FORMULATION DEVELOPMENT AND EVALUATION OF VALSARTAN FILM COATED TABLETS

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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CERTIFICATE

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TO WHOMSOEVER IT MAY CONCERN

This is to certify that Mr.Jaya Prakash.M, M.Pharm student of C.L. Baid Metha College of Pharmacy, Chennai – 600 097, has undergone project work in "Formulation Development and Evaluation of Valsartan Film Coated Tablets " at our factory from 01st July 2012 to 23rd February 2013.

We wish him all success in his future endeavors.

For Tablets (India) Limited

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DECLARATION

I do hereby declare that the thesis entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF VALSARTAN FILM COATED TABLETS"** by **Reg.No:26111006** submitted in partial fulfilment for the degree of **Master of Pharmacy in Pharmaceutics** was carried out at C. L. Baid Metha college of Pharmacy, Chennai-97 under the guidance and supervision of **Dr. U.UBAIDULLA M. Pharm., Ph.D.,** and industrial guide **Mr. VASUDEVAN** and co-guide **Mr. BABU (TABLETS INDIA PVT LTD)** during the academic year 2012-2013. The work embodied in this thesis is original, and is not submitted in part or full for any other degree of this or any other University.

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ABBREVIATIONS

API	Active pharmaceutical Ingredient
HCL	Hydrochloric Acid
HPLC	High performance liquid chromatography
HPMC	Hydroxyl propyl methyl cellulose
FTIR	Fourier transformer infrared spectroscopy
IR	Infrared spectroscopy
MCC	Micro crystalline cellulose
UV	Ultraviolet
PVP	Polyvinyl pyrrolidine
RH	Relative Humidity
USP	United States Pharmacopoeia
IP	Indian Pharmacopoeia
CI	Compressibility Index
HR	Hausner Ratio
WHO	World Health Organisation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm^2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
ng-hr/ml	Nanogram-hour/millilitre
Nm	Nanometer
SD	Standard Deviation
Sec	Seconds

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INTRODUCTION [1]

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug .The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world.

ORAL DRUG DELIVERY [2,3]

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process

Oral drug delivery is the most desirable and preferred method of administering and pharmacodynamics profiles with an acceptable level of safety to the patient.therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient compliance and convenience in administration. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient

compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is the difficulty to swallow

Current technologies in oral drug delivery

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced DDS are manufactured or fabricated in traditional pharmaceutical formulations, such as Tablets, Capsules, Sachets, Suspensions, Emulsions, and Solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities. Based on the desired therapeutic objectives, oral DDS may be assorted into three categories:

- Immediate-release preparations,
- Controlled-release preparations and
- Targeted- release preparations.

Immediate-Release Preparations [4]

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastricabsorption, Convenience in drug administration to dysphasic patients, especially the elderly and bedridden.Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, crosscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

Super disintegrants in immediate release [5]:

These are especially important for an immediate release product where rapid release of dug substance is required. A disintegrant can be added to powder blend for direct compression.

Table-1 list of Super Disintegrants

Super disintegrants	Example	Mechanism of action	Special comment
Crosscarmellose	Crosslinked Cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation
Crospovidone	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Pre Gelatinized Starch	Starch 1500	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix

Mechanism of tablet disintegration [5]:

Disintegrants , an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of disintegration of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The tablet breaks to primary particles by one or more of the mechanisms:

- Capillary action (wicking)
- Swelling

- Due to deformation
- Due to release of gases

Capillary action (Wicking):

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides way for the penetration of fluid into tablets. The disintegrant particles (with cohesiveness and compressibility) themselves act to enhance porosity and provide these capillaries into the tablet. Liquid is drawn up or leak into these ways by capillary action and rupture the inter-particulate bonds causing the tablet to break into small particles

Swelling:

Not all disintegrants swell in contact with water swelling is believed to be a mechanism in which; certain disintegrating agents (like starch) impart their disintegrating effect. By swelling on contact with water the adhesiveness of other ingredients in a tablet is overcome causing the tablet to disintegrate.

Deformation:

Starch grains are generally thought to be “elastic” in nature that is the grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression force involved in tableting, these grains are permanently deformed and are said to be “Energy Rich” with these energy being released upon exposure to water, i.e. the ability for starch to swell is higher in “Energy Rich starch” grains than in starch grains that have not been deformed under pressure. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms

Release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when we needs to formulate very rapidly dissolving tablets or fast disintegrating tablet.

Controlled-Release Preparations (CR)

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

Targeted-Release Preparations

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within the gastro Intestinal (GI) tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively

easier than in the stomach and the small and large intestines. The latter requires consideration of both longitudinal and transverse aspects of GI constraints.

TABLETS [2, 3, 6]

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer.

Advantages of the Tablet dosage form are:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Delayed release product is possible by enteric coating.
7. Objectionable odour and bitter taste can be masked by coating technique.
8. Suitable for large scale production.
9. Greatest chemical and microbial stability over all oral dosage form.

10. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Tablet dosage form are:

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

General properties of Tablet dosage forms:

1. A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes over time.
4. The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
5. Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

Different types of Tablets:

(A) Tablets ingested orally:

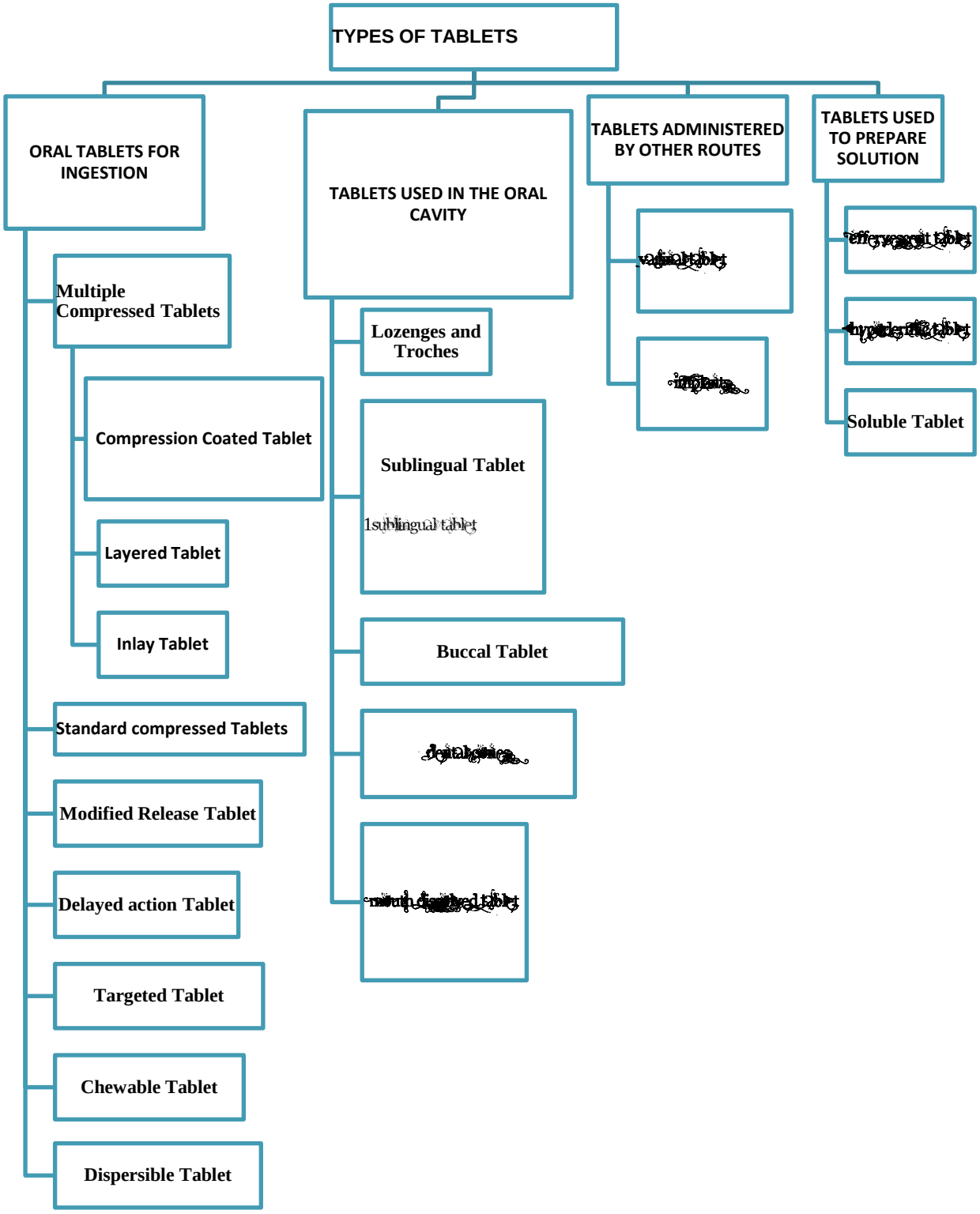
1. Compressed tablet, e.g. Paracetamol tablet
2. Multiple compressed tablet
3. Repeat action tablet

4. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet
5. Sugar coated tablet, e.g. Multivitamin tablet
6. Film coated tablet, e.g. Metronidazole tablet
7. Chewable tablet, eg: antacid tablet

(B) Tablets used in oral cavity:

1. Buccal tablet,
2. Sublingual tablet,
3. Troches or lozenges
4. Dental cone

Fig:1, Flow chart for types of tablets:



A.TABLETS INGESTED ORALLY

1. Compressed tablets

These tablets are uncoated and made by compression of granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets contain water-soluble drugs, which after swallowing get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body e.g. Paracetamol tablet

2. Multiple compressed tablets:

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action prolonged action products.

For incompatible components these are:

A) Layered tablet- either two layered (for two components) or three layered (for three components) tablet.

