibuprofen and acetaminophen. The effect of heating and grinding process on the formation of inclusion complex between acetaminophen and α-cyclodextrin and β-cyclodextrin were investigated by Lin, Shan, Young in 1992. The interaction of excess amounts of acetaminophen-cyclodextrin system was also examined. The process of grinding or freeze-drying did not cause any interaction between acetaminophen, α-cyclodextrin, but heating could result in its complex formation. However, all the processes (heating, freeze-drying, grinding) could improve the inclusion formation of acetaminophen and β-cyclodextrin (109).

In one study, double compression technique was used to prepare spironolactone-β-cyclodextrin complex which showed an increased dissolution rate (110). Similarly the release of ibuprofen from suppository was significantly increased by complexation with HP-β-cyclodextrin (111).

Lin, Shan, Yang et al. studied that acetaminophen easily forms inclusion complex with β-cyclodextrins by heating. Similarly Asitileon
et al. formed inclusion complex of diclofenic sodium with β-cyclodextrin which shows chemical shifts by NMR spectroscopy (112, 113).

Penkler, Lawrence, John et al. formed inclusion complex of NSAIDs with β-cyclodextrin e.g. diclofenic sodium (114) and combined it with physiologically accepted alkali agent and found that the alkali agent forms a diffusion layer around the compound in GIT.

Ammer et al. (115) showed improvement of some pharmaceutical properties of drugs by cyclodextrin complexation. The study indicate that β-cyclodextrin leads to a marked protection of the drug (colchicine) against photo degradation.

Cyclodextrins have been extensively studied in order to improve the water solubility of drugs with a view to increase their bioavailability. However, due to a number of regulatory delays and to the appearance of new derivatives today. There are new possibilities for the use of cyclodextrins and their derivatives. Some of these new possibilities take the form of carriers in dermal and parenteral forms, penetration enhances for nasal administration incorporation in macrospheres and the preparation of nano-particles (116). Schipper in 1993 (117) studied the nasal absorption enhancer.

Cyclodextrins had strong accelerating effects on the release of salicylic acid from various ointment bases (118). Cyclodextrins are used
as complexing agent in study of enzyme action. Among these
β-cyclodextrin is good as direct compression excipient (119).

Takahshi et al. (120) al showed improved bioavailability of oral
composition containing therapeutic basic compounds and cyclodextrins.

Penklar et al. (121) also showed that pharmacokinetic properties
are enhanced in oral and parenteral diclofenic/β-cyclodextrin delivery
system. Significant enhancement was shown in both intravenous and
intramuscular pharmacokinetics. Sharma et al. proved that cyclodextrin
can increase the solubility and stability of some poorly water soluble
drugs (122).
2. EXPERIMENTAL WORK
EXPERIMENTAL WORK

MATERIALS

Paracetamol  B.P grade
Mefenamic acid  B.P grade
β-cyclodextrin  U.S.P grade
Gelatin  U.S.P grade
Corn starch  U.S.P grade
Na-Methylparaben  U.S.P grade
Na-Propylparaben  U.S.P grade
Talc  U.S.P grade
Magnesium stearate  B.P grade
Lactose  U.S.P grade

ASSAY REAGENT

0.1 N NaOH  Merck
0.1 N HCl  B.D.H
Ethanol  B.D.H
Phenol red  May & Baker
Phenolphthalein  B.D.H

APPARATUS

Tableting machine  Single Punch Tablet Press
Model: TDP. Max Pressure 1.5 T
Sieve  No. 08, 12 and 30 mesh (B.P)
Balance: Sartorius GMBH type A 6801
Micrometer screw guage: 15mm
Hardness Tester: Fujiwara hardness tester
Friability Tester: D 2800 BREMEN type FU44E2/114
Disintegration Apparatus: Erweka ZT2
Dissolution Apparatus: Erweka DT
UV Spectrophotometer: Shimadzu UV-150-02 Double beam spectrophotometer

METHODOLOGY

Wet granulation method was used to prepare tablets. There were in total three types of formulation for each drug. Each formulation contained three different sets.

All the formulation was compressed at same pressure. So in this way three batches of paracetamol tablets 500 mg were produced and in each batch 80 tablets were produced, and three batches of mefenamic acid tablets 250 mg were produced, each batch containing 100 tablets. Each batch was tested for official and unofficial test.

PARACETAMOL TABLETS

Paracetamol powder was mixed with half of the disintegrant (β-cyclodextin) geometrically for 10 minutes. Three different sets were used.
Cornstarch and gelatin were suspended in distilled water by heating on water-bath separately. These binders were then added to previously mixed active substance, and mixed for 10 minutes.

Na-methyl paraben and Na-propyl paraben, which are used as preservatives, were dissolved in 1-ml water and added to the wet mass and mixed for 10 minutes. The wet mass was passed through sieve of mesh size 8 to form the granules. The granules were dried at 45ºC for 2 hours after spreading into tray.

The dried granules were again passed through sieve of mesh size 12 and remaining half of the disintegrant (β-cyclodextrin) and lubricants (talc and magnesium stearate) were added and blended for 15 minutes.

The granules were compressed and to eliminate the variation in weight due to the initial flow resistance, insufficient weight of the granules in the hopper, and excess fines, the first ten tablets from every batch were discarded.

MEFENAMIC ACID TABLETS

Active ingredients (mefenamic acid powder), half of the disintegrant (β-cyclodextrin) and diluent (lactose) were mixed for 10 minutes geometrically.

Binders were added in the same manner as in paracetamol tablets and mixed for 10 minutes. Then preservatives were added and mixed for
10 minutes. After granulation and drying (same as in paracetamol tablets), disintegrants and lubricants were added and blended for 15 minutes.

