STUDY ON THE EFFECT OF METHOD OF ADDITION OF PAPAYA PULP POWDER AS A DISINTEGRANT IN TABLET FORMULATION AND ITS *IN VITRO* EVALUATION

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CERTIFICATE

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CONTENTS

INTRODUCTION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents, prepared by either compression or molding[1].

Advantages

- They are unit dosage forms and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all oral dosage forms.
- Product identification is potentially simplest and cheapest, requiring no additional processing steps when employing an embossed (or) monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for “hang up” above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as enteric (or) delayed release products.
- They are better suited to large-scale production than other unit oral dosage forms.
- They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral dosage forms.
- Tablet is a tamper proof dosage form.

Disadvantages

- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages or any combination of these features may be difficult (or) impossible to formulate and manufacture as a tablet.
- Some drugs resist compression into dense compact, owing to their amorphous nature (or) flocculent, low density character.
- Bitter tasting drugs, drugs with an objectionable odor (or) drugs that are sensitive to oxygen (or) atmospheric moisture may require encapsulation (or) the tablets may require coating. In such cases the capsule may offer the best and lowest cost approach.

Properties of Tablets

The attributes of an acceptable tablet are as follows:

1. The tablet must be sufficiently strong and resistant to shock and abrasion, to withstand handling during manufacture, packaging, shipping and use. This property is measured by two tests, the hardness and friability tests.
2. Tablets must be elegant in appearance and must have the characteristic shape, color, and other markings necessary to identify the product. Markings are usually the monogram (or) logo of the manufacturer.
3. Tablets often have the National Drug Code Compendium of the Food and Drug Administration. Another marking that may appear on the tablet is a score (or) crease across the face, which is intended to permit breaking the tablet into equal parts for the administration of half a tablet.

However, it has been shown that substantial variation in drug dose can occur in the manually broken tablets.

4. Tablets must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation test and the content uniformity test.
5. The drug content of the tablet must be bioavailable. This property is also measured by two tests, the disintegration test and the dissolution test.
6. Bioavailability of a drug from a tablet (or) other dosage form is a very complex problem and the results of these two tests do not by themselves provide an index of bioavailability. This must be done by drug levels in blood.
7. Tablets must retain all of their functional attributes, which include drug stability and efficacy.

Ideal Characteristics of Tablet Dosage Form

- It has its own identity free of chips, cracks, discoloration and contamination.
- Should have strength to withstand vigorous mechanical shocks encounters in its production, packaging, shipping and dispensing.
- Should have chemical and physical stability.

On the other hand,

a. It must be able to release the medicinal agent in the body in a predictable and reproducible manner.
b. Must have a suitable chemical stability over time so as not to allow alterations of the medicinal agent.
c. Pre-compression of amorphous powders case negative effect on dissolution and disintegration rates.

Types and Classes of Tablets

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.

Tablets Ingested Orally

1) Compressed Tablets (CT)
2) Multiple Compressed Tablets (MCT)
    a) Layered Tablets
    b) Compression Coated Tablets
3) Repeat Action Tablets
4) Delayed Action and Enteric Coated Tablets
5) Sugar and Chocolate-Coated Tablets
6) Film Coated Tablets
7) Air Suspension Coated Tablets
8) Chewable Tablets

Tablets Used in Oral Cavity

1) Buccal Tablets
2) Sublingual Tablets
3) Troches, Lozenges and Dental Cone

Tablets Administered by Other Routes

1) Implantation Tablets
2) Vaginal Tablets

Tablets Used to Prepare Solution

1) Effervescent Tablets
2) Dispensing Tablets(DT)
3) Hypodermic Tablets(HT)
4) Tablet Triturate(TT)

Tabletting Methods

The four basic methods for the preparation of compressed tablets are[8]

1) Wet Granulation Method
2) Fluid- Bed Granulation
3) Dry Granulation Method and
4) Direct Compression

Wet Granulation

The most widely used and general method of tablet preparation is the wet granulation method**.** The steps involved in the wet method are weighing, mixing, wetting, granulation, screening the damp mass, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch.

The active ingredients, diluents and disintegrants are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars. The powder blend may be sifted through a screen of suitable fines to remove or break up lumps. This screening also affords additional mixing.

Solutions of the binding agents are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is over wetted, the granules will be hard, requiring considerable pressure to form tablets and the resulted tablets will have mottled appearance. If the powder mixture is not wetted sufficiently, the resulting

granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6 or 8 mesh screen. For large quantities one of several comminuting mills like stokes tornado mill, stokes oscillator, etc. can be used.

Moist materials from the wet milling step is placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. Now-a-days fluid bed dryers are used. In drying granules it is desirable to maintain a residual amount of moisture in the granules. This is necessary to maintain the various granulation ingredients such as gums in a hydrated state. Residual moisture also contributes to the reduction of static electric charges on particles.

After drying, the granulation is reduced in particle size by passing it through smaller mesh screen. Following dry screening, the granules tend to be more uniform.

The lubricants are added as fine powders after dry granulation. It is usually screened through 60 or 100 mesh nylon cloth to eliminate lumps as well as to increase the covering power of the lubricants. The lubricants are blended with the granules very gently, preferably in a blender.

There are number of types of tablet presses or tableting machines, each varying in its productivity but similar in its basic operation. The operation is the compression of the tablet granulation within a steel die cavity by the pressure exerted

by the movement of the two steel punches, a lower and upper punch.

Advantages of Wet Granulation[19]

1. The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles causing them to adhere to each other so they can be formed into agglomerates called granules. By this method the properties of the formulation components are modified to overcome their tabletting deficiencies. During the compaction process, the granules are fractured exposing fresh powder surfaces, which also improve their compressibility. Lower pressures are therefore needed to compress the tablets resulting in improvements in tooling life and decreased machine wear.
2. Drugs having a high dosage and poor flow and/or compressibility must be granulated by the wet method to obtain suitable flow and cohesion for compression. In this case, the proportion of the binder required to impart adequate compressibility and flow is much less than that of the dry binder needed to produce a tablet by direct compression.
3. Good distribution and uniform content for soluble, low-dosage drugs and color additives are obtained if these are dissolved in the binder solution. This represents a distinct advantage over direct compression where the content uniformity of drugs and uniform color dispersion can be a problem.

4. A wide variety of powders can be processed together in a single batch and in so doing, their individual physical characteristics are altered to facilitate tabletting.
5. Bulky and dusty powders can be handled without producing a great deal of dust and airborne contamination.

Fluid-Bed Granulation[9]

The fluid-bed granulation method is an extension of wet granulation method, as it incorporates many of its concepts. In this method, particles of an inert material or the active drug are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation that is ready for compression after the addition of the lubricant. The main benefit of this system is the rapid granulation and drying of a batch in a single piece of equipment.

The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume and moisture of the air all play an important role in the quality and performance of the final product.

Dry Granulation

When tablet ingredients are sensitive to moisture or unable to withstand elevated temperatures during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties slugging may be used to form granules. This method is referred as dry granulation, pre compression

or double compression. Steps involved are weighing, mixing, slugging, dry screening, lubrication and compression.

The active ingredients, diluents (if required) and part of lubricants are blended. One of the constituents must have cohesive property. The powdered material is then “slugged” or compressed into large flat tablets or pellets of about 1 inch diameter. The slugs are then comminuted through desirable mesh screen either by hand or for larger quantities by mills. The lubricants remaining is added to the granulation and blended gently and the material is compressed into tablets.

Direct Compression

Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. It involves only two operations, in sequence, powder mixing and tableting. The advantage of this is reduced cost production. The vehicles or carriers used must have good flow and compressible characteristics. Tablet excipients having the desired characteristics include:

Fillers – Spry dried lactose, microcrystalline cellulose, dicalcium phosphate, micro crystals of alpha monohydrate lactose.

Disintegrating agent – direct compression starch, sodium carboxy methyl starch, cross linked carboxy methyl cellulose fibres, cross linked polyvinyl pyrrolidone.

Lubricants – magnesim stearate, talc.

Glidants – fumed silicon dioxide.

Typical unit operations involved in Wet granulation, Dry granulation and Direct compression[11]

Table 1

Wet Granulation	**Dry Granulation**	**Direct Compression**
Milling and mixing of drug and excipients	Milling and mixing of drug and excipients	Milling and mixing of drug and excipients
Preparation of binder solution	Compression into slugs or roll compaction	Compression of tablets
Wet masses by addition of binder solution or granulating solvent	Milling and screening of slugs and compacted powder	
Screening of wet	Mixing with	

mass	lubricants and disintegrants	
Drying the wet granules	Compression of tablets	
Screening of dry granules		
Blending with lubricants and disintegrants to produce “running powder”		
Compression of tablets		

A Systemic and Modern Approach to Tablet Product Design

Tablet product design requires two major activities. First, formulation activities begin by identifying the excipients most suited for a prototype formulation of the drug. Second, the levels of those excipients in the prototype formula must be optimally selected to satisfy all process/product quality constraints[13].

Factors Affecting the Type of Excipients Used in a Tablet Formulation

The type of excipients used may vary depending on a number of preformulation, medical, marketing, economic and process/product quality factors as discussed in the following sections. Here we mainly focus on the process/product quality.

Typical tests preformed on tablets are as follows:

- Weight variation
- Hardness
- Friability
- Disintegration time
- Dissolution
- Water content
- Potency
- Content uniformity

Product quality is most often addressed at the tablet development stage. However, it is also important to monitor the processing quality of a formulation during development. They are:-

a. To optimize the process as well as the product.

b. To establish in-process quality control tests for routine production

It is more difficult to quantify the processing quality of a formulation than it is to measure the product quality. Some measurements that could be preformed on the process include:-

- Ejection force
- Capping
- Sticking
- Take-off force
- Flow of lubricated mixture
- Press speed (maximum)
- Frequency of weight control adjustments
- Sensitivity of formula to different presses
- Tooling wear
- Effect of consolidation load (Batch size)
- Hopper angle for acceptable flow
- Hopper orifice diameter for acceptable flow
- Compressional forces
- Environmental conditions (temperature, humidity and dust)

Each of the above processing parameters can become a source of trouble in scale-up (or) routine production. By monitoring these parameters in development, it may be possible to adjust the formula (or) process early enough to alleviate the source of trouble. The expected production output (number of tablets) per unit time will determine what speed tablet press will be required for a particular tablet product. If the anticipated unit output for a tablet product is expected to be large, a high-speed press will be required.

Attempts should be made in formulation development to design a tablet formula that will perform well on a high-speed press. A formula to run on a high-speed press should have excellent flow to maintain uniform die fill during compressing. It should have good bonding characteristics so that it can compress with a minimal dwell time.

Compressed Tablets by Wet Granulation

Compressed tablets are defined as solid-unit dosage forms made by compaction of a formulation containing the drug and certain fillers (or) excipients selected to aid in the processing and properties of the drug product.

Formulation of Tablets and Factors to be Considered

The size and to some extent, the shape of the tablet are determined by the active ingredients. Drugs having very small doses in the microgram require the addition of fillers also called excipients to be added to produce a mass (or) volume of material that can be made into tablets of a size that is convenient for patients.

As the dose increases, so does the size of the tablet. Drugs with a dose of 100 to 200mg may require tablet weights of 150 to 300mg and round die diameters of 1/4 to 7/16 inches. The diameter depends on the density and compressibility of the powders used. As the dose of the active ingredient increases, the amount of the excipients and the size of the tablet may vary considerably depending on requirements of each to produce an acceptable tablet. While the diameter of the tablet may in some cases be fixed, the thickness is variable thus allowing the formulator considerable latitude and flexibility in adjusting formulations.

As the dose, and therefore the size of the tablet increases, the formulator uses his expertise and knowledge of excipients to keep the size of the tablet as small as possible without sacrificing its necessary attributes.

Formulation of a tablet then requires the following considerations:

1. Size of the dose (or) quantity of active ingredients
2. Stability of active ingredients.
3. Solubility of active ingredients.
4. Density of active ingredients.
5. Compressibility of active ingredients.
6. Selection of excipients.
7. Method of granulation (preparation for compression)
8. Character of granulation
9. Tablet press, type, size, capacity.
10. Environmental conditions (ambient (or) humidity control)

11. Stability of final product.
12. Bioavailability of the active drug content of the tablet.

The selection of excipients is critical in the formulation of tablets. Once the formulator has become familiar with the physical and chemical properties of the drug, the process of selecting excipients is begun. The stability of the drug should be determined with each proposed excipients. This can be accomplished as follows:

In the laboratory, prepare an intimate mixture of the drug with an excess of each individual excipients and hold at 60˚C for 72 hrs in a glass container. At the end of this period analyze for the drug using a stability-indicating assay.

Tabletting Properties

Granules Size and Shape[14]

The size of the granule is known to affect the average tablet weight, tablet weight variation and disintegration time.

The size can be determined by using[13]

1. Optical micrometer
2. Sieving
3. Sedimentation
4. Particle volume measurement
5. Coulter counter

Surface Area

The determination of surface area of finely divided drug powders may be of value to drugs that have only limited water solubility. The two most common methods for determination of surface area of solid particles are:

a) Gas adsorption method (e.g. Quantasorb)
b) Air permeability technique (e.g. Fisher subsieve sizer)

Density

Granule density may influence compressibility, tablet porosity dissolution and other properties. The granule density is measured by pycnometer. The intrusion fluid used may be benzene (or) mercury.

Types of Densities

There are three types of densities:

1. **True density:** True density of the material itself exclusive of the voids and intra-particle pores larger than molecular (or) atomic dimensions in the crystal lattices.
2. **Granule density:** Granular density may be determined by the displacement of mercury which does not penetrate at ordinary pressure into pores smaller than about 10µm (or) by using pycnometer.
3. **Bulk density:** Bulk density is determined from the bulk volume and the weight.