B) Compressed coated type- either tablet within a tablet or tablet within a tablet within a tablet. Tablet in this category are usually prepared for two reasons

1. To separate physically or chemically incompatible ingredients.
2. To produce repeat action or prolong action product.

3. Multilayered tablets

These tablets consist of two or more layer of materials compressed successively in the same tablets. The color of each layer may be the same or different. The tablets having layers of different colours are known as "multicoloured tablets".

4. Enteric-coated tablets

These are compressed tablets meant for administration by swallowing and are designed to bypass the stomach and get disintegrated in the intestine only. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine. Eg: tablets containing anthelmentics, and amoebiacid.

5.Sugar coated tablets

The compressed tablets which have an sugar coating are called " sugar coated tablets". Primary role of sugar coating is to produce an glossy, elegant tablets .these are used for preparing multivitamin tablets and minerals combination . , e.g. Multivitamin tablet

6. Film coated tablets

One type of coated tablet in which drug is not required in coating .polymers such as hydroxyl propylmethyl cellulose,hydroxy propyl cellulose,collidol dispersion of cellulose are commonly used. advantages of film coat than sugar coat is better mechanical strength, flexibility and little increase in tablet weight. Application of thin polymer based coatings to tablet/granules by a spray atomization technique. Thickness of such coating is usually between 20-100 µm . eg. Metronidazole tablet

7. Chewable tablets

These tablets are chewed in the mouth and broken into small pieces. In this way, the disintegration time is reduced and the rate of absorption of the medicament is increased.

e.g: aluminium hydroxide tablets, and phenolphthalein tablets.

B.TABLETS USED IN ORAL CAVITY

1. Sublingual tablets

These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT.

Eg: tablets of glyceryl trinities

2. Buccal tablets

These tablets are to be placed in the buccal pouch or between the gums and lips or cheek where they dissolve or disintegrate slowly and are absorbed directly without passing into the alimentary canal. Eg: tablets of ethisterone

3. Lozenge and torches

These tablets are designed to external local effect in the mouth or throat. These tablets are commonly used to treat sore throat or to control coughing in common cold. They may contain local anaesthetics antiseptic, antibacterial agents, astringent and antitussives.

C.TABLETS USED TO PREPARE SOLUTION

1. Effervescent tablets:

Tablets are designed to produce a solution rapidly with the release of carbondioxide.the tablets are prepared by compressing the active ingredient with mixture of organic acid such as citric acid and sodium bi carbonate

2. Hypodermic tablets:

These tablets are composed of one or more drugs with water soluble ingredients. Drug is added to sterile water to prepare sterile solution, which Is inject able.

3. Dispensing tablets:

These tablets provide a convenient quality of potent drug that can be incorporated readily in to powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are, supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

D. Tablets administered by other route

1. Dental cones

These are relatively minor compressed tablets meant for placing them in the empty socket-after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow releasing antibacterial compounds or to reduce bleeding by containing the astringent. These cones generally get dissolved in 20 to 40 min time.

2. Implantation tablets

These tablets are placed under the skin or inserted subcutaneous by means of minor surgical operation and are slowly absorbed. These implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for administration of hormones such as testosterone, and deoxycorticosterone etc.

3. Vaginal tablets

These tablets are meant to dissolve slowly in the vaginal cavity. These tablets are typically ovoid or pear shaped to facilitate retention in the vagina. This tablet form is used to release steroids, antibacterial agents, antiseptics or astringents to treat vaginal infections.

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration that is, the drug delivery system should delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment

MANUFACTURING METHODS [6,7]

There are four general methods of tablet preparation.

- Direct compression
- Wet granulation method
- Dry granulation method
- Fluidized bed granulation

In the tablet-pressing process, it is important that all ingredients be dry, powdered, and of uniform grain size as much as possible. The main guideline in manufacture is to ensure that the appropriate amount of active ingredient is equal in each tablet so ingredients should be well-mixed. Compressed tablets are exerted to great pressure in order to compact the material. If a sufficiently homogenous mix of the components cannot be obtained with simple mixing, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to prepare powders for granulation into a tablet: wet granulation and dry granulation.Powders that can be mixed well do not require granulation and can be compressed into tablets through Direct Compression.

A. Direct Compression:

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration or the excipients used in formulation are not conducive to direct compression.Granulation is the process of collecting particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablet manufacture is wet granulation. Dry granulation is another method used to form granules.

Commonly used direct compression diluent are: microcrystallinecellulose , lactose, mannitol etc.,

Steps involved in direct compression:

Raw material → weighing → screening → mixing → compression

The ideal requirements of excipients used in direct compression and its advantages, limitations

Table: 2 Ideal Requirements,Advantages and Limitation of Direct compression

Ideal requirements	Advantages	Limitations
Flow ability	Cost effectiveness production	Segregation
Compressibility	Better stability of drug	Variation in functionality
Diluent pontential	Faster dissolution	Low dissolution potential
Stability	Simplified validation	Poor compressibility
Controlled particle size