The granules were compressed and the first and last ten tablets were discarded to eliminate variation in weight.
PARACETAMOL FORMULATIONS

FORMULATION NO. 1 (A1)

Paracetamol tablets = 500 mg

Batch size = 50 g

No. of tablets = 80

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>IN 80 TABLETS</th>
<th>PER TABLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>40 g</td>
<td>0.5 g</td>
</tr>
<tr>
<td>Lactose</td>
<td>10 g</td>
<td>0.125 g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>2 g</td>
<td>0.025 g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>6 g</td>
<td>0.075 g</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>2 g</td>
<td>0.025 g</td>
</tr>
<tr>
<td>Na-methyl paraben</td>
<td>0.009 g</td>
<td>0.0001125 g</td>
</tr>
<tr>
<td>Na-propyl paraben</td>
<td>0.002 g</td>
<td>0.000025 g</td>
</tr>
<tr>
<td>Talc</td>
<td>0.4 g</td>
<td>0.005 g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.2 g</td>
<td>0.0025 g</td>
</tr>
</tbody>
</table>

ANALYTICAL DATA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Experimental tablets</th>
<th>Commercial tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight</td>
<td>614.5mg</td>
<td>581 mg</td>
</tr>
<tr>
<td>Average thickness</td>
<td>4.22mm</td>
<td>3.88 mm</td>
</tr>
<tr>
<td>Average diameter</td>
<td>12.69mm</td>
<td>12.67 mm</td>
</tr>
<tr>
<td>Average hardness</td>
<td>11.29kg</td>
<td>10.19 kg</td>
</tr>
<tr>
<td>Friability</td>
<td>0.15%</td>
<td>0.34%</td>
</tr>
<tr>
<td>Content of active ingredient</td>
<td>102.10%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>13min</td>
<td>15 min</td>
</tr>
<tr>
<td>70% dissolution</td>
<td>15min</td>
<td>20 min</td>
</tr>
</tbody>
</table>
FORMULATION NO. 2 (A2)

Paracetamol tablets = 500 mg
Batch size = 50 g
No. of tablets = 80

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>IN 80 TABLETS</th>
<th>PER TABLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>40g</td>
<td>0.5g</td>
</tr>
<tr>
<td>Lactose</td>
<td>5g</td>
<td>0.0625g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>6g</td>
<td>0.075g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>6g</td>
<td>0.075g</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>3g</td>
<td>0.0375g</td>
</tr>
<tr>
<td>Na-methyl paraben</td>
<td>0.009g</td>
<td>0.0001125g</td>
</tr>
<tr>
<td>Na-propyl paraben</td>
<td>0.002g</td>
<td>0.000025g</td>
</tr>
<tr>
<td>Talc</td>
<td>0.4g</td>
<td>0.005g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.2g</td>
<td>0.0025g</td>
</tr>
</tbody>
</table>

ANALYTICAL DATA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Experimental tablets</th>
<th>Commercial tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight</td>
<td>630.5mg</td>
<td>581 mg</td>
</tr>
<tr>
<td>Average thickness</td>
<td>4.23mm</td>
<td>3.88 mm</td>
</tr>
<tr>
<td>Average diameter</td>
<td>12.69mm</td>
<td>12.67 mm</td>
</tr>
<tr>
<td>Average hardness</td>
<td>10.20kg</td>
<td>10.19 kg</td>
</tr>
<tr>
<td>Friability</td>
<td>0.29%</td>
<td>0.34%</td>
</tr>
<tr>
<td>Content of active ingredient</td>
<td>103.8%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>10min</td>
<td>15 min</td>
</tr>
<tr>
<td>70% dissolution</td>
<td>15min</td>
<td>20 min</td>
</tr>
</tbody>
</table>
FORMULATION NO. 3 (A3)

Paracetamol tablets = 500 mg
Batch size = 50 g
No. of tablets = 80

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>IN 80 TABLETS</th>
<th>PER TABLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>40g</td>
<td>0.5g</td>
</tr>
<tr>
<td>Lactose</td>
<td>8g</td>
<td>0.1g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>4g</td>
<td>0.05g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>4g</td>
<td>0.05g</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>4g</td>
<td>0.05g</td>
</tr>
<tr>
<td>Na-methyl paraben</td>
<td>0.009g</td>
<td>0.001125g</td>
</tr>
<tr>
<td>Na-propyl paraben</td>
<td>0.002g</td>
<td>0.000025g</td>
</tr>
<tr>
<td>Talc</td>
<td>0.4g</td>
<td>0.005g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.2g</td>
<td>0.0025g</td>
</tr>
</tbody>
</table>

ANALYTICAL DATA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Experimental tablets</th>
<th>Commercial tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight</td>
<td>626mg</td>
<td>581 mg</td>
</tr>
<tr>
<td>Average thickness</td>
<td>4.23mm</td>
<td>3.88 mm</td>
</tr>
<tr>
<td>Average diameter</td>
<td>12.70mm</td>
<td>12.67 mm</td>
</tr>
<tr>
<td>Average hardness</td>
<td>9.62kg</td>
<td>10.19 kg</td>
</tr>
<tr>
<td>Friability</td>
<td>0.43%</td>
<td>0.34%</td>
</tr>
<tr>
<td>Content of active ingredient</td>
<td>100.5%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>8min</td>
<td>15 min</td>
</tr>
<tr>
<td>70% dissolution</td>
<td>10min</td>
<td>20 min</td>
</tr>
</tbody>
</table>
MEFENAMIC ACID FORMULATIONS

FORMULATION NO. 1 (B1)