The bulk density of a powder is always less than the true density of its component particles, because the powder contains interparticle pores (or) voids

Bulk density α True density

Bulk density = K true density

$$K = \frac{Bulk\ \ density}{True\ \ density}$$

= packaging fraction (or) fractional solids. Content bulk density increases when particle size is more and if the particle size is less bulk density decreases.

Strength and Friability

A granule is an aggregation of compound particles i.e. held together by bonds of finite strength. The strength of a wet granule is mainly due to the surface tension of liquid and capillary forces. To determine granule strength two distinct types of measurements are made.

They are:

1. Compression strength
2. Friability measurement

Flow Properties

The flow properties of a material result from many forces. There are many types of forces that can act between particles.

1. Frictional force
2. Surface tension force
3. Cohesive (or) Vanderwaal force
4. Mechanical force
5. Electrostatic force

The tests to determine flow rate are of two types. They include direct methods and indirect methods.

Direct methods include hopper flow method and recording flow meter method.

Indirect methods include determination of angle of repose, measurement of bulk density and compressibility index, Carr's index, Hausner's ratio and angle of repose, shear cell determinations and critical orifice diameter determination.

Compressibility Index

This is an indirect method of measuring powder flow from bulk densities and was developed by "Carr"

Carr's Index

It is given by the equation

$$Carr's\ index\ (\%) = \frac{Tapped\ \ density - Poured\ \ density}{Tapped\ \ density}\ X\ \ 100$$

Carr's index is related to flowability and is shown in the above information on compressibility index.

A similar index has been defined by Hausner.

$$Hausner's\ \ ratio = \frac{Tapped\ \ density}{Poured\ \ density}$$

Hausner's ratio

< 1.25 – Good flow = 20% Carr

>1.25 – Poor flow = 33% Carr

1.25 > Hausner's ratio < 1.5 Added glidant normally improves flow.

Angle of Repose

A static heap of powder, when only gravity acts upon it will tend to form a conical mount. If the horizontal surface radius is R and the height of the heap is H.

Then $\theta = \tan^{-1} (H/R)$ where θ = angle of repose in degrees

Table 2

Angle of repose (θ)	**Type of flow**
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Solubility

Solid drugs, which are administered into the body, must undergo dissolution prior to absorption. So the solubility of dosage form is essential for the formation of solution. As a rule of thumb the compounds with aqueous solubility of less than 1% w/v are considered to posses dissolution related absorption problems.

The solubility of every new drug must be determined as a function of pH over pH range 1- 8. If the intrinsic dissolution rate was greater than 1mg/cm^2/min. the absorption was greater than 1mg/cm^2/min. the absorption was unimpeded. Dissolution rates of less than 0.1mg/cm^2/min. were likely to give dissolution rate limited absorption since

dissolution rate and solubility are proportional under sink conditions.

Different Adjuvants used in Tablet Formulation

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials called as additives or excipients. Excipients are specified according to the function they perform in the tablet. They are classified as follows

- Fillers (Diluents)
- Binders
- Disintegrants
- Glidants
- Lubricants
- Antiadherents
- Adsorbents
- Moistening agents
- Coloring agents
- Sweetening agents
- Flavoring agents

Although they were considered to be inert they themselves should not exert therapeutic (or) biological action, it is now recognized that they can potentially influence rate and (or) extent of absorption. E.g. Formation of poorly soluble, non-absorbable drug-excipient complexes between tetracyclines and dicalcium phosphate, amphetamine and sodium carboxy methyl cellulose and phenobarbitone and PEG_{4000}

Diluents or Fillers[10]

These are the inert substances which will increase the bulk of tablet. Selecting the diluent is an important character while tableting. These agents may not be necessary if the dose of drug per tablet is high. Generally, a tablet should weigh atleast 50mg and therefore very low dose drugs will invariably require diluents to bring the overall tablet weight to atleast 50mg.

Diluents or fillers fall into two general categories:

1. Carbohydrate and modified carbohydrate excipients.
2. Inorganic materials

In wet granulation process, such carbohydrate substances as sugars, starches and cellulose may also function as binder. Whereas in direct compression systems, they serve as diluent carrier. The inorganic excipients, when used in either system, are not binders that are a cohesive agent, in directly compressible system. Hence they function more as a carrier.

Microcrystalline cellulose (MCC) (AVICEL) is most widely used as direct compression tablet filler. It has a function of disintegrant besides that of a dry binder and is compatible with most excipients and active ingredients.

Lactose is an inexpensive, soluble and easily granulatable diluent. Since it lacks flowability and compressibility in its common form, lactose in modified form can only be used in direct compression.

The other commonly used diluents are mannitol, kaolin, dry starch, calcium sulfate, dicalcium phosphate.

Binders or Adhesives[12]

Binders are solid materials used in the manufacture of solid dosage forms because of their adhesive and cohesive properties. Their role is to assist size enlargement by adding cohesiveness to powders, thereby providing granules and tablets with necessary bond strength. They improve the appearance, hardness and friability of preparations but are not intended to influence the dissolution or disintegration of active substances.

Binders are either starch, gelatin, sugars or polymeric substances. The latter fall into two classes

a. Natural polymers such as starches or gum including acacia, tragacanth, gelatin.
b. Synthetic polymers such as poly vinyl pyrrolidone, methyl and ethyl cellulose and hydroxy propyl cellulose.

The quantity of binder used has a considerable effect on the characteristic of the compressed tablets. The use of too much binder or too strong binder will make a hard tablet that will not disintegrate easily. Binders are used both as solution and in dry form, depending on other ingredients in the formulation and method of preparation. However pregelatinized starches available are intended to be added in dry form so that water alone can be used for granulating solution.

Hydrophilic binders show better dissolution profiles with poorly soluble drugs like phenacetin by imparting hydrophilic properties to the granule surface. Non-aqueous binders like ethyl cellulose retard drug dissolution.

The direct compression method for preparing tablets requires a material that is not only free flowing but also sufficiently cohesive to act as a binder. For this microcrystalline cellulose, amylase and polyvinyl pyrrolidone is used.

MCC is a non fibrous form of cellulose. It is water insoluble but has the ability to draw fluid into tablet by capillary action. It swells on contact and thus acts as disintegrating agents. The material flows well and has a degree of self lubricating qualities.

Starch paste is a common binder. Starch extracted from maize, potato, rice, wheat is widely used as tablet binder. It has a concentration between 5 and 25%. It produces relatively soft and friable granules and tablets disintegrate readily. High

viscosity is its draw back. Pregelatinized starch can be used instead of starch paste.

Disintegrants[15,19]

Disintegrant is the term applied to various agents added to tablet granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in aqueous environment. Basically the disintegrant's major function is to oppose the efficiency of tablet binder and the physical forces that act under compression to form tablet. The stronger the binder, the more effective must be the disintegrating agent in order for the tablet to release its medication. Ideally it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into the powder particle from which the granulation was prepared.

The ideal disintegrant has-

1. Poor solubility
2. Poor gel formation
3. Good hydration capacity
4. Good molding and flow properties
5. No tendency to form complexes with the drugs

There are two methods used for incorporating disintegrating agents into the tablet.

1. External addition
2. Internal addition

In external addition method, the disintegrant is added to the sized granulation with mixing just prior to compression.

In the internal addition method, the disintegrant is mixed with some other powders before wetting the powder mixture with granulating solution. Thus, the disintegrant is incorporated within the granule. When this method is used, part of the disintegrant can be added internally, and part externally. This provides immediate disruption of tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

Disintegrants act by different mechanisms:-

- They enhance action of capillaries in producing a rapid uptake of aqueous fluids. eg. Starch, microcrystalline cellulose.
- Those that swell on contact with water. eg. Sodium starch glycolate, carboxy methyl cellulose.
- That release gas to disrupt the tablet structure. eg. Certain peroxides.
- That destroys the binder by enzymatic action. eg. Starch amylase

Disintegrants constitute a group of material that on contact with water swell, hydrate, and change in volume or form, to react chemically to produce a disruptive change in tablet. These groups include various forms of starch, cellulose, bentonite, algins, vegetable gums, clays, ion

exchange resins and acid base combinations. Carboxy methyl cellulose, corn and potato starch are popular disintegrants. They have great affinity for water and swell when moistened, then facilitating, the rupture of tablet matrix. Starch usually 5-15% is used.

A decrease in amount of disintegrant can significantly lower bioavailability. Adsorbing disintegrants like bentonite and veegum should be avoided with low dose drugs like digoxin, alkaloids and steroids since a large amount of dose is permanently adsorbed and only a fraction is available for absorption.

A group of materials known as super disintegrants have gained popularity. Croscarmelose, crospovidone and sodium starch glycolate represent examples of a cross linked cellulose, a cross linked polymer and cross linked starch respectively.

Sodium lauryl sulphate in combination with starch is an effective disintegrant. In some cases the effectiveness of surfactants in improving tablet disintegration is postulated as due to an increase in the rate of swelling.

The binder, tablet hardness, lubricants can also affect disintegration time.

Glidants[7]

Glidants improve the flow characteristics of the powder mixture. These materials are added in the dry state just prior to compression. They act by reducing the inter-particulate friction and reduce the frictional forces between the granules and dies. Colloidal silicon dioxide is the most commonly used glidant and generally used in low concentration of 1% or less. Talc is also used and may serve the dual purpose of glidant/ lubricant.

It is important to optimize the order of addition and mixing process of these materials to maximize their effect and to make sure that their influence on lubricants is minimized.

Lubricants

They have a number of functions in tablet manufacture:-

- They prevent adhesion of the tablet material to the surface of the dies and punches
- Reduce interparticle friction
- Facilitate the ejection of tablets from the die cavity
- Improves the rate of flow of tablet granulation

Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils. Most lubricants are used in concentration below 1% when used alone. Talc is used in concentration as high as 5%. Lubricants are mostly hydrophobic materials. Poor selection or excessive amounts can result in water proofing the tablets, resulting in poor tablet disintegration and / or delayed dissolution of drug substance.

Antiadherents

These are useful in tablet formulation, which have a tendency to pick easily. Multivitamin products containing high vitamin E levels often display extensive picking which can be minimized through the use of colloidal silica such as syloid (0.1-0.5%)

Adsorbents

Adsorbents are substances included in a formulation that are capable of holding quantities of fluids in an apparently dry state. Oil soluble drugs fluid extractors (or) oils can be mixed with adsorbents and then granulated and compressed into tablet.

Coloring Agents

Color helps the manufacturer to control the product during its preparation, as well as serving as means of identification to the users. All colorants used in pharmaceuticals must be approved by FDA. Lake is the combination of a water soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye. The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulation process. Migration of colors may be reduced by drying the granules slowly at lower temperature and stirring the granules while it is drying.

Different colorants used are D and C Red 33, Iron oxide, red-caramel, Titanium oxide, Cochineal extract.

Moistening Agents

In wet granulation a moistening agent is required usually water. In cases where, water cannot be used because of hydrolysis, alcohol is often substituted. Other moistening agents are industrial methylated spirits, isopropyl alcohol, etc.

Sweetening Agents

In addition to the sweetness which may be afforded by the diluents of the chewable tablet. eg. Mannitol (or) lactose. Sweeteners other than sugar that have an advantage of reducing the bulk volume are cyclamates, saccharin, aspartame (Searle)

Surfactants

Molecules (or) ions that are adsorbed at interfaces are termed as surfactants. Depending on the number and nature of the polar and non-polar groups presented, the amphiphile may be predominantly hydrophilic suggesting that the molecules (or) ion have a certain affinity for both polar and non-polar solvents.

The hydrophilic portion of the surfactant is soluble in the polar solvent and the lipophilic portion is soluble in the non-polar solvent. The surfactant occupies the interface to decrease interfacial tension and thereby increases the solubility. Release of poorly soluble drugs from tablet and hard gelatin capsules may be increased by the inclusion of surfactants in the formulations.

The ability of surfactants to reduce the solid liquid interfacial tension will permit gastrointestinal fluids to wet

more effectively and to come into more intimate contact with solid dosage forms. This wetting effect may thus aid the penetration of GI fluids into the mass of capsule contents which often remains when hard gelatin shell has dissolved and reduces the tendency of poorly soluble drug particles to aggregate in the GI fluids. In each case the resulting increase in total effective surface area of drug in contact with the GI fluids would tend to increase the dissolution and absorption rate of drugs.

Production of Tablets

Tablets are made by compressing the formulation containing a drug or drugs with excipients on stamping machines called presses. Tablet compression machine or tablet presses are designed with the following basic components.

1. Hoppers for holding and feeding granulation to be compressed
2. Dies that define the size and shape of the tablet.
3. Punches for compressing the granulation within the dies.
4. Camtracks for guiding the movement of the punches.
5. A feeding mechanism for moving granulation from the hopper into the dies.

Punches and Dies

They are usually fabricated from special steels, the working surface being accurately machined and highly polished to ensure proper mechanical operation and well finished tablets.

Punches and dies (toolings) must be stored, lightly oiled, in containers which prevent accidental contact. The ease of manufacture and the final appearance of the tablet depend on unblemished, highly polished working surfaces. Punch edges must be sharp and free from burrs.

Working

Once the machine has been assembled, trial tablets may be made with the press. The optimum tablet hardness depends on the material to be compacted and the ultimate use of the tablets.

As the head of the press rotate, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression and ejection. The portions of the head that hold the upper and lower punches are called the upper and lower turrets respectively and the portion holding the dies is called the die table. At the start of a compression cycle, granulation stored in a hopper empties into the feed frame which has several interconnected compartments. These compartments spread the granulation over a wide area to provide time for the dies. The pull down cam guides the lower punches to the bottom of their vertical travel, allowing the dies to overfill. The punches then pass over a weight control cam which reduces the fill in the dies to the desired amount. A wipe off blade at the end of the feed frame removes the excess granules and directs it around the turret and back into the front of the feed frame. Next the lower punches travel over the lower compression roll, while simultaneously the upper punches ride beneath the upper compression roll. The

upper punches enter a fixed distance into the dies, while the lower punches are raised to squeeze and compact the granulation within the dies. After the movement of compression, the upper punches are withdrawn. The lower punches ride up the cam which brings the tablets flush with or slightly above the surface of the dies. The tablet strike a sweep-off blade affixed to the front of the feed frame and slide down a chute into a receptacle. At the same time the lower punches reenter the pulldown cam and the cycle is repeated.