Mafenamic acid = 250 mg
Batch size = 60 g
No. of tablets = 100

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>IN 80 TABLETS</th>
<th>PER TABLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mafenamic acid</td>
<td>25g</td>
<td>0.25g</td>
</tr>
<tr>
<td>Lactose</td>
<td>18g</td>
<td>0.18g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>6g</td>
<td>0.06g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>4.5g</td>
<td>0.45g</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>3g</td>
<td>0.03g</td>
</tr>
<tr>
<td>Na-methyl paraben</td>
<td>0.01g</td>
<td>0.0001g</td>
</tr>
<tr>
<td>Na-propyl paraben</td>
<td>0.002g</td>
<td>0.00002g</td>
</tr>
<tr>
<td>Talc</td>
<td>1g</td>
<td>0.01g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.2g</td>
<td>0.002g</td>
</tr>
</tbody>
</table>

ANALYTICAL DATA

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<thead>
<tr>
<th>Characteristics</th>
<th>Experimental tablets</th>
<th>Commercial tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight</td>
<td>606.5mg</td>
<td>592mg</td>
</tr>
<tr>
<td>Average thickness</td>
<td>4.02mm</td>
<td>3.88mm</td>
</tr>
<tr>
<td>Average diameter</td>
<td>12.70mm</td>
<td>12.02mm</td>
</tr>
<tr>
<td>Average hardness</td>
<td>10.45kg</td>
<td>9.86kg</td>
</tr>
<tr>
<td>Friability</td>
<td>0.31%</td>
<td>33%</td>
</tr>
<tr>
<td>Content of active ingredient</td>
<td>101.38%</td>
<td>100.58%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>15min</td>
<td>15min</td>
</tr>
<tr>
<td>70% dissolution</td>
<td>20min</td>
<td>20min</td>
</tr>
</tbody>
</table>
FORMULATION NO. 2 (B2)

Mefenamic acid = 250 mg  
Batch size = 60 g  
No. of tablets = 100

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>IN 80 TABLETS</th>
<th>PER TABLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefenamic acid</td>
<td>25g</td>
<td>0.25g</td>
</tr>
<tr>
<td>Lactose</td>
<td>20g</td>
<td>0.20g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>2g</td>
<td>0.02g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>5.5g</td>
<td>0.055g</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>4g</td>
<td>0.04g</td>
</tr>
<tr>
<td>Na-methyl paraben</td>
<td>0.01g</td>
<td>0.0001g</td>
</tr>
<tr>
<td>Na-propyl paraben</td>
<td>0.002g</td>
<td>0.00002g</td>
</tr>
<tr>
<td>Talc</td>
<td>1g</td>
<td>0.01g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.2g</td>
<td>0.002g</td>
</tr>
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ANALYTICAL DATA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Experimental tablets</th>
<th>Commercial tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight</td>
<td>603mg</td>
<td>592mg</td>
</tr>
<tr>
<td>Average thickness</td>
<td>4.03mm</td>
<td>3.88mm</td>
</tr>
<tr>
<td>Average diameter</td>
<td>12.70mm</td>
<td>12.02mm</td>
</tr>
<tr>
<td>Average hardness</td>
<td>10.35kg</td>
<td>9.86kg</td>
</tr>
<tr>
<td>Friability</td>
<td>0.46%</td>
<td>33%</td>
</tr>
<tr>
<td>Content of active ingredient</td>
<td>95.86%</td>
<td>100.58%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>11min</td>
<td>15min</td>
</tr>
<tr>
<td>70% dissolution</td>
<td>15min</td>
<td>20min</td>
</tr>
</tbody>
</table>
FORMULATION NO. 3 (B3)

Mefenamic acid = 250 mg  
Batch size = 60 g  
No. of tablets = 100

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>IN 80 TABLETS</th>
<th>PER TABLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefenamic acid</td>
<td>25g</td>
<td>0.25g</td>
</tr>
<tr>
<td>Lactose</td>
<td>18g</td>
<td>0.18g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>5.5g</td>
<td>0.055g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>4g</td>
<td>0.04g</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>5g</td>
<td>0.05g</td>
</tr>
<tr>
<td>Na-methyl paraben</td>
<td>0.01g</td>
<td>0.0001g</td>
</tr>
<tr>
<td>Na-propyl paraben</td>
<td>0.002g</td>
<td>0.00002g</td>
</tr>
<tr>
<td>Talc</td>
<td>1g</td>
<td>0.01g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.2g</td>
<td>0.002g</td>
</tr>
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</table>

ANALYTICAL DATA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Experimental tablets</th>
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<td>592mg</td>
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<tr>
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<td>3.88mm</td>
</tr>
<tr>
<td>Average diameter</td>
<td>12.71mm</td>
<td>12.02mm</td>
</tr>
<tr>
<td>Average hardness</td>
<td>10.36kg</td>
<td>9.86kg</td>
</tr>
<tr>
<td>Friability</td>
<td>0.46%</td>
<td>33%</td>
</tr>
<tr>
<td>Content of active ingredient</td>
<td>106.22%</td>
<td>100.58%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>10min</td>
<td>15min</td>
</tr>
<tr>
<td>70% dissolution</td>
<td>15min</td>
<td>20min</td>
</tr>
</tbody>
</table>
PHARMACOPOEIAL CONTROL TESTS

UNIFORMITY OF WEIGHT

From each batch, 20 tablets were selected randomly. The tablets were weighed individually on an electric balance. Average weight, range and standard deviation were calculated. The observed variations have been summarized in Table 1 with respect to the standard deviation.

UNIFORMITY OF DIAMETER

A random sample of 20 tablets was selected from each batch of the lab prepared tablets and the diameter of the individual tablet was measured in mm with the help of a micrometer screw gauge. The average value of diameter (mm) range and standard deviation were calculated and are given in Table 2.

CONTENT UNIFORMITY

Procedure for Paracetamol

Weigh and powder 20 tablets. Weigh 200 mg powder and dissolve in 50 ml 0.1N NaOH. Make up the volume to 100 ml with distilled water. Shake for 15 minutes and filter. Take 10 ml filtrate and dilute to 100 ml with distilled water. Take 10 ml of this dilution and add 10 ml 0.1N NaOH and make up the volume to 100 ml with water. Repeat the procedure with standard. Take absorbance at 257 nm. Calculate the percentage of active ingredient by the following formula:
Absorbance of test \times \text{Weight of standard} \times \text{Average weight of tablet} \over \text{Absorbance of standard} \times \text{Weight of sample}

\textbf{Procedure for Mefenamic Acid}

Dissolve 0.6g in 100ml of warm absolute ethanol previously neutralized to phenol red solution and titrate it with 0.1M NaOH VS using phenol red solution as indicator. Each ml of 0.1 M NaOH VS is equivalent to 0.02413g of mefenamic acid. Calculate the %age by the following formula.

\[
\text{Percentage} = \frac{0.2413 \times \text{end point} \times 100}{5.00}
\]

The content of active ingredients was calculated by average assay method and were found within the B.P (1988) limit. The percentage of content of active ingredient in different formulations of both the drugs are given below in Table 6.

\textbf{TABLET DISINTEGRATION}

An Erweka GmbH disintegration apparatus type ZT-2 was used for the measurement of disintegration time. It consists of device containing 6 tubes having 10-mesh screen at the bottom end of the basket rack assembly. A beaker containing 1000 ml of disintegration medium was placed in water bath. When temperature of beaker reached 37°C, the
basket was lifted and 6 tablets (selected randomly from each batch) were placed into each tube. The frequency was 30 cycles per minute without any jerk. When all the particles passed through screen, the disintegration time was noted. Disintegration medium for paracetamol was distilled water and for mefenamic acid was 0.1 N HCl.

The disintegration time of different formulations of paracetamol and mefenamic acid tablets prepared for our experimental purposes are given in Table 7 which are compared with the commercially available tablets of same strength.

**DISSOLUTION TEST**

**PREPARATION OF STANDARD CALIBRATING CURVE**

100 mg of the dried drug substance was accurately weighed and dissolve in a volumetric flask of 1000 ml containing dissolution medium. After shaking for 15 minutes. The calculated volumes of this solution were taken to obtain the following dilution. 1, 2, 6, 8 and 10 µg/ml. The absorbance of the above solutions were obtained on UV spectrophotometer and plotted against the concentration. The above procedure was repeated several times to get a reliable calibration curve.

**DETERMINATION OF DISSOLUTION RATE**

An Erweka GmbH type DT apparatus was used, which meet the requirement of USP XIX apparatus II. The cylindrical vessel with the hemispherical bottom placed in the water bath fitted with the
thermostat. The vessel was filled with 900 ml of dissolution medium. The temperature of the medium was set at 37°C. At this temperature, one tablet was dropped in the vessel and the apparatus was switched on. The rotational speed of the paddle was adjusted to 150 rpm. The vessel was covered to prevent the evaporation of the medium. Sample was withdrawn after different time intervals till the drug dissolve. The samples were filtered, diluted and analysed on UV spectrophotometer at the given wavelength against the bank of dissolution medium. The amount of drug dissolved was calculated with the help of standard calibration curve. The dissolution rate of drug from our different formulation is given in Table 8.

NON-PHARMACOPOEIAL CONTROL TEST

UNIFORMITY OF THICKNESS

Thickness of the tablets were determined with the help of a micrometer screw gauge. 20 tablets were randomly selected from each batch and the thickness of individual tablet was measured in mm. Generally a deviation of ± 5% in thickness is allowed, however the difference in thickness depends on the size of the tablets. Using the thickness value of the individual tablet, different statistical parameters were calculated. The values of thickness for the tablet of different formulation are given in Table 3.
HARDNESS OF TABLETS

Hardness test is a non-official test. The ability of a tablet to withstand the shock of handling, packing and shipping has been the traditional measure of tablet strength requirement.

10 tablets were selected randomly from each batch. Each tablet was placed in an electric hardness tester upon a fix axil and the force is transmitted to it by means of a moving plunger. Final reading is noted from the scale. Hardness is measured in Kgs. The values of hardness for the tablets of different formulation are listed in Table 4.

FRIABILITY OF TABLETS

Friability test is a non-official test. It is to measure the breakdown of a tablet due to rubbing under shock or vibration. It was carried out by Rosche Friabilator. 10 tablet was placed into the plastic chamber, and was allowed to revolve for 4 minutes (100 revolution). The tablets were cleaned and reweighed and so the percentage weight loss was calculated. Conventional compressed tablets that loose than 0.5-1 % in weight are generally considered acceptable. The percent friability of different formulations of both the drugs is listed in Table 5.
3. RESULTS AND DISCUSSION
**RESULT AND DISCUSSION**

**TABLE 1**

Weight variations of different formulations.