EVALUATION OF TABLETS

In the evaluation of tablets the physical, chemical and bioavailability properties of tablets should be evaluated. The following are the different properties, which are to be evaluated.

Official Tests

Weight Variation[1,3,7]:

The weight variation test would be satisfactory method for determining drug content uniformity and drug distribution. In practice, this test is performed by taking 20 tablets from a batch. Then 20 tablet, are weighed and the average weight is taken. Then the tablet is weighed individually. The percentage deviation can be determined by using the following formula.

$$Deviation = \frac{Average\ \ weight\ - Individual\ \ weight}{Average\ \ weight}\ X\ 100$$

The percentage deviation limit based on average weight is shown in the following table according to I.P, B.P and U.S.P.

Table 3

Sl. No	Average weight (I.P)	Average weight (B.P)	Average weight (U.S.P)	% Deviation allowed
1	80mg (or) less	80mg (or) less	130mg (or) less	10.0
2	80-250 mg	80-250mg	130-324mg	7.5
3	>250mg	>250mg	>324mg	5.0

Hardness Test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture; packaging and shipping. The relationship of hardness to tablet disintegration and perhaps more significantly, to the drug dissolution release rate, has become apparent. The hardness of tablets from each batch can be tested by using Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. The other hardness testers available are Pfizer tester, Strong-Cobb tester, Erweka tester and the Schleuniger tester.

Friability

It is a measure of tablet strength. The friability is determined by using Roche friabilator. This device, subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm, dropping the tablets at a distance of six inches with each revolution. Normally a preweighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets were then dusted and reweighed. The percentage weight loss was calculated by using the following formula.

$$F = 100\,X\,(1 - w/w_o)$$

Where, w_o = Weight of tablets before friability

w = Weight of tablets after friability

Conventional compressed tablets that do not lose more than 0.5 to 1.0% of their weight are generally considered acceptable. When capping is observed on friability testing, the tablet should not be considered for commercial use.

Disintegration

For most tablets the first important step towards solution is break down of the tablet into smaller particles or granules, a process known as disintegration. The time that it takes to disintegrates is measured in a device described in the USP/NF.

The apparatus consists of 6 glass tubes that are open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. One tablet is placed in each tube, and basket rack is positioned in a 1L beaker of water or simulated gastric fluid at 37ºC ± 2ºC. A standard motor driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles/min. Perforated plastic disc may also be used in the test which are placed on top of the tablets and impart an abrasion action on the tablets. Uncoated USP tablets have disintegration time standards as low as 5 min, but majority of the tablets have a maximum disintegration time of 30min whereas for other coated tablets, the disintegration time will vary accordingly.

Dissolution

The breakdown of tablet into granules and formation of clear solution is dissolution. According to IP, BP and USP/NF the various apparatus like rotating basket, rotating paddle and reciprocating cylinder, etc. are used to determine dissolution.Common dissolution tolerance in the USP/NF is not less than 75% dissolved in 45 min.

The pharmacopoeial requirements for dissolution tests are shown in the following table.

Table 4

Stage	**No. of tablets tested**	**Acceptance criteria**
S_1	6	Each unit is not less than D-5%
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to (or) greater than D, and no unit is less than D-15%
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to (or) greater than D, not more than 2 units are less than D-25%

D = The amount of dissolved active ingredients specified in monograph expressed as a percentage of the state amount.

Appearance

The general appearance of a tablet, its visual identity and overall “elegance,” is essential for consumer acceptance. The control of the general appearance of a tablet involves the measurement of a number of attributes such as a tablet’s size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

DISSOLUTION

"Dissolution[25] is defined as the process by which solid substances enters in solvent to yield a solution. Fundamentally, it is controlled by the affinity between the solid substance and the solvent." The physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the swelling process, the disintegration and the deaggregation of the dosage forms are few of the factors that influence the dissolution characteristic of drugs.

Wagner proposed a scheme for the processes involved in the dissolution of solid dosage forms.

Carstensen proposed a scheme incorporating some other factors in the following sequence[9]:

1. Initial mechanical lag
2. Wetting of the dosage form
3. Penetration of the dissolution medium into the dosage form
4. Disintegration
5. Deaggregation of the dosage form and dislodgement of the granules
6. Dissolution
7. Occlusion of some particles of the drug.

In order for a drug to be absorbed, first it must be dissolved in the fluid at the absorption site. For instance, a drug administered orally in tablet or capsule form cannot be

absorbed until the drug particles are dissolved by the fluids at some point within the gastrointestinal tract.

For instance, when the solubility of a drug is dependent upon either an acidic or basic medium, the drug would be dissolved in the stomach or intestines respectively. The process by which a drug particle dissolves is termed as dissolution. i.e. dissolution is the process by which a solid of only fair solubility characteristics enters into solution.

The rate of dissolution of drug substance is determined by the rate at which solvent-solute forces of attraction overcome the cohesive forces present in the solid. This process is rate-limiting when the release of solute into solution is slow and the transport into the bulk solution is fast. In this case the dissolution is said to be interfacially controlled. Dissolution may also be diffusion controlled, where the solvent-solute interaction is fast compared to transport of solute into the bulk solution. In diffusion-controlled process, a stationary diffusion layer of solute adjacent to the solid/liquid interface is postulated. The saturation concentration of solute develops at the interface and decreases with distance across the diffusion layer.

Apparatus

The breakdown of tablet into granules and formation of clear solution is dissolution. According to IP, BP and USP/NF the following apparatus are used to determine dissolution.

1) Apparatus I (Rotating Basket)
2) Apparatus II (Rotating Paddle)

3) Apparatus III (Reciprocating Cylinder)
4) Apparatus IV (Flow through cell)
5) Apparatus V (Paddle Over Disk)
6) Apparatus VI (Cylinder)

Apparatus I (Rotating Basket Apparatus)

The assembly consists of the following, a covered vessel made of glass or other inert transparent material, a motor, a metallic drive shaft and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel 37±0.2 ºC during the test and keeping the bath fluid in constant smooth motion.

Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 180mm to 175mm high, its inside diameter is 98mm to 106mm and its nominal capacity is 1000ml. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. The shaft is positioned so that its axis is not more than 2mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%. Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications. Unless otherwise specified in the individual monograph, use 40-mesh cloth or a basket having gold coating 0.0001-inch (2.5mm) thickness may be

used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25±2mm during the test.

Theory of Dissolution

Diffusion Layer Model (Film Theory) [8,26]

In 1897 Noyes & Whitney developed an equation based on Fick's 2nd law to describe the dissolution phenomenon.

$$\frac{dc}{dt} = K(C_s - C_t) \qquad (1)$$

Where $\frac{dc}{dt}$ → dissolution rate of the drug

K → Proportionality constant

C_s → Saturation concentration (maximum stability)

C_t → Concentration at time t

$C_s - C_t$ → Concentration gradient

The proportionality constant K is also known as dissolution constant and the equation has been shown to obey first order kinetics.

In their experiments Noyes and Whitney maintained a constant surface area. However, because such a condition is not always applicable, Brunner and Tolloczko modified equation (1) to incorporate the surface area, S, as a separate variable.

$$\frac{dc}{dt} = K_1 S(C_s - C_t) \qquad (2)$$

In order to explain the mechanism of dissolution, Nernst in 1940 proposed the film-model theory. Under the influence of no reactive or chemical force, a solid particle immersed in a liquid, undergoes two consecutive steps

1. The solution of the solid at the interface, forming a thin stagnant layer of film 'h' around the particle and
2. The diffusion from this layer at the boundary to the bulk of the fluid.

In the 1st step, solution formation is almost instantaneous; in the 2nd step diffusion is much slower and, therefore, is the rate-limiting step.

By using Fick's first law of diffusion and Nernst's newly proposed film theory, Brunner expanded equation (2) to include the diffusion co-efficient, D. the thickness of the stagnant diffusion layer, h, and the volume of the dissolution medium, "v" producing

$$\frac{dc}{dt} = K_2 \frac{DS}{vh}(C_s - C_t) \qquad (3)$$

The proportionality constant K_2 is known as the intrinsic dissolution rate constant and is characteristic of each chemical compound.

Sink Condition

The term sink condition originated from the fact that the drug concentration on both sides of the epithelial layer of the internal wall approaches equilibrium in a short time, and that the gastrointestinal tract acts as a natural sink. i.e. the drug is absorbed instantaneously the moment it dissolves.

Therefore, under *in vivo* conditions, there is no concentration build up and hence the retarding effect of the concentration gradient on the dissolution rate, as predicted by equation (1), does not occur. In order to simulate the *in vivo* sink condition, *in vitro* dissolution testing usually is conducted using either a large volume of the dissolution medium or a mechanism by which the dissolution medium is replenished constantly with fresh solvent at a specified rate so that the concentration of the solute never reaches more than 10 to 15% of its maximum solubility. If such a parameter is maintained, the dissolution testing is said to be conducted under sink conditions. i.e. not under the influence of the concentration gradient. This can be seen from the following mathematical gradient.

Assuming that $C_s >> C_t$, equation (3) becomes

$$\frac{dc}{dt} = K_2 \frac{DS}{vh} C_s \quad (4)$$

C_s and D are constants for each specific chemical substance. Therefore, they could be incorporated in K_2 and appear in equation (5) as K_3

$$\frac{dc}{dt} = K_3 \frac{S}{vh} \qquad (5)$$

If the volume of the dissolution medium and the surface area are kept constant during the duration of the dissolution test, then

$$\frac{dc}{dt} = K \qquad (6)$$

Equation (6) predicts a constant dissolution rate under sink condition and represents a zero order kinetic process; i.e. the concentration of the drug increases linearly with time.

Equation (6) is also believed to be approximate the *in vivo* condition where the dissolution rate of sparingly soluble drugs plays a fundamental role in determining their bioavailability.

Hixson & Crowell Cubic Root Law for Dissolution

In equation (2), the surface area was considered constant for the duration of the dissolution test. Although this could be achieved by using a nondisintegrating disk of the chemical substance, a technique usually employed for the determination of the intrinsic dissolution rate, the same could not be maintained in dissolving crystal or a regular solid dosage form where a complete disintegration is a priority. Therefore, in order to develop a dissolution equation that is based on a changing surface area, Hixson and Crowell modified equation (2) to represent the rate of appearance of the solute in the solution by multiplying each side of the equation by v (volume), letting $K_1v = K$

$$\frac{dW}{dt} = KS(C_s - C_t) \qquad (7)$$

Where, W = Weight of the solute in solution

They also assumed that $S = kw^{2/3}$, where k is a constant containing the shape factor and the density of the particle, and w is the weight of the undissolved particles at time t.

$$\frac{dW}{dt} = Kkw^{2/3}(C_s - C_t) \quad (8)$$

After mathematical treatment involving the application of Fick's first law and integration under the condition that w is equal to w_o, the initial weight of the particle at time zero, equation (9) results.

$$w_{o}^{1/3} - w^{1/3} = K_1 t \qquad (9)$$

Equation (9) is called the Hixson and Crowell's "Cubic root law" for dissolution.

Dissolution

Absorption
(In vivo)

Dissolution 

Wagner's schematic diagram illustrates the processes involved in the dissolution of solid dosage forms

Factors Affecting the Rate of Dissolution Relating to the Solid Dosage Form

Factors affecting the dissolution rate of drugs from a dosage form include the following[9,18,25]:

1. Factors related to the physicochemical properties of the drug
2. Factors related to drug product information
3. Effect of processing factors on the dissolution rate
4. Factors related to the dosage form
5. Factors related to dissolution test parameters
6. Miscellaneous factors

Factors Related to the Physicochemical Properties of the Drug

Effect of Solubility

The modified Noyes and Whitney equation shows that the aqueous solubility of the drug is the major factor that determines its dissolution rate. The drug solubility data should be taken into consideration in the formulation design.

Effect of Particle Size

According to Nernst-Brunner theory, the dissolution rate is directly proportional to the surface area of the drug exposed to the dissolution media. In order therefore to increase the dissolution rate for a given amount of drug, the effective surface area has to be increased. This can be achieved easily by decreasing the particle size of the drug. But the particle size reduction of the hydrophobic drug may produce a smaller effective area and a reduction in dissolution rate. The mechanism by which the reduction in particle size improves dissolution is usually through the enhancement of the drug solubility.

Effect of Solid Phase Characteristics of the Drug

Amorphicity and crystallinity, the two important solid-phase characteristics of drugs affect their dissolution profile. Numerous studies have demonstrated that the amorphous form of a drug usually exhibits greater solubility and higher dissolution rate as compared to that exhibited by the crystalline form. For example, novobiocin and the contradictory example is that of erythromycin esteolate.

Effect of Polymorphism

Polymorphism and the state of hydration, salvation and /or complexation markedly influence the dissolution characteristics of the drug. Examples are tolbutamide, chloramphenicol and others.

Factors Related to Drug Product Formulation

Effect of Binding Agents

Binding agents are incorporated into tablets during granulation in order to improve the flowability of the drug and to enhance compressibility. These agents coat the drug particles and therefore the rate of solution of the binder in water can determine the release rate from the tableted drug. Tablets containing soluble binders (hydrolysed gelatin and PVP) had rapid dissolution rates whereas slow and incomplete disintegration of tablets formulated with starch paste led to protracted release of drug.