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Av.Wt</th>
<th>Range</th>
<th>S.D</th>
<th>Variance</th>
<th>No. of tablets in X±S</th>
<th>X±2S</th>
<th>X±3S</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>614.5mg</td>
<td>40</td>
<td>11.16</td>
<td>124.54</td>
<td>11</td>
<td>17</td>
<td>all</td>
</tr>
<tr>
<td>A2</td>
<td>630.5mg</td>
<td>50</td>
<td>14.65</td>
<td>214.62</td>
<td>13</td>
<td>18</td>
<td>all</td>
</tr>
<tr>
<td>A3</td>
<td>626mg</td>
<td>60</td>
<td>16.35</td>
<td>267.32</td>
<td>14</td>
<td>18</td>
<td>all</td>
</tr>
<tr>
<td>A4</td>
<td>581mg</td>
<td>50</td>
<td>12.60</td>
<td>158.76</td>
<td>15</td>
<td>19</td>
<td>all</td>
</tr>
<tr>
<td>B1</td>
<td>606.5mg</td>
<td>60</td>
<td>18.51</td>
<td>342.62</td>
<td>13</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>B2</td>
<td>603mg</td>
<td>50</td>
<td>17.63</td>
<td>310.81</td>
<td>13</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>B3</td>
<td>596mg</td>
<td>50</td>
<td>16.55</td>
<td>273.90</td>
<td>16</td>
<td>19</td>
<td>all</td>
</tr>
<tr>
<td>B4</td>
<td>592mg</td>
<td>50</td>
<td>12.88</td>
<td>165.89</td>
<td>15</td>
<td>19</td>
<td>all</td>
</tr>
</tbody>
</table>

A1 = Paracetamol exp. formulation no 1  
A2 = Paracetamol exp. formulation no 2  
A3 = Paracetamol exp. formulation no 3  
A4 = Paracetamol by Nicholas  

B1 = Mefenamic acid exp. formulation no 1  
B2 = Mefenamic acid exp. formulation no 2  
B3 = Mefenamic acid exp. formulation no 3  
B4 = Mefenamic acid by Park Davis
### TABLE 2

**Diameter variation of different formulation.**

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Av.Dia</th>
<th>Range</th>
<th>S.D</th>
<th>Variance</th>
<th>No. of tablets in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X+S</td>
</tr>
<tr>
<td>A₁</td>
<td>12.69 mm</td>
<td>0.04</td>
<td>0.016</td>
<td>0.000256</td>
<td>15</td>
</tr>
<tr>
<td>A₂</td>
<td>12.69 mm</td>
<td>0.06</td>
<td>0.016</td>
<td>0.000256</td>
<td>15</td>
</tr>
<tr>
<td>A₃</td>
<td>12.70 mm</td>
<td>0.06</td>
<td>0.015</td>
<td>0.000225</td>
<td>17</td>
</tr>
<tr>
<td>A₄</td>
<td>12.67 mm</td>
<td>0.04</td>
<td>0.017</td>
<td>0.000306</td>
<td>15</td>
</tr>
<tr>
<td>B₁</td>
<td>12.70 mm</td>
<td>0.05</td>
<td>0.017</td>
<td>0.000289</td>
<td>17</td>
</tr>
<tr>
<td>B₂</td>
<td>12.70 mm</td>
<td>0.07</td>
<td>0.020</td>
<td>0.000262</td>
<td>18</td>
</tr>
<tr>
<td>B₃</td>
<td>12.71 mm</td>
<td>0.07</td>
<td>0.022</td>
<td>0.000256</td>
<td>15</td>
</tr>
<tr>
<td>B₄</td>
<td>12.02 mm</td>
<td>0.10</td>
<td>0.028</td>
<td>0.000784</td>
<td>15</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1
A₂ = Paracetamol exp. formulation no 2
A₃ = Paracetamol exp. formulation no 3
A₄ = Paracetamol by Nicholas

B₁ = Mefenamic acid exp. formulation no 1
B₂ = Mefenamic acid exp. formulation no 2
B₃ = Mefenamic acid exp. formulation no 3
B₄ = Mefenamic acid by Park Davis
### TABLE 3

**Thickness variation of different formulation**

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Av.Thick</th>
<th>Range</th>
<th>S.D</th>
<th>Variance</th>
<th>No.of tablets in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X+S</td>
</tr>
<tr>
<td>A₁</td>
<td>4.22mm</td>
<td>0.06</td>
<td>0.022</td>
<td>0.000484</td>
<td>12</td>
</tr>
<tr>
<td>A₂</td>
<td>4.23mm</td>
<td>0.08</td>
<td>0.0241</td>
<td>0.000576</td>
<td>17</td>
</tr>
<tr>
<td>A₃</td>
<td>4.23mm</td>
<td>0.07</td>
<td>0.025</td>
<td>0.000625</td>
<td>12</td>
</tr>
<tr>
<td>A₄</td>
<td>3.88mm</td>
<td>0.06</td>
<td>0.0176</td>
<td>0.000309</td>
<td>15</td>
</tr>
<tr>
<td>B₁</td>
<td>4.02mm</td>
<td>0.05</td>
<td>0.016</td>
<td>0.000256</td>
<td>16</td>
</tr>
<tr>
<td>B₂</td>
<td>4.03mm</td>
<td>0.04</td>
<td>0.015</td>
<td>0.000225</td>
<td>14</td>
</tr>
<tr>
<td>B₃</td>
<td>4.02mm</td>
<td>0.06</td>
<td>0.017</td>
<td>0.000289</td>
<td>15</td>
</tr>
<tr>
<td>B₄</td>
<td>3.88mm</td>
<td>0.16</td>
<td>0.055</td>
<td>0.00324</td>
<td>17</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1  
A₂ = Paracetamol exp. formulation no 2  
A₃ = Paracetamol exp. formulation no 3  
A₄ = Paracetamol by Nicholas  
B₁ = Mefenamic acid exp. formulation no 1  
B₂ = Mefenamic acid exp. formulation no 2  
B₃ = Mefenamic acid exp. formulation no 3  
B₄ = Mefenamic acid by Park Davis
### TABLE 4

**Hardness variation of different formulation**

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Av. Hard</th>
<th>Range</th>
<th>S.D</th>
<th>Variance</th>
<th>No. of tablets in X±1S</th>
<th>X±2S</th>
<th>X±3S</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>11.29 Kg</td>
<td>2.7</td>
<td>0.79</td>
<td>0.6241</td>
<td>7</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>A₂</td>
<td>10.20 Kg</td>
<td>0.08</td>
<td>0.290</td>
<td>0.841</td>
<td>7</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>A₃</td>
<td>9.62 Kg</td>
<td>1.35</td>
<td>0.420</td>
<td>0.1764</td>
<td>6</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>A₄</td>
<td>10.19 Kg</td>
<td>1.95</td>
<td>0.63</td>
<td>0.3969</td>
<td>5</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>B₁</td>
<td>10.45 Kg</td>
<td>2.22</td>
<td>0.64</td>
<td>0.4096</td>
<td>7</td>
<td>9</td>
<td>all</td>
</tr>
<tr>
<td>B₂</td>
<td>10.35 Kg</td>
<td>1.2</td>
<td>0.40</td>
<td>0.16</td>
<td>6</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>B₃</td>
<td>10.36 Kg</td>
<td>1.55</td>
<td>0.47</td>
<td>0.2209</td>
<td>6</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>B₄</td>
<td>9.86 Kg</td>
<td>1.37</td>
<td>0.41</td>
<td>0.1681</td>
<td>7</td>
<td>all</td>
<td>all</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1  
A₂ = Paracetamol exp. formulation no 2  
A₃ = Paracetamol exp. formulation no 3  
A₄ = Paracetamol by Nicholas  

B₁ = Mefenamic acid exp. formulation no 2  
B₃ = Mefenamic acid exp. formulation no 3  
B₄ = Mefenamic acid by Park Davis
TABLE 5

% friability of different formulation

<table>
<thead>
<tr>
<th>Tablets</th>
<th>% friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>0.15%</td>
</tr>
<tr>
<td>A₂</td>
<td>0.29%</td>
</tr>
<tr>
<td>A₃</td>
<td>0.43%</td>
</tr>
<tr>
<td>A₄</td>
<td>0.34%</td>
</tr>
<tr>
<td>B₁</td>
<td>0.31%</td>
</tr>
<tr>
<td>B₂</td>
<td>0.46%</td>
</tr>
<tr>
<td>B₃</td>
<td>0.46%</td>
</tr>
<tr>
<td>B₄</td>
<td>0.33%</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1
A₂ = Paracetamol exp. formulation no 2
A₃ = Paracetamol exp. formulation no 3
A₄ = Paracetamol by Nicholas

B₁ = Mefenamic acid exp. formulation no 1
B₂ = Mefenamic acid exp. formulation no 2
B₃ = Mefenamic acid exp. formulation no 3
B₄ = Mefenamic acid by Park Davis
Table 6

% Drug contents of different formulation

<table>
<thead>
<tr>
<th>Tablets</th>
<th>% Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>102.10%</td>
</tr>
<tr>
<td>A₂</td>
<td>103.80%</td>
</tr>
<tr>
<td>A₃</td>
<td>100.5%</td>
</tr>
<tr>
<td>A₄</td>
<td>99.1%</td>
</tr>
<tr>
<td>B₁</td>
<td>101.38%</td>
</tr>
<tr>
<td>B₂</td>
<td>95.86%</td>
</tr>
<tr>
<td>B₃</td>
<td>106.22%</td>
</tr>
<tr>
<td>B₄</td>
<td>100.58%</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1
A₂ = Paracetamol exp. formulation no 2
A₃ = Paracetamol exp. formulation no 3
A₄ = Paracetamol by Nicholas

B₁ = Mefenamic acid exp. formulation no 1
B₂ = Mefenamic acid exp. formulation no 2
B₃ = Mefenamic acid exp. formulation
B₄ = Mefenamic acid by Park Davis
Table 7

Disintegration times of different formulation

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Disintegration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>13min</td>
</tr>
<tr>
<td>A₂</td>
<td>10min</td>
</tr>
<tr>
<td>A₃</td>
<td>8min</td>
</tr>
<tr>
<td>A₄</td>
<td>15min</td>
</tr>
<tr>
<td>B₁</td>
<td>15min</td>
</tr>
<tr>
<td>B₂</td>
<td>11min</td>
</tr>
<tr>
<td>B₃</td>
<td>10min</td>
</tr>
<tr>
<td>B₄</td>
<td>15min</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1
A₂ = Paracetamol exp. formulation no 2
A₃ = Paracetamol exp. formulation no 3
A₄ = Paracetamol by Nicholas

B₁ = Mefenamic acid exp. formulation no 1
B₂ = Mefenamic acid exp. formulation no 2
B₃ = Mefenamic acid exp. formulation no 3
B₄ = Mefenamic acid by Park Davis
Table 8

% dissolution of different formulation

<table>
<thead>
<tr>
<th>Tablets</th>
<th>% Drug dissolved in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>A₁</td>
<td>40.5</td>
</tr>
<tr>
<td>A₂</td>
<td>45</td>
</tr>
<tr>
<td>A₃</td>
<td>59.4</td>
</tr>
<tr>
<td>A₄</td>
<td>52.2</td>
</tr>
<tr>
<td>B₁</td>
<td>30.6</td>
</tr>
<tr>
<td>B₂</td>
<td>39.6</td>
</tr>
<tr>
<td>B₃</td>
<td>43.2</td>
</tr>
<tr>
<td>B₄</td>
<td>36</td>
</tr>
</tbody>
</table>

A₁ = Paracetamol exp. formulation no 1
A₂ = Paracetamol exp. formulation no 2
A₃ = Paracetamol exp. formulation no 3
A₄ = Paracetamol by Nicholas

B₁ = Mefenamic acid exp. formulation no 1
B₂ = Mefenamic acid exp. formulation no 2
B₃ = Mefenamic acid exp. formulation no 3
B₄ = Mefenamic acid by Park Davis
Q.C CHART BASED ON WEIGHT VARIATION OF PARACETAMOL FORMULATIONS A3 & A4

Tablet weight in mg

No. of tablets.