Effect of Disintegrants

To enhance the disintegration of tablets and capsules, disintegrants are added. Disintegrants act by either bursting open the tablet and/or promoting the rapid ingress of water into the center of the tablet or capsule. In many cases capillarity and therefore the rate of water penetration predominates in causing disruption. Sodium starch glycollate possesses high swelling capacity and high hydration capacity and is superior in dissolution properties than microcrystalline cellulose and cross-linked polyvinyl pyrrolidone

Effect of Lubricants

Lubricants are added to dosage form to prevent it from sticking to the processing machinery. Magnesium stearate, a hydrophobic-lubricant tends to retard the dissolution rate of salicylic acid tablets, while a water soluble surface active lubricant, sodium lauryl sulphate enhanced the dissolution. The enhancing effect of Sodium lauryl sulphate , on the other hand, was suggested to be due, in part, to an increase in the microenvironment pH surrounding the sparingly soluble weak acid and to increase wetting and better solvent penetration into the tablets and granules as a result of lowering the interfacial tension between the solid surface and the solvent. The most effective lubricants are very hydrophobic and they must therefore be properly formulated to avoid reducing dissolution rate and bioavailability.

Effect of Diluents

Increasing the starch content (most commonly using diluent) from 5 to 20% resulted in the dissolution rate of salicylic acid tablets. This was attributed to better disintegration. Later, Finholt suggested that the hydrophobic drug crystals acquire a surface layer of fine starch particles that imparts a hydrophilic property to the granular formulation and thereby increase the effective surface area and hence the dissolution rate.

Effect of Granulating Agents

Wet granulation has been shown to improve dissolution rates of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules.

Factors Related to Processing

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

Method of Granulation

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 considered as a superior method compared to the dry of double compression procedure. With the advent of newer tableting machines and materials, 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 process.

Effect of Compression Force

T. Higuchi (1953), 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 the crushing effect

and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness and, 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.

Factors Related to the Dosage Form

Drug Excipient Interaction

These interactions can occur during any unit operation, such as mixing, blending, drying, and/or granulating, resulting in a change in dissolution pattern of the dosage form in question. The effect of magnesium stearate on the disintegration time of tablets containing either potato starch or sodium starch glycolate was found to depend on the swelling characteristics of the disintegrants. By minimizing, if not eliminating, these interactions, adverse effects on the performance of the final product can be avoided. The better process control is also possible with noninteracting drug-excipient interactions.

Deaggregation

Deaggregation is often a prerequisite for dissolution. In such cases it can control dissolution

Factors Related to Dissolution Test Parameters[9,24]

Agitation

The relationship between intensity of agitation and the rate of dissolution varies considerably according to the types of agitation used, the degree of laminar and turbulent flow in the system, the shape and design of the stirrer and physicochemical properties of the solid.

When a stirring device is used, such as the basket, paddle, or rotating filler, the speed of agitation generates a flow that continuously changes the liquid-solid interface between the solvent and the drug in a way similar to the flow rate in the flow-through dissolution apparatus. In order to prevent turbulence and sustain a reproducing laminar flow, which is essential for obtaining reliable results, either the speed of agitation or the flow rate, depending on the type of apparatus employed, should be maintained at a relatively low level.

The empirical relationship between the rate of dissolution and the intensity of agitation is

$$K = a\,(N)^b$$

Where N is the speed of agitation, K is the dissolution rate and a & b are constants.

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

Generally a temperature of 37ºC is always maintained during the dissolution determinations. The effect of temperature variation of the dissolution medium depends mainly on the temperature/solubility curves of the drug and excipients in the formulation. For a dissolved molecules, the diffusion coefficient, D, depends on the temperature T according to the Stokes equation.

$$D = kT\ (6\pi\eta r)$$

Where K is the Boltzmann constant and $6\pi\eta r$ is the Stokes force for a spherical molecule (η is the viscosity in cgs or poise units, and r is the radius of the molecule)

Dissolution Medium[9]

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 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 0.1NHCL or buffered solutions with a pH close to that of the gastric juice (pH – 1.2). The acidic solutions tend to increase the dissolution rate by increasing the effective surface area. Because of the corroding action of the acid fumes on the dissolution equipment, currently it is a general practice to use distilled water unless investigate studies show a specific need for the acidic solutions in order to generate meaningful dissolution data. Another approach for avoiding

the deleterious effects of hydrochloric acid is to replace it with acidic buffers, such as sodium acid phosphate, to maintain the required low pH.

Surface Tension of the Dissolution Medium

Surfactants and wetting agents lower the contact angle and thereby improve the penetration process of the matrix by the dissolution medium. Measurable enhancement in the dissolution rate of salicylic acid from an inert matrix was reported by Singh and co-workers when the contact angle, θ, was lowered from 92º (water) to 32º (using 0.01% dioctyl sodium sulfosuccinate). The surface tension also was correspondingly lowered from 60 to 31 dynes/cm. The same findings were obtained in benzocaine studies when polysorbate 80 was used as the surface-active agent. Low levels of surfactants were recommended to be included in the dissolution medium as this seemed to give a better correlation between the *in vitro* data and *in vivo* condition.

Viscosity of the Medium

In the case of diffusion-controlled dissolution processes, it would be expected that the dissolution rate decrease with an increase in viscosity. In the case of interfacial-controlled dissolution processes, however, viscosity should have very little effect. The Stokes-Einstein equation describes the diffusion coefficient, D, as a function of viscosity.

Miscellaneous Factors

Adsorption

The adsorbent has an influence on the dissolution rate of a slightly soluble solid. It was also reported that the adsorbent is capable of increasing the dissolution rate observed in water under conditions of a decreased concentration gradient applying Nernst-Brunner film theory.

Sorption

It was found that water sorption from the atmosphere into the tablet containing microcrystalline cellulose is a very rapid first-order process, resulting in substantial changes in the physical properties. These changes are attributed to the breaking of the hydrogen bonds. The relative density of the tablets was found to decrease, resulting in increased disintegration time with increase in water sorption-rate constants. These changes were found to be irreversible.

Humidity

Moisture has shown to influence the dissolution rate of many drugs from solid dosage forms. Environmental conditions to which dosage forms are exposed, moisture in particular, should be rigorously assessed if reproducible and reliable dissolution data are to be obtained. Additionally, humidity during the manufacture of the dosage forms should be carefully controlled to reproduce the quality of the product from batch to batch.

Detection Errors

Two most common variables leading to interlaboratory disagreement are the failure to use standards during analysis, and external vibration. Extreme care must be exercised when laboratory methods are introduced into quality control to ensure that no part of the equipment interferes with sensitive determinations. Despite the fundamental relationship between bioavailability and dissolution rate, the present evidence suggests that no single dissolution-rate test can be applied to all drugs.

Compendial Methods

When selecting apparatus for dissolution testing, routine quality control, new drug development, or complying with regulatory requirements, the analyst must follow the latest issue of compendia, including revisions.

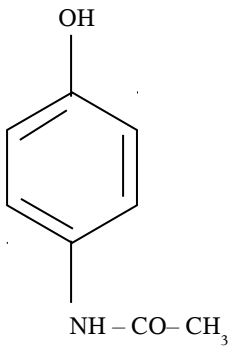
DRUG PROFILE

PARACETAMOL[27,28,28,30]

Category

Analgesic, Antipyretic

Structure



Synonyms

Acetaminophen, N-Acetyl-p-aminophenol

Chemical Name

4-L Hydroxy Acetanilide

Molecular Formula

$C_8H_9NO_2$

Molecular Weight

151.16

Dose

500mg to 1gm every 4-6 hrs. upto 4gm daily in divided dose.

Description

White odorless crystals (or) crystalline powder, tastes bitter.

Therapeutic Concentration

Plasma concentration 10-20µg/ml

Solubility

Freely soluble in ethanol (95%) and in acetone. Sparingly soluble in water, Very slightly soluble in chloroform. Practically insoluble in ether. Soluble in solutions of alkali hydroxides.

Dissociation Constant

pK_a 9.5 (24°)

Melting Point

168˚C to 172˚C

Storage

Store in air tight, light resistant containers.

Standards

Paracetamol contains not less than 99.0% and not more than 101.05% or $C_8H_9NO_2$ calculated with reference to the dried substance.

Identification

The infra red spectrum is concordant with the reference spectrum of paracetamol or with the spectrum obtained from paracetamol.

Adverse Effects

Side effects of paracetamol are usually mild, although hematological reactions have been reported. Skin rashes and other allergic reactions occur occasionally. Symptoms of paracetamol over dosage in the first 24 hours are nausea, vomiting, anorexia and abdominal pain.

Allergy

Fixed drug eruption due to paracetamol is reported.

Precautions

Paracetamol should be given with care to patients with impaired kidney or liver functions. It should also be given with care to the patients taking other drugs that effect liver.

Interaction

Alcohol-paracetamol hepatotoxicity was enhanced by alcohol in patients.

Mechanism of Action

The recent research (2) has shown the presence of a new, previously known cyclooxygenase enzyme COX-3, found in the brain and spinal cord, which is selectively inhibited by paracetamol, and is distinct from the two already known cyclooxygenase enzymes COX-1 and COX-2. It is now believed that this selective inhibition of the enzyme COX-3 in the brain and spinal cord explains the effectiveness of paracetamol in relieving pain and reducing fever without having unwanted gastrointestinal side effects.

Half Life

Adults – 1.5-3 hrs

Clearance

Plasma clearance about 5ml/min/kg

Protein Binding

Above 60µg/ml

Absorption and Fate

Paracetamol is readily absorbed from the gastro intestinal tract with peak plasma concentrations occurring about 30 min to 2 hrs. after ingestion. It is metabolized in the liver and excreted in the urine mainly as the glucoronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol.

Uses

Paracetamol has analgesic and antipyretic actions similar to those of aspirin, but it has no useful anti-inflammatory properties. The adult dose is 0.5gm to 1gm every 4 hrs upto a maximum of 4gm daily.

EXCIPIENTS PROFILE

STARCH[20]

Non Proprietary Names

BP: Maize starch, Potato starch, Rice starch, Tapioca starch, Wheat starch

Synonyms

Amido, amidon, amilo, amylum, Aytex P, Cassava starch.

Chemical Name

Starch

Empirical Formula

$(C_6H_{10}O_5)_n$

Where n = 300 – 1000

Functional Category

Glidant, tablet and capsule diluent, tablet and capsule disintegrant, tablet binder.

Application In Pharmaceutical Formulation (or) Technology

Starch is widely used as an excipient primarily in oral solid dosage formulation where it is utilized as a binder, diluent and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations for volume adjustment of the fill matrix.

In tablet formulation, freshly prepared starch paste is used in concentration of 5-25% w/w in tablet granules as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate and dissolution rate. Starch is one of the most commonly used tablet disintegrant at concentration of 3-5%w/w.

Description

Starch occurs as an odorless and tasteless, fine white-colored powder comprising of very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attached by micro-organisms to form a wide variety of starch derivatives and modified starches which have unique physical properties.

PAPAYA PULP POWDER[21,22,23]

Papaya

The papaya (Carica papaya) is a long bulbous fruit with a point at the broad end. This large fruit has a thin greenish skin, which encloses a yellowish orange to pinkish red colored flesh. The center of the fruit is hollow with nestle black rounded seeds.

General Description

The papaya is a common tropical fruit in India, often grown in family gardens. The papaya tree is unusual in structure as it consists of a very narrow straight trunk with no bark. The product papaya pulp is extracted from full unripe papaya, after blanching peeling, removing seeds and passing through 0.7mm sieve maintaining the essential composition and quality characteristics of natural papaya.

Solubility

Papaya is incompletely soluble in water or glycerol and it is mostly insoluble in most of the organic solvents.

Enzymes Present

Papain and chymo papain are the main enzymes present in papaya.

Applications

The ripe papaya fruit is stomachic, digestive, carminative, galactagogue and diuretic. It is effective in dysentery and chronic diarrhea.

Raw papaya is a good source of pectin that is widely used in fruit industry for preparation of jams, jellies. It is also used in textiles, explosives, lacquers, pharmaceutical, etc.The unripe fruit is laxative, diuretic, posses abortifacient activity.

TALC

Non Proprietary Name

Purified talc, talc

Synonyms

Magsil osmanthus, Magsil star, powdered talc.

Empirical Formula

It is purified hydrated, magnesium silicate.

Approximate formula: $Mg_6(Si_2O_5)_4$

It may contain small amounts of aluminum silicate and iron.

Functional Category

Glidant, tablet and capsule diluent, tablet and capsule lubricant

Applications in Pharmaceutical Formulation (or) Technology

It is widely used in oral solid dosage formulations as a glidant and diluent. It is also used in topical preparations of dusting powder, although it should not be dust in surgical gloves. It is additionally used to clarify liquids and is also used only for its lubricant properties in cosmetics and food products.

Table.5

Description

It is a very fine white to grayish white colored, odorless, crystalline powder. It adheres readily to the skin, soft to touch and free from grit.

Stability and Storage Conditions

Talc is a stable material. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibility

Incompatible with quaternary ammonium compounds.

Safety

Talc is mainly used in tablet and capsule formulations. Following oral ingestion talc is not absorbed systemically and may thus be regarded as an essentially nontoxic material. Talc is an irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. Eye protection, gloves and a respirator are recommended.

MAGNESIUM STEARATE

Non Proprietary Name

BP : Magnesium stearate

USPNF : Magnesium stearate

Synonyms

Magnesium octa decanoate, stearic acid magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt.

Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$

591.27

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation (or) Technology

Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture of concentrations between 0.25 to 5.0%

Description

Magnesium stearate is a fine white precipitate or milled powder of low density, having faint, characteristic odor and taste. The powder is greasy to touch and readily adheres to skin.

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool dry place.

Incompatibility

Incompatible with strong acids, alkali and iron salts. Avoid mixing with strong oxidizing materials.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being non toxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation. Inhalation of magnesium stearate powder is harmful and has resulted in fatalities.

LACTOSE

Nonproprietary Names

BP: Lactose

Synonyms

Lactochem, lactohale, lactopress, microfine, microtose, milk sugar, pharmatose, respitose, tablettose, wyndale.

Chemical Name

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous.

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate.

Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ & 342.30 (anhydrous)

$C_{12}H_{22}O_{11}.H_2O$ & 360.31 (monohydrate)

Functional Category

Diluent for dry-powder inhalers, tablets and capsules.

Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets, capsules and dry-powder inhalations and to a more limited extent in lyophilized products and infant feed formulas.

Various lactose grades commercially available are selected on the basis of dosage form being developed. Lactose is used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

Description

Lactose occurs as white or off-white crystalline particles or powder. Lactose is odorless and slightly sweet tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than the α-form. Several different forms of lactose are commercially available: anhydrous α-lactose, α-lactose monohydrate and to a lesser extent, anhydrous β-lactose.

Stability and Storage Conditions

Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The color stabilities of various lactoses also differ. Saturated solutions of β-lactose may precipitate crystals of α-lactose on

standing. Solutions also show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with amino acids, aminophylline, amphetamines and lisinopril.

Safety

Adverse reactions like abdominal cramps, diarrhea, distension and flatulence to lactose are largely attributed to lactose intolerance, which in persons with a deficiency of the intestinal enzyme lactase. Lower doses of lactose produce fewer adverse effects, and lactose is better tolerated if taken with other foods.

Handling Precautions

Normal precautions appropriate to the circumstances and quantity of material handled should be observed. Excessive generation of dust, or dust inhalation, should be avoided.

LITERATURE SURVEY

1. Marc Gordon S., et al., studied the effect of aging on the dissolution of wet granulated tablets containing super disintegrants. The results indicated that aging decreased the dissolution efficiency of super disintegrants in wet granulated tablets[32].
2. Holgado M.A., et al., studied the influence of diluents and manufacturing method on the *in vitro* dissolution of carteolol hydrochloride matrix tablets. The study shown that the lots containing mannitol presented more rapid release rates due to the high solubility of this filler. On the other hand, the use of PEG- 6000 as diluent significantly decreased drug release[33].
3. Andries F., et al., studied Effect of compression force, humidity and disintegrant concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant[34].
4. Pandit J.K., et al., studied the effect of diluents and disintegrant on the dissolution rate of directly compressed frusemide tablets. It was found that drug released from frusemide tablet is considerably affected by the process of manufacture and the physico-chemical properties of tablet additives[35].
5. Dr. K.P.R.Chowdary., et al., studied the effect of binding agents on the dissolution of phenylbutazone tablets. The result obtained from the dissolution test revealed that gelatin, polyvinyl pyrrolidone and methyl cellulose were found to be good binders for phenylbutazone tablets[36].
6. Mishra D.N., et al., studied the effect of some formulation variables on dissolution and bioavailability of frusemide tablets[37].

7. Dr. Rama Rao N., et al., studied the influence of pregelatinized starch on the dissolution of Acetaminophen from capsule formulations. Marked increase in the dissolution of Acetaminophen was observed with capsules formulated using pregelatinized starch[38].
8. Desai D.S., et al., studied the effect of different types of lactose and disintegrant on dissolution stability of hydrochlorothiazide capsule formulations[39].
9. Veiga M.D., et al., studied the influence of agitation intensity and addition of several substances to the dissolution medium in the dissolution study of spiramycin. It was shown that sodium lauryl sulphate has considerable wetting power even greater than that of tween 20[40].
10. Sallam E., et al., studied the dissolution characteristics of interactive powder mixture for effects of additives on the dissolution of griseofulvin from emcompress carrier. The result was a reduction in the dissolution of griseofulvin from such interactive powder system relative to those excipients, which have smooth paniculate surfaces[42].
11. Devotham Reddy T., et al., used tween 80 as tablet additive for its effect on the dissolution of hydrophobic drugs. Model drugs are phenylbutazone and chlorpropamide. Significant increase in the disintegration time was obtained as the percentage of tween 80 was increased[43].
12. Jinichi Fukami ., et al., Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose[41].
13. Costa P., studied an alternative method to the evaluation of similarity factor in dissolution testing[44].

14. N. Visavarungroj and J. P. Remon studied the Crosslinked starch as a disintegrating agent[45].
15. Sarafadeen A. Adebayo., et al., studied Comparative disintegrant activities of breadfruit starch and official corn starch[46].
16. Desai D.S., Rubitski B.S., et al., studied the physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution[47].
17. Proost J.H., et al., The effect of the swelling capacity of disintegrants on the *in vitro* and *in vivo* availability of diazepam tablets, containing magnesium stearate as a lubricant[48].
18. Lucy S. C. Wan and Kanneganti P. P. Prasad studied the uptake of water by excipients in tablets[49].
19. Tomer G., et al., studied the influence of type and quantity of model drug on the extrusion/spheronization of mixtures with microcrystalline cellulose[50].
20. Butler, W.C.G., Bateman, S.R., studied a flow through dissolution method for a two component drug formulation where the actives have markedly differing solubility properties[51].
21. Chebli C., Cartilier L., Cross linked cellulose as a tablet excipient: A binding/disintegrating agent[52].
22. S.Kuppusamy, T.K Ravi and Prasobh G.R studied the use of papaya pulp powder in the formulation of tablets containing cefadroxil and its *in vitro* evaluation[53].
23. Smitha, T.K. Ravi, Gopal Rao, S. Kuppusamy studied the formulation Of cefadroxil dispersible tablets using papaya pulp powder, its evaluation and stability[54].

24. B. Rajkapoor., B.Jayakar, et al., studied the effect of dried fruits of Carica Papaya Linn on hepatotoxicity[55].
25. Uncoated tablets include single-layer tablets resulting from a single compression of particles[4].
26. Adebowale Adebiyi and Ganesan Adaikan P., studied the effect of crude papaya latex on rat's pregnancy[56].
27. Papaya (Carica papaya), Description, chemistry, toxicity, germplasm, distribution, ecology, cultivation, harvesting, uses, folk medicines, yields and economics, energy, biotic factors[57].
28. Papain used as a protein digestant, for combating dyspepsia and other digestive disorders[58].
29. Papaya, having enzyme papain used in dissolution of proteins, softening and disintegrating qualities in alkaline combination[58]..
30. Hadi A. Garekani., et al., Highly compressible paracetamol-II. Compression properties[59].
31. Abdelbary G., et al., The preparation of orally disintegrating tablets using a hydrophilic waxy binder[60].
32. Naji Najib and Ibrahim Jalal., Correlation between dissolution and disintegration rate constants for acetaminophen tablets[61].
33. Graham, Garry G., et al., Mechanism of Action of Paracetamol[62].
34. Lennartz P and Mielck J.B., Minitabletting: improving the compactability of paracetamol powder mixtures[63].
35. Garr J.S.M and Rubinstein M.H., An investigation into the capping of paracetamol at increasing speeds of compression[64].

OBJECTIVE OF THE WORK

The objective of the present work is:

- To study the effect of disintegrating and binding agents on the dissolution of formulation containing paracetamol
- To establish the use of a natural binding and disintegrating agent papaya pulp powder in formulating oral dosage form. i.e. tablets.
- To find out the suitable method of incorporation of papaya pulp powder as disintegrant
- To find out a suitable concentration of papaya pulp powder as disintegrant in the best method of addition of disintegrant.
- To evaluate the formulated tablets.

The present work was carried out in the following lines

- Preformulation studies were carried out on the purity of the drug and its compatibility between the additives used by the IR spectral analysis.
- Formulation of tablets containing paracetamol using papaya pulp powder as disintegrant, lactose as diluent, starch as binder, magnesium stearate as glidant and talc as lubricant.
- Papaya pulp powder is added in three methods to the drug
  a. Internal method (prior to granulation)
  b. External method (prior to compression)
  c. Internal and external method (half portion prior to granulation and half portion prior to compression)
- In vitro evaluation of the formulated tablets.

MATERIALS AND EQUIPMENTS

MATERIALS USED

Table 6

Materials	Grade	Source
Paracetamol	IP	Vega pharmaceuticals
Papaya pulp powder	IP	Natural source
Lactose	IP	S.D.fine chem Limited
Maize starch	IP	Loba chemi Pvt. Limited
Magnesium stearate	IP	Loba chemi Pvt. Limited
Talc	IP	Himedia laboratories Pvt.Limited

EQUIPMENTS USED

Table 7

Equipment	Model / Company
UV-visible spectrophotometer	Jasco V-530
FT-IR spectrophotometer	Jasco 410
Digital balance	Denver Instruments XP-300
Balance	Dhona 200-D
Hot air oven	Inlab Equipments (Madras) Pvt.Ltd
Disintegration apparatus	Remi Equipments
Dissolution test apparatus	Electrolab
Friabilator	Excel Enterprises, Kolkata
Tablet punching machine	Rimex Mini Press
Sieves	Tayant Scientific Industries, Mumbai
Hardness tester	Pfizer
Tray drier	Cadmach-Bom

PREFORMULATION STUDIES

Before formulation of drug substances into a dosage form, it is essential that it should be chemically and physically characterized. Preformulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

In the present work, preformulation studies on the purity, development of calibration curve of the drug candidate and the compatibility between drug and excipients were carried out.

Development of Calibration Curve for Paracetamol

Spectral Measurement

The standard solution of Paracetamol was scanned at 249nm using UV-visible spectrophotometer.

Standard Graph of Paracetamol

A spectrophotometric method based on the measurement of absorbance at 249nm in phosphate buffer of pH 7.8 was used in the present study for the estimation of Paracetamol

An accurately weighed 10mg of Paracetamol was dissolved in phosphate buffer of pH 7.8 in a 100ml volumetric flask and the solution was made upto the volume with phosphate buffer of pH 7.8 to give 100µg/ml solution. A little quantity of methanol was used to dissolve paracetamol. From the above solution 1, 2, 3, 4 and 5ml was diluted to 10ml

using phosphate buffer pH 7.8 to obtain a series of dilutions containing 10, 20, 30, 40 and 50 µg/ml of solution. These solutions were scanned at 249nm using a Shimadzu 1400 double beam UV-Visible spectrophotometer At this wavelength, the absorbances of all the other solutions are measured using the phosphate buffer of pH 7.8 as blank. The concentration of paracetamol and the corresponding absorbance values are given in Table.8. The absorbance values were plotted against concentrations of paracetamol.The method obeyed Beer-lambert's law in the concentration range of 10-50 µg/ml.

Compatibility Studies

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible interaction between paracetamol and its excipients.

Weighed amount of drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-50ºC). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm^{-1} in IR spectrophotometer.

IR Spectral Analysis

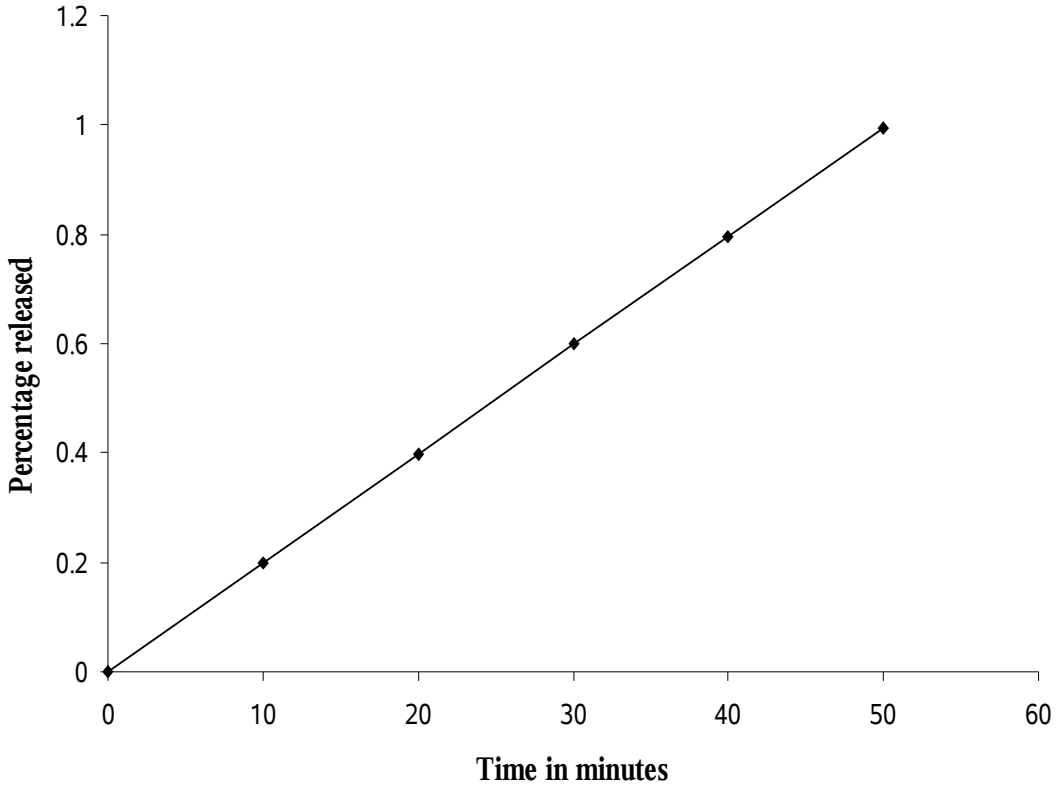
Using FTIR 410 PC spectrometer the compatibility studies between drug and the carrier was carried out.