A3

A4
Q.C CHART BASED ON THICKNESS VARIATION OF PARACETMOL FORMULATIONS A3 & A4
Q.C CHART BASED ON DIAMETER VARIATION OF PARACETAMOL FORMULATIONS A3 & A4

No. of tablets.
Q.C CHART BASED ON HARDNESS VARIATION OF PARACETAMOL FORMULATIONS A3 & A4.
CALIBERATING CURVE OF PARACETAMOL.
% DISSOLUTION OF DIFFERENT FORMULATIONS OF PARACETAMOL.
QC CHART BASED ON WEIGHT VARIATION OF MEFENAMIC ACID FORMULATIONS B3 & B4
Q.C CHART BASED ON THICKNESS VARIATION OF MEFENAMIC ACID FORMULATIONS B3 & B4

Tablet thickness in mm

NO. of tablets.

B3

B4
Q.C CHART BASED ON DIAMETER VARIATION OF MEFENAMIC ACID FORMULATIONS B3 & B4

Tablet diameter in mm

No. of tablets.
Q.C CHART BASED ON HARDNESS VARIATION OF MEFENAMIC ACID FORMULATIONS B3 & B4.
CALIBRATING CURVE OF MEFENAMIC ACID

Absorbance at 254 nm

Concentration in μg/ml
% DISSOLUTION OF DIFFERENT FORMULATIONS OF MEFENAMIC ACID

% drug dissolved in minutes.

Time in minutes.
EVALUATION OF TABLETS

The pharmacopoeial and non-pharmacopoeial control tests were used to evaluate for the uniformity of weight, thickness, diameter, friability, hardness, uniformity of drug content and the release of drug from paracetamol and mefenamic acid tablets. The tests were performed on both experimental and commercially available tablets and a comparative study was made. Q.C charts are made for these two formulations and compared with the commercially available drugs. The analytical data of these tablets are given in the experimental section in tables 1-8. In our experimental tablets formulaion No. 3 of both paracetamol and mefenamic acid tablets showed the as regard to the disintegration time and dissolution rate.

UNIFORMITY OF WEIGHT

From the results (Table 1) it was found that the tablets were of average weight 623 mg (±5%) in case of mefenamic acid and 603 mg (±5%) in case of paracetamol. It is in agreement with the limits in variation of weight given in B.P (1988). Weight of a tablet being compressed is determined by the amount of granulation in the die prior to compression. Therefore anything that can alter the die filling process can alter the tablet weight and cause weight variation.
UNIFORMITY OF DIAMETER

Diameter of formulated tablets given in table 2 are within the B.P limits i.e. ±5%. The slight variation in diameter of tablets may either be due to an uneven surfaces of punches and die or due to the less precise measurement with the micrometer screw gauge.

CONTENT UNIFORMITY.

In all formulations value of the active ingredients are in confirmation with the limits given in B.P (1988) that is ±5 % for paracetamol and ± 7.5 % for mefenamic acid (Table 6).

TABLET DISINTEGRATION.

Tablets to be swallowed must break up in the stomach or intestine so that the drug is available for absorption. Tablet disintegration is also important for those tablets containing medicinal agent (such as antacid and antidiarrheals) that are not intended to be absorbed but rather to act locally within the GIT. In these instances, tablet disintegration provides drug particles with a greater surface area for localized activity with in the body.

The disintegration determines whether tablets or capsules disintegrate within a prescribed period of time when placed in a liquid medium under the prescribed experimental conditions (141). For compressed uncoated tablets, the testing fluid is usually water at 37°C,
but in some cases the monographs direct the simulated gastric fluid TS to be used (123).

Table 7 shows that in case of paracetamol formulations, the disintegration time of experimental tablets lies between 8 to 13 minutes and the best result is obtained from formulation no 3 in which the disintegration time is 8 minutes which is less than the commercially available tablets of same strength. In case of mefenamic acid tablets, the disintegration time lies between 10 to 15 minutes and the best result is obtained from formulation no 3 in which the disintegration time is 10 minutes which is less than commercially available tablets of same strength.

Here β-cyclodextrin is used as disintegrant and the result shows that the disintegration decreases as the quantity of β-- cyclodextrin increases. Disintegration time also relates directly with hardness of the tablets. But the effect of hardness on disintegration time is not very sharp i.e. there is a very little increases in disintegration time as the hardness increases. The possible reason of this may be due to poor compressibility of disintegrant as reported by Susan and Spring (127). Kennon and Joseph, Swintowsky (128) reported that the disintegration time of sulphathiazole tablets containing corn starch as disintegrant was increased as the hardness of the tablets was increased. The same result also reported by James Ingram et al. (124). According to them there is an increase in disintegration time with increasing hardness of aspirin
tablets containing corn starch. It was also reported by Shikfumi Kitazawa et al. (125) that the disintegration time of uncoated caffeine tablets having 3% potato starch was increased by increasing hardness. Fassihi (126) has also reported the same result for theophylline tablet containing corn starch.