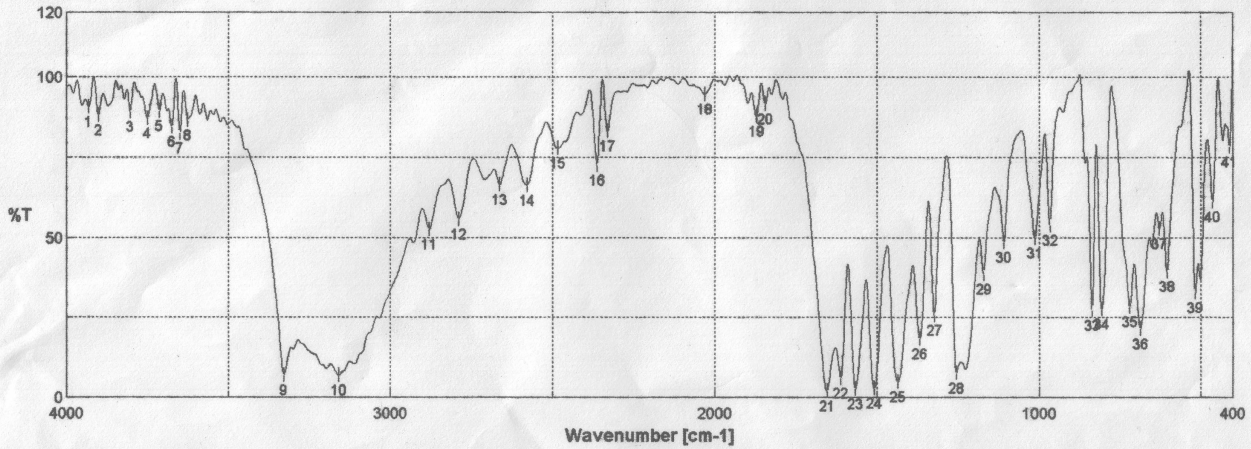
There was no appearance or disappearance of any characteristic peak, which confirms the absence of chemical interaction between drug and carrier.

CALIBRATION CURVE OF PARACETAMOL

Table 8

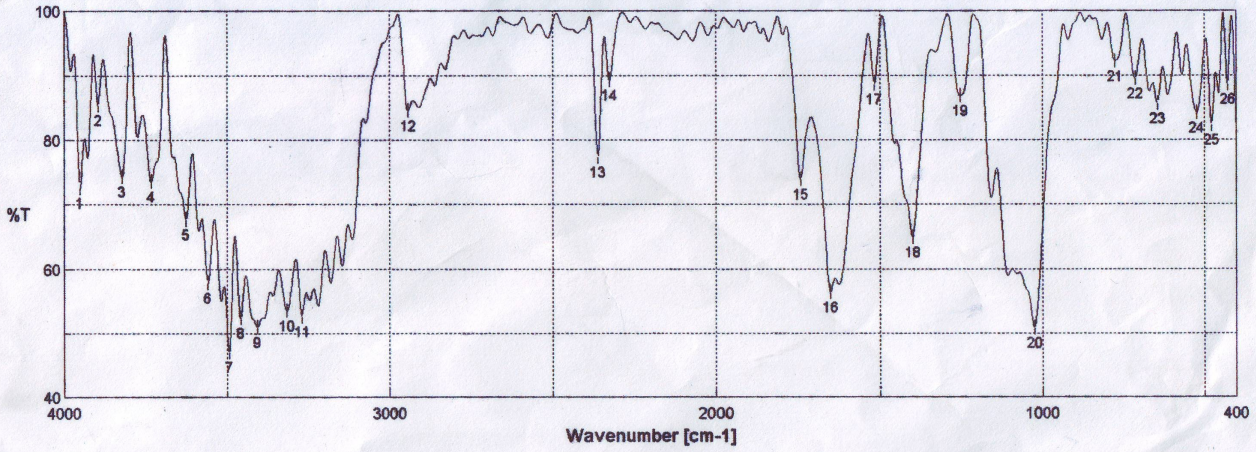
S. No	Concentration (mcg/ml)	Absorbance at 290nm
1	0	0.0000
2	10	0.1986
3	20	0.3988
4	30	0.6014
5	40	0.7958
6	50	0.9043





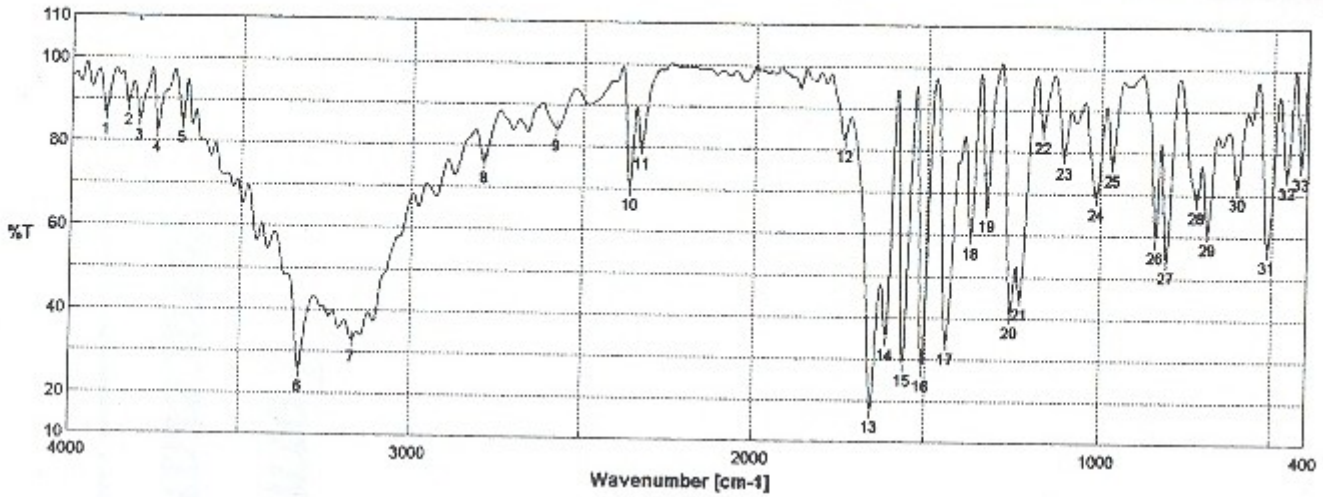
Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	1/22/2008 0:35PM	Update	1/23/2008 2:37PM
Operator	C.Geetha		
File Name	Paracetamol		
Sample Name	Paracetamol		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3931.18	90.769	2	3901.29	88.0304	3	3801.01	89.1392	4	3748.94	87.1191	5	3712.3	89.4809
6	3675.66	84.5276	7	3649.62	82.5039	8	3626.48	86.4383	9	3327.57	7.18229	10	3161.72	7.07408
11	2880.17	52.5942	12	2792.42	55.7722	13	2666.11	66.5639	14	2581.25	66.3563	15	2484.83	77.8173
16	2366.23	72.5856	17	2335.37	83.1144	18	2031.84	94.743	19	1875.43	87.7784	20	1847.47	91.5157
21	1654.62	2.27592	22	1611.23	6.28398	23	1564.95	2.92852	24	1508.06	3.07976	25	1436.71	5.0491
26	1370.18	18.5169	27	1324.86	25.6685	28	1255.43	7.82831	29	1170.58	38.6686	30	1106.94	48.5875
31	1013.41	49.883	32	967.126	53.9589	33	835.99	27.3816	34	804.171	27.7078	35	715.461	28.3709
36	682.677	21.6247	37	624.823	52.7044	38	601.682	39.3763	39	516.829	32.7263	40	463.796	61.1956
41	410.763	78.2462												



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	1/22/2008 0:44PM	Update	1/23/2008 2:25PM
Operator	C.Geetha		
File Name	Papaya		
Sample Name	Papaya		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3950.46	72.5864	2	3894.54	85.5122	3	3821.26	74.3339	4	3733.51	73.5535	5	3626.48	67.7559
6	3558.99	57.8314	7	3494.38	47.0806	8	3458.71	52.3974	9	3407.6	51.021	10	3317.93	53.5075
11	3273.57	52.6955	12	2942.84	84.5909	13	2367.19	77.3522	14	2332.48	89.3231	15	1743.33	73.92
16	1648.84	56.4667	17	1515.77	88.7058	18	1400.07	64.9698	19	1249.65	86.876	20	1024.02	50.9185
21	770.423	92.26	22	710.64	89.573	23	644.108	85.7397	24	523.579	84.2646	25	477.296	82.3884
26	427.155	88.7135												



Accumulation	16
Zero Filing	ON
Gain	8
Date/Time	1/22/2008 1:06PM
Operator	C.Geetha
File Name	paracetamol+ papaya
Sample Name	paracetamol+ papaya
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	1/23/2008 2:35PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3901.29	86.4526	2	3834.76	88.8301	3	3800.04	85.1973	4	3747.98	82.4425	5	3678.62	84.8392
6	3325.64	25.5945	7	3175.22	32.6947	8	2793.38	76.1202	9	2582.22	84.1602	10	2366.23	70.1974
11	2333.44	80.1295	12	1743.33	82.3951	13	1655.58	17.821	14	1613.16	34.9588	15	1563.99	26.9152
16	1509.03	27.5725	17	1439.6	33.9572	18	1370.18	59.4897	19	1323.89	66.1458	20	1255.43	40.4354
21	1227.47	44.8588	22	1187.69	84.9831	23	1105.96	78.9087	24	1013.41	69.1037	25	966.162	77.1907
26	836.955	58.9255	27	804.171	54.0961	28	719.354	68.5533	29	684.806	61.1012	30	601.682	71.9082
31	513.036	58.9333	32	459.939	74.6859	33	419.442	78.9532						

FORMULATION OF PARACETAMOL TABLETS

Manufacturing of Paracetamol Tablets

The characteristics of a tablet that makes it a popular oral dosage form, e.g. compactness, physical stability, rapid production capability, chemical stability and efficacy are dictated primarily by the qualities of the granules from which it is made. The ideal physical form for compaction into a tablet is a sphere. Therefore granulation is done to convert powdered materials into regularly shaped aggregates called granules.

Preparation of tablet involved the following steps:

a. Mixing
b. Granulation
c. Compression

Preparation of Granules by Wet Granulation Method

The first step i.e. mixing was done by geometric dilution method. Before mixing, all the powders were passed through a sieve. In the method of internal addition of disintegrant, required amount of drug (Paracetamol) lactose, papaya pulp powder as disintegrant, each in the concentration of 2%, 4%, 6%, 8% and 10% were added individually and triturated for 20 minutes in a mixer.

The binding solution which was prepared by dispersing starch in hot demineralized water was then added to the above sieved and mixed mixtures slowly with constant stirring until a coherent mass was obtained. The above wet granules were subjected to semi drying for 15 minutes at 45-50˚C. Then

immediately the wet mass sieved to prepare wet granules through sieve no 12. Dried the granules at 45-50˚C till the loss on drying is 3-3.5%. The dried granules were passed through the sieve no.14. The above mixture was lubricated with talc and magnesium for 30 minutes.

Method

Fifteen formulations ($F_1 – F_{15}$) were formulated using natural disintegrant Papaya pulp powder in various concentrations of 2%, 4%, 6%, 8% and 10%

In formulations ($F_1 – F_5$) papaya pulp powder was added as internal disintegrant. In those formulations the disintegrant was mixed in different concentrations 2%, 4%, 6%, 8% and 10% respectively with the required amount of drug and the diluent lactose prior to granulation. To the prepared granules, magnesium stearate and talc were added as glidant and lubricant respectively. All these were mixed uniformly.

In formulations ($F_6 – F_{10}$) papaya pulp powder was added both as internal and external disintegrant. In those formulations the disintegrant was mixed in different concentrations 2%, 4%, 6%, 8% and 10% respectively half prior to granulation of the drug and lactose, and half prior to compression of the granules. To the prepared granules, magnesium stearate and talc are added as glidant and lubricant respectively. All these were mixed uniformly.

In formulations (F11 – F15) papaya pulp powder was added as external disintegrant. In those formulations the

disintegrant was mixed in different concentrations 2%, 4%, 6%, 8% and 10% respectively to the granules prior to compression. To the prepared granules, magnesium stearate and talc were added as glidant and lubricant respectively. All these were mixed uniformly.

The practical weight loss of the tablets was calculated and the tablets were punched keeping the hardness of the tablets between 3-5 kg/sq.cm. The tablets were then evaluated.

Tablet formulations containing paracetamol with papaya pulp powder as internal disintegrant in different concentrations

Table 9

Sl.No	Ingredients	Product code				
		F_1(mg)	F_2(mg)	F_3(mg)	F_4(mg)	F_5(mg)
1	Paracetamol	250	250	250	250	250
2	Lactose	190	180	170	160	150
3	Papaya pulp powder	2%	4%	6%	8%	10%
4	Starch	q.s	q.s	q.s	q.s	q.s
5	Magnesium stearate	25	25	25	25	25
6	Talc	25	25	25	25	25
	Average weight of tablet	500	500	500	500	500

Tablet formulations containing paracetamol with papaya pulp powder as both internal and external disintegrant in different concentrations

Table 10

Sl.No	Ingredients	Product code				
		F_6(mg)	F_7(mg)	F_8(mg)	F_9(mg)	F_{10}(mg)
1	Paracetamol	250	250	250	250	250
2	Lactose	190	180	170	160	150
3	Papaya pulp powder	2%	4%	6%	8%	10%
4	Starch	q.s	q.s	q.s	q.s	q.s
5	Magnesium stearate	25	25	25	25	25
6	Talc	25	25	25	25	25
	Average weight of tablet	500	500	500	500	500

Tablet formulations containing paracetamol with papaya pulp powder as external disintegrant in different concentrations

Table 11

Sl.No	Ingredients	Product code				
		F_{11}(mg)	F_{12}(mg)	F_{13}(mg)	F_{14}(mg)	F_{15}(mg)
1	Paracetamol	250	250	250	250	250
2	Lactose	190	180	170	160	150
3	Papaya pulp powder	2%	4%	6%	8%	10%
4	Starch	q.s	q.s	q.s	q.s	q.s
5	Magnesium stearate	25	25	25	25	25
6	Talc	25	25	25	25	25
	Average weight of tablet	500	500	500	500	500

EVALUATION OF TABLETS

All the formulated dosage forms of paracetamol tablets have been subjected to the following quality control tests[7, 3]:

1. Weight Variation
2. Hardness
3. Friability
4. Uniformity of Dispersion
5. Disintegration
6. Dissolution

Weight Variation:

The USP weight variation test is performed by taking 20 tablets from a batch. Then 20 tablet, are weighed and the average weight is taken. Then each tablet is weighed individually. The percentage deviation can be determined by using the following formula.

$$Deviation = \frac{Average\ \ weight - Individual\ \ weight}{Average\ \ weight} X\ 100$$

All the batches of the formulated tablets passed the weight variation test according to IP, BP and USP.

Hardness Test

Pfizer hardness tester was used for measuring the hardness of the formulated paracetamol tablets. From each batch five tablets were taken at random and subjected to test. The mean of these five tablets are given in the table.12

Friability

It is a measure of tablet strength. The friability is determined by using Roche Friabilator. 10 tablets were taken and their weight determined. Then they were placed in the friabilator and allowed to make 100 revolutions at 25rpm. The tablets were then dusted and reweighed. The percentage weight loss was calculated by using the following formula.

$$F = 100\,X(1 - w/w_o)$$

Where, w_o = Weight of tablets before friability

w = Weight of tablets after friability

All the batches of the formulated paracetamol tablets were found to be within the official specified limits.

Uniformity of Dispersion

Place two tablets in 100ml water. Stir gently until completely dispersed. A smooth dispersion is obtained which passes through sieve screen 710µm (sieve no 22).

Disintegration

The USP apparatus to test disintegration consists of 6 glass tubes that are open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. One tablet is placed in each tube, and basket rack is positioned in a 1L beaker of water or simulated gastric fluid at 37ºC ± 2ºC. A standard motor driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles/min. Perforated plastic disc may also be used in the test. The results were given in the table.12.

Dissolution

The breakdown of tablet into granules and formation of clear solution is dissolution.

Apparatus II

Dissolution was carried out using USP dissolution apparatus 2 (Rotating paddle apparatus). Dissolution of tablets was carried out in 900ml-dissolution medium.The dissolution medium for paracetamol tablet was pH 7.8. The temperature of dissolution medium was maintained at 37ºC ± 2ºC. The agitation intensity was 50rpm. The sampling time specified was modified instead of withdrawing a single sample at 5-min interval serial sampling was done at 0, 5, 10, 15, 20, 25 and 30 min for uncoated tablets. Equal volume of fresh medium having same temperature was replaced at each time. The samples were suitably diluted and the amount of active ingredient was determined spectrophotometrically with respect to the reported methods.

Tolerances

Not less than 80% (Q) of the labeled amount of $C_8H_9NO_2$ paracetamol is dissolved in 30 minutes.

RESULTS OF EVALUATION PARAMETERS

Table 12

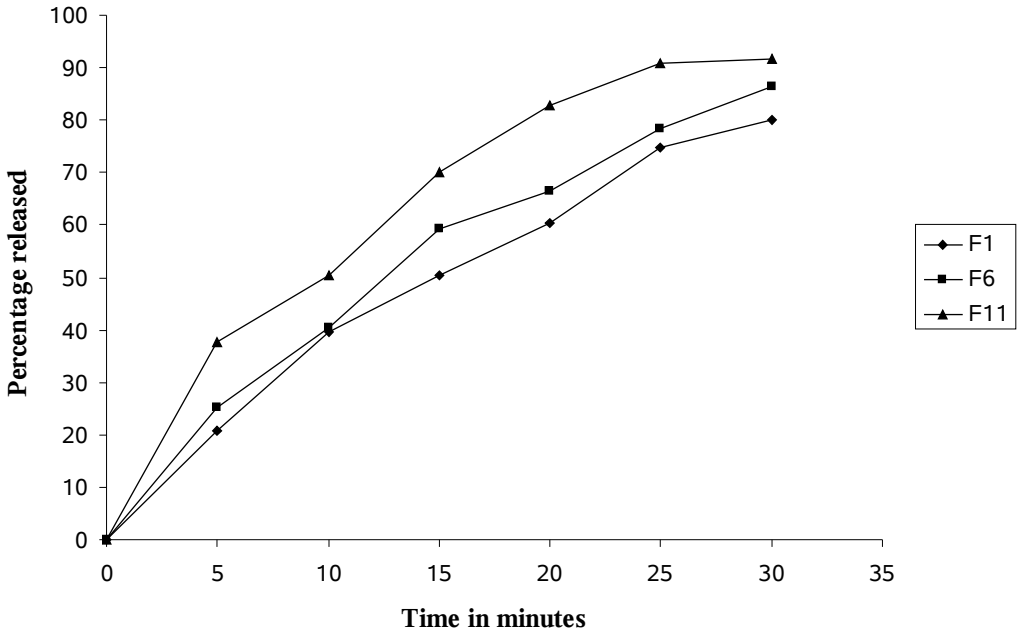
Sl.No	Product code	Disintegration time (min)	Average weight (mg)	Uniformity weight (mg)	Hardness (Kg/cm^2)	Friability (%)
1	F1	8.00	498.5	498 to 500	4.9	0.95
2	F2	7.30	499.5	497 to 502	4.5	0.82
3	F3	7.15	500.0	498.5 to 502	4.5	0.84
4	F4	6.40	501.0	498 to 503.5	4.0	0.91
5	F5	6.00	500.5	499 to 502	4.7	0.86
6	F6	5.00	500.0	497.5 to 502	4.1	0.85
7	F7	4.40	501.5	498 to 501	3.9	0.84
8	F8	4.30	499.0	497 to 500	4.5	0.92
9	F9	4.30	500.0	497 to 502.5	3.7	0.90
10	F10	4.15	502.5	499.5 to 503.5	4.9	0.94
11	F11	3.00	498.5	497 to 501	4.0	0.82
12	F12	3.00	502.0	498 to 504	4.1	0.88
13	F13	3.00	501.0	497.5 to 502.5	3.5	0.92
14	F14	2.45	499.0	498 to 502	4.5	0.85
15	F15	2.10	500.0	498 to 502.5	3.9	0.90

DISSOLUTION RATE OF PARACETAMOL

Dissolution rate of paracetamol with papaya pulp powder in 2% concentration

Table 13

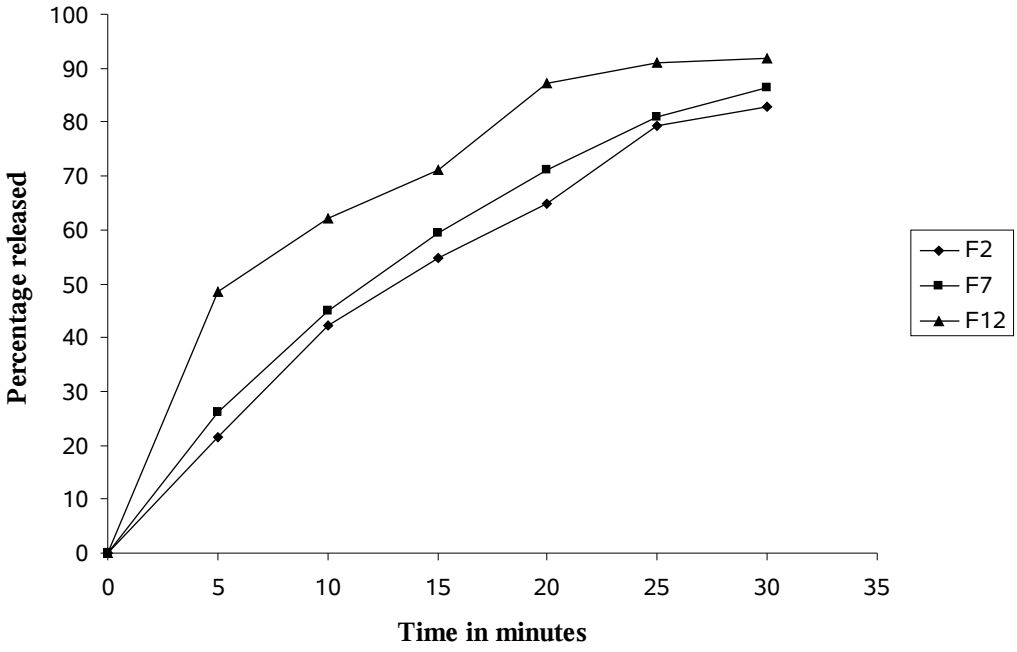
Sl.No	Time (min)	Percentage released		
		F_1 (internal)	F_6(internal & external)	F_{11}(external)
1	5	20.7	25.2	37.8
2	10	39.6	40.5	50.4
3	15	50.4	59.4	70.2
4	20	60.3	66.6	82.8
5	25	74.7	78.3	90.9
6	30	80.1	86.4	91.8



Dissolution rate of paracetamol with papaya pulp powder in 4% concentration

Table 14

Sl.No	Time (min)	Percentage released		
		F_2 (internal)	F_7(internal & external)	F_{12}(external)
1	5	21.6	26.1	48.6
2	10	42.3	45	62.1
3	15	54.9	59.4	71.1
4	20	64.8	71.1	87.3
5	25	79.2	81	90.9
6	30	82.8	86.4	91.8

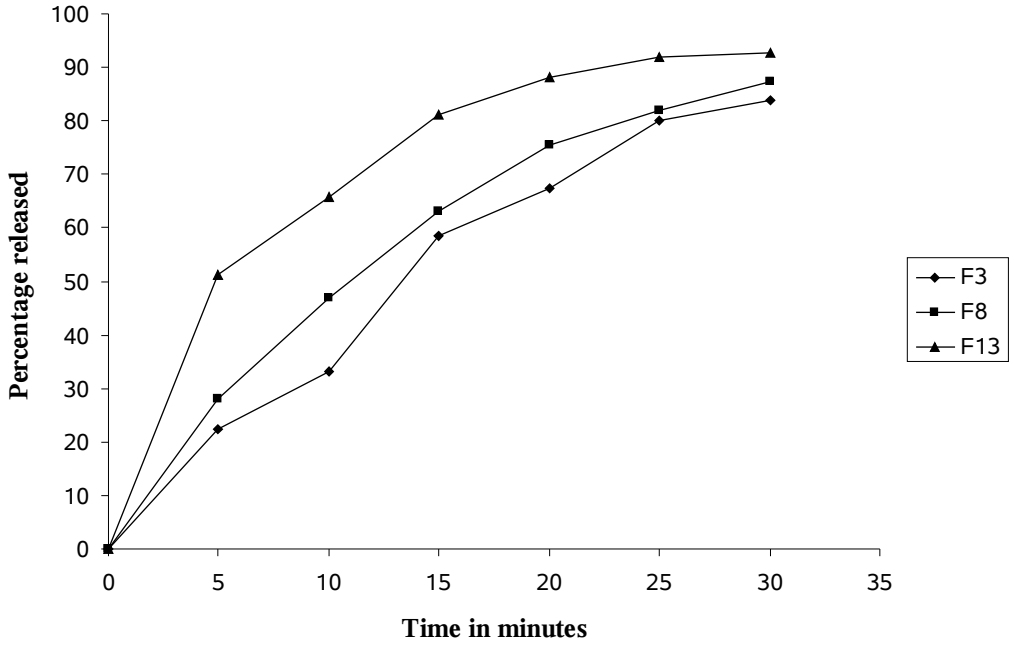


Dissolution rate of paracetamol with papaya pulp powder in 6%

concentration

Table 15

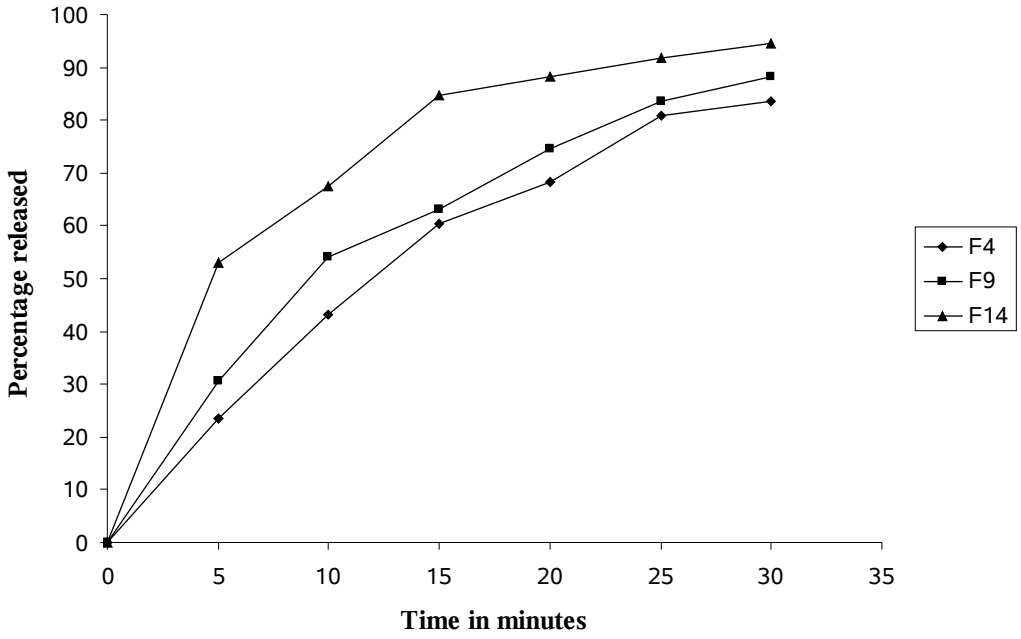
Sl.No	Time (min)	Percentage released		
		F_3 (internal)	F_8(internal & external)	F_{13}(external)
1	5	22.5	27.9	51.3
2	10	33.2	46.8	65.7
3	15	58.5	63	81
4	20	67.5	75.6	88.2
5	25	80.1	81.9	91.8
6	30	83.7	87.3	92.7