**TABLET DISSOLUTION**

Like the disintegration test, the dissolution test for measuring the time required for a given %age of the drug substance in a tablet to go into solution under a specified set of conditions in an *in-vitro* test. It is intended to provide a step towards the evaluation of the physiological availability of the drug substance, but as currently described it is not designed to measure the safety or efficacy of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate in vivo studies and clinical evaluation. Like the disintegration test, the dissolution test does provide a means of control in assuring that a given tablet formulation is the same as regards dissolution as the batch of tablets shown initially to be clinically effective. It also provide an in vitro control procedure to eliminate variations among production batches (129). It is clear from table 8 that the dissolution rate of both paracetamol and mefenamic acid tablets containing β-cyclodextrin as tablet disintegrant is increased.
This result is in concordant with many workers. The inclusion complex with ketoprofen with β and HP-β-cyclodextrin showed an improve in dissolution profile. (143) Ithal et al. also complexed norfloxacin with β-cyclodextrin which resulted an increased stability and increased in vitro and in vivo release of drug inocular implants for local drug delivery (131). Saleh et al. formulated the inclusion complex of ketoprofen with β-cyclodextrin into tablets, capsules and suppositories and found that the dissolution rate of all the three dosage forms was faster than the commercially available simple dosage forms (132). Gazzaniga et al. (133) formed inclusion complex of β-cyclodextrin and acetaminophen by powder compaction. This study also showed phase transformation. Samy et al. (134) developed new gel delivery system for local application of NSAIDs with β-cyclodextrin which showed increased stability and increased in vitro release. James (135) formulated a pharmaceutical composition containing drug/β-cyclodextrin complex in combination with acid base couple which helps the drug to dissolve it cold water. Nurten (136) improved the dissolution properties of furosemide by complexation with β-cyclodextrin.

Weiming et al. (137) prepared diclofenic sodium/β-cyclodextrin inclusion compound and found that stabilities and dissolution rate of the inclusion complexes were greater. Gavriline et al. (138) prepared inclusion complex of cartisone acetate with β-cyclodextrin and found increased in solubility of cartisone acetate 8-10 folds. Ventura et al. 
(139) compared the inclusion compounds of 4-biphenyl acetic acid with β, HP-β and dimethyl-β-cyclodextrins and found that DM-β-cyclodextrin is more effective than β-cyclodextrin in improving the pharmaceutical properties of biphenyl acetic acid.

A study showed an increase in dissolution rate of carbamazepine tablets with β & HP β-cyclodextrin (140). Similarly improvement in dissolution of clofibrate seen by complexation with β-cyclodextrin (141). The dissolution rate for norfloxacain was also improved through cyclodextrin complexation (142). Beom et al. (143) found enhancement of solubility and dissolution rate of poorly water soluble naproxaen by complexation with 2 HP-β-cyclodextrin. Szente (144) formed a multi component base-type drugs with cyclodextrins in presence of acid which resulted in high solubility enhancement. Similarly dissolution enhancement of nifedipine was found in simulated gastric fluid by forming an inclusion complex with β-cyclodextrin (145). Cappello et al. (146) again showed increase in dissolution rate of diclofenic sodium and β-cyclodextrin inclusion complex. Ibuprofen-β-cyclodextrin complex is prepared for taste masking of ibuprofen in oral pharmaceuticals. Different formation of ibuprofen β-cyclodextrin complex which dissolve in hot water give a clear pleasant taste in solution (147).

Ibuprofen-β-cyclodextrin complex (1:6, w/w) was prepared by J.Guan in 1993 using ethanol as the solvent, the solubility and
dissolution of ibuprofen were markedly increased (148). In 1992, X. Teng et al. studied the bioavailability of ibuprofen. β-cyclodextrin in rats and human volunteers by HPLC. The ratio of the bioavailability of the complex in rats to that of compressed tablets was 169.8%. The release of the complex in rats was fast and constant. The bioavailability ratio of the complex in human was fast (149). In 1991, Abdul Rahman et al. examined the chloramphenicol-β-cyclodextrin inclusion complex by IR spectroscopy and x-ray diffraction. The apparent rates of dissolution and permeation of chloramphenicol-β-cyclodextrin complex were increased by the formation of inclusion complex (150).

This study and all work shows that β-cyclodextrin is a suitable disintegrant for a variety of drugs. The solubilities, disintegration and dissolution rate of poorly water soluble drugs are found to be increased by utilizing β-cyclodextrin as a tablet disintegrant.

**UNIFORMITY OF THICKNESS**

From the result given in Table 3, it is shown that the deviation in thickness is within ±5%. This is tolerable for the normal manufacturing practices. The thickness may vary due to differences in the density of the granules and pressure applied to the tablets, wear and tear on length of the punches as well as on the speed of tablet compression (123). Tablet thickness is generally controlled to minimize appearance problems, to assure that tablets can be accurately counted by the filling equipment.
Some filling equipment depend on the uniform thickness of the tablets as a counting mechanism.

**UNIFORMITY OF HARDNESS**

Hardness variation is a problem that has same reasons as weight variation. Hardness depends on the volume of material and space between upper and lower punches at the moment of compression. If the material volume varies or the distance between the punches varies, hardness likewise is inconsistent. Hardness of tablets has been associated with other properties, such as density and porosity, all of which affect the disintegration time. Hardness generally shows a tendency to increase with normal storage of tablets. It is important; therefore that tablet should not be harder than necessary for adequate handling and shipping and dispensing.

The degree of hardness of tablet depends on its physical size and shape together with the characteristics of chemicals that are put into the formulation and the pressure applied during compression. If the tablet is initially too hard it may not disintegrate in the requisite period of time. Should it too soft, it may not withstand and the necessary multiple shocks occurring during handling, shipping and dispensing.

When the tablets were evaluated for the uniformity of hardness (Table 4), it was found that all tablets lie within $X \pm 2S$ limits.
FRIABILITY OF TABLETS

Friability test is a non-official test. It is to measure the breakdown of a tablet due to rubbing under shock or vibration.

Table 5 shows that greater the hardness of tablets, the lesser is the percentage friability. The possible reason for this result may be that at high compressional force the force the granules are packed strongly together and there is low degree of crumbling during friability. Percentage friability of all the formulations prepared in laboratory lies within the limits i.e. within 1%.
4. BIBLIOGRAPHY
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