Dissolution rate of paracetamol with papaya pulp powder in 8% concentration

Table 16

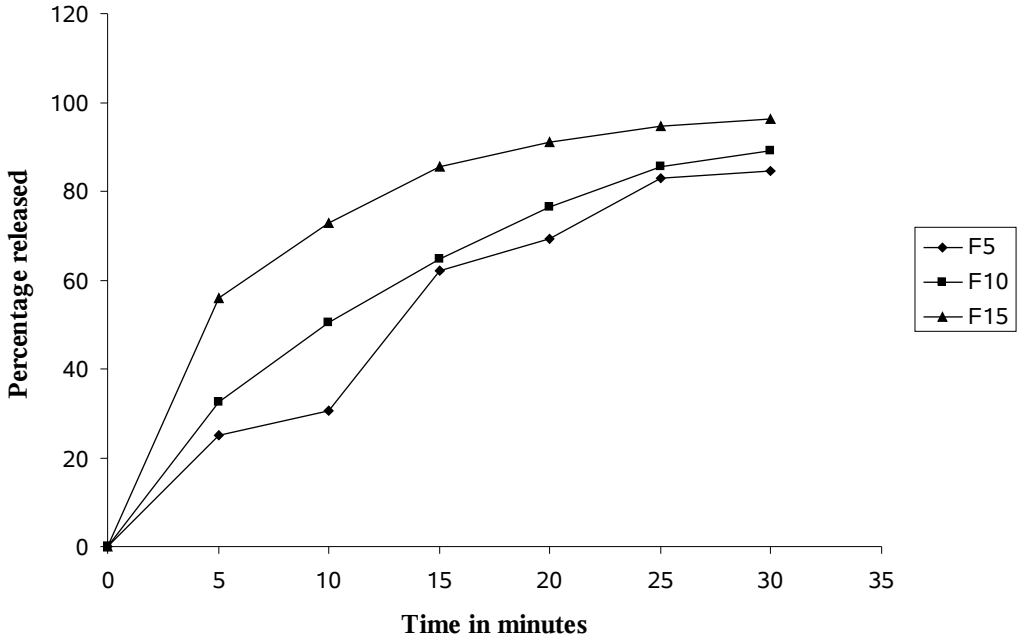
Sl.No	Time (min)	Percentage released		
		F_4 (internal)	F_9(internal & external)	F_{14}(external)
1	5	23.4	30.6	53.1
2	10	33.2	54	67.5
3	15	60.3	63	84.6
4	20	68.4	74.7	88.2
5	25	81	83.7	91.8
6	30	83.7	88.2	94.5



Dissolution rate of paracetamol with papaya pulp powder in 10% concentration

Table 17

Sl.No	Time (min)	Percentage released		
		F_5 (internal)	F_{10}(internal & external)	F_{15}(external)
1	5	25.2	32.4	55.8
2	10	30.6	50.4	72.9
3	15	62.1	64.8	85.5
4	20	69.3	76.5	90.9
5	25	82.8	85.5	94.5
6	30	84.6	89.1	96.3



RESULTS AND DISCUSSION

An attempt was made to identify the best method of addition of the natural disintegrating agent papaya pulp powder in the formulation of paracetamol tablets. To find the best method of addition, three methods of addition of disintegrating agents were used and fifteen formulations were prepared. All the formulations were subjected to *in vitro* evaluation and the results were compared.

Fifteen different formulations F_1 to F_{15} were prepared using papaya pulp as internal, external and both as internal and external disintegrant each in the concentration of 2%, 4%, 6%, 8% and 10%

Observing the evaluation results for disintegration it was found that F_{15} containing papaya pulp powder as the external disintegrant in the concentration of 10% disintegrated faster than the others. It was then followed by F_{14} and then F_{13}

The results obtained for the other parameters like weight variation, hardness and friability were within the specific limit for tablet formulation.

From the results obtained from dissolution studies it was seen that formulations (F_{14} and F_{15}) containing papaya pulp powder as external disintegrant (concentration 8% and 10%) exhibited better dissolution characteristics when compared to other formulations.

Out of the fifteen formulations F_{15} containing papaya pulp powder as the external disintegrant in the concentration 10% was found to be the best formulation since it showed good dissolution and disintegration characteristics.

Nevertheless formulation F_{14} containing papaya pulp powder as external disintegrant showed good disintegration and dissolution characteristics which were found to be within the limits specified in the pharmacopoeia.

Formulations $F_{11,}$ $F_{12,}$ F_{13} and F_{14} containing papaya pulp powder as the external disintegrant also exhibited good disintegration and dissolution characteristics.

All the formulations were prepared by wet granulation method and all of them showed good flow properties and compression characteristics.

SUMMARY AND CONCLUSION

An attempt was made to study the use and the best method of incorporation of papaya pulp powder as a disintegrant in the formulation of paracetamol tablets. In order to find out the percentage and the best method of incorporation of the papaya pulp powder that could be used to formulate a product containing good disintegration and dissolution characteristics, different concentrations of the papaya pulp powder was used. Fifteen formulations were prepared with a natural disintegrant papaya pulp powder in the concentration of 2%, 4%, 6%, 8% and 10%. The papaya pulp powder is incorporated in the formulation by three methods. i.e. internal method, both internal and external method and external method. The tablets were evaluated and results were compared with each other. Among the formulated tablets it was found that F_{15} containing papaya pulp powder as external disintegrant showed good dissolution and disintegration characteristics.

Although the disintegration and dissolution characteristics of the formulation containing papaya pulp powder as internal disintegrant were lower than the other formulation, they were within the limits specified in the pharmacopoeia. The results indicated that external method of incorporation of papaya pulp powder results in faster dissolution than internal and external method of incorporation which is in turn superior to internal method of incorporation. Its characteristics can further be improved by varying the concentration of papaya pulp powder

REFERENCES

1. The Theory and Practice of Industrial Pharmacy – 3rd Edition by Leon Lachman, Hebert A. Lieberman, Joseph L. Kanig, Pg. 293-333.

2. Pharmacy Review, Leon Shargel, Pg. 48-52.

3. Indian Pharmacopoeia; Govt. of India, Ministry of Health and Family Welfare; Controller of Publication (Delhi) (1996) Vol. II, Pg. 554-556.

4. British Pharmacopoeia (1993), Vol I, Pg. 483-484.

5. European Pharmacopoeia – 5th Edition, Vol. II, Pg. 2184

6. Modern pharmaceutics – 3rd Edition by Gilbert S. Banker and Christopher T. Rhodes (1996), Marcel Deckker Inc, New York, Pg. 830-834

7. Remington : Pharmaceutical Sciences, 18th Edition, Vol. II, Mack Publishing Company, Easton, Pennsylvania (1990), Pg. 1038,1109-1110

8. Remington : The Science and Practice of Pharmacy - 20th Edition, Vol. I, Pg. 860-870

9. Remington: The Science and Practice of Pharmacy - 21st Edition, vol. I, Pg. 672-687, 889-918.

10. Encyclopedia of Pharmaceutical Technology, James Swarbrick, James C. Boylan, Vol. IV, Pg. 37-80.

11. Encyclopedia of Pharmaceutical Technology, James Swarbrick, James C. Boylan, Vol. XIV, Pg. 392.

12. Encyclopedia of Pharmaceutical Technology, James Swarbrick, James C. Boylan, Vol.I, Pg. 451-464.

13. Pharmaceutical Dosage Forms; Tablets - 2nd Edition, edited by Herbert A. Lieberman, Leon Lachman and Joseph B. Schwartz, Vol. II, Pg. 245-339.

14. Physical Pharmacy – 4th Edition by Alfred Martin, Pg. 430-448.

15. Modern pharmaceutics – 3rd Edition by Gilbert S. Banker and Christopher T. Rhodes (1996), Marcel Deckker Inc, New York, Pg. 333-364.

16. Indian Pharmacopoeia; Govt. of India, Ministry of Health and Family Welfare; Controller of Publication (Delhi) (1985), Vol. I, Pg. 359-360

17. British Pharmacopoeia (2003), Vol. III, Pg. 2544-2546.

18. Pharmaceutics-The Science of Dosage Form Design, edited by M.E. Aulton, Pg. 304-320.

19. Pharmaceutical Dosage Forms; Tablets - 2nd Edition, edited by Herbert A. Lieberman, Leon Lachman and Joseph B. Schwartz, Vol. I, Pg. 148-179.

20. Handbook of Pharmaceutical Excipients – 4th Edition edited by Raymond C Rowe, Paul J Sheskey and Paul J Weller, Pg. 323-331, 354-356, 603-608, 641-642.

21. Textbook of Practical Pharmacognosy by Rasheeduz Zafar, Neerja Gandhi. Pg.88.

22. AHFS drug information 2004, American Society of Health- System Pharmacists, Pg. 2083 -2091.

23. Pharmacognosy – 15th Edition by Trease & Evans, Pg. 472-535.

24. Pharmaceutical Dosage Forms and Drug Delivery Systems – 6th Edition by H.C. Ansel, N.G. Popovich, L.V.Allen Jr, Pg. 183-204.

25. Bentley's Textbook of Pharmaceutics – 8th Edition edited by E.A.Rawlins (1984), Pg. 269-310.

26. Bio Pharmaceutics and Pharmacokinetics –A Treatise – 1st Edition by D.M. Brahmankar and Sunil B. Jaiswal (1995), Pg. 20-45.

27. Clarke's Isolation and Identification of Drugs - 2nd Edition, The Pharmaceutical Press, London (1986). Pg. 849-850

28. Essentials of Medical Pharmacology – 5th Edition by Tripathi KD. Pg. 81-182.

29. Martindale's Extra Pharmacopoeia – 28th Edition edited by J E F Reynolds, The Pharmaceutical Press, London, Pg. 54, 268-271, 503-505, 653-654, 1442.

30. Physician's Desk Reference: Product Information; Bristol-Myers Squibb, Pg. 2009.

31. Indian Pharmaceutical Guide 1997, Pg. 1411.

32. Marc Gordon S., et al., International Journal of Pharmaceutics, Volume 97, Issues 1-3, August 1993, Pg. 119-131.

33. Holgado M.A., et al., International Journal of Pharmaceutics, Volume 118, Issue 2, May 1995, Pg. 151-160.

34. Andries F., et al., Tropical Journal of Pharmaceutical Research, Vol. 2, No.1, June, 2003. Pg. 125-135.

35. Pandit J.K., et al., Indian Drugs (1997) 34(5); May: Pg. 296-300.

36. Dr. K. P. R.Chowdary., et al., The Eastern Pharmacist (1989), April: Pg. 121-123.

37. Mishra D.N., et al., The Eastern Pharmacist (1994) Sep: Pg.121-123.

38. Dr. Rama Rao N., et al., The Eastern Pharmacist (1999) Aug: Pg. 127-129.

39. Desai D.S., et al., International Journal of Pharmaceutics, Volume 110, Issue 3, September 1994, Pg. 257-265.

40. Veiga M.D., et al., International Journal of Pharmaceutics, Volume 110, Issue 3, September 1994, Pg. 223-229.

41. Jinichi Fukami., et al., International Journal of Pharmaceutics, Volume 310, Issues 1-2, March 2006, Pg. 101-109.

42. Sallam E., et al., International Journal of Pharmaceutics, Volume 67, Issue 3, January 1991, Pg. 247-257.

43. Devotham Reddy T., et al., The Eastern Pharmacist (1990) April: Pg. 137-139.

44. Costa P., International Journal of Pharmaceutics, Volume 220, Issues 1-2, June 2001, Pg. 77-83.

45. N. Visavarungroj & J. P. Remon., International Journal of Pharmaceutics, Volume 62, Issues 2-3, July 1990, Pg. 125-131.

46. Sarafadeen A. Adebayo., et al., Powder Technology, In Press, Corrected Proof, Available online December 2006.

47. Desai D.S., et al., International Journal of Pharmaceutics, Volume 91, Issues 2-3, April 1993, Pg. 217-226.

48. Proost J.H., et al., International Journal of Pharmaceutics, Volume 13, Issue 3, February 1983, Pg. 287-296.

49. Lucy S. C. Wan and Kanneganti P. P. Prasad., International Journal of Pharmaceutics, Volume 50, Issue 2, March 1989, Pg. 147-153.

50. Tomer G., et al., International Journal of Pharmaceutics, Volume 217, Issues 1-2, April 2001, Pg. 237-248.

51. Butler, W.C.G., Bateman, S.R., International Journal of Pharmaceutics, Volume 173, Issues 1-2, October 1998, Pg. 211-219.

52. Chebli C., Cartilier L., International Journal of Pharmaceutics, Volume 171, Issue 1, August 1998, Pg. 101-110.

53. Papaya Pulp Powder in Cefadroxil Tablet Formulation by S.Kuppusamy, T.K. Ravi & Prosobh G.R. Pg.1-4 (www. Pharma.info.net)

54. Papaya Pulp Powder in Cefadroxil Dispersible Tablet Formulation by Smitha, T.K. Ravi, Gopal Rao, S. Kuppusamy Pg.1-4 (www. Pharma.info.net)

55. B. Rajkapoor., et al., Biol Pharm Bull. 2002, Dec; 25(12), Pg.1645-1646.

56. Novel Compounds From Natural Products in The New Millennium by Benny K. H. Tan, Boon-Huat Bay, Yi-Zhun Zhu. Pg. 123-127.

57. James A. Duke. 1983. Handbook of Energy Crops. unpublished: (From Purdue online)

58. King's American Dispensatory, 1898 by Harvey Wickes Felter, M.D., and John Uri Lloyd, Phr. M., Pg. 2.

59. Hadi A. Garekani., et al., International Journal of Pharmaceutics, Volume 208, Issues 1-2, November 2000, Pg. 101-110.

60. Abdelbary G., et al., International Journal of Pharmaceutics, Volume 278, Issue 2, July 2004, Pg. 423-433.

61. Naji Najib and Ibrahim Jalal., International Journal of Pharmaceutics, Volume 44, Issues 1-3, June 1988, Pg. 43-47.

62. Graham, Garry G., et al. American Journal of Therapeutics. 12(1), January/February 2005, Pg. 46-55.

63. Lennartz P. and Mielck J.B., International Journal of Pharmaceutics, Volume 173, Issues 1-2, October 1998, Pg. 75-85.

64. Garr J.S.M and Rubinstein M.H., International Journal of Pharmaceutics, Volume 72, Issue 2, May 1991, Pg. 117-122.

65. www. Pharmainfo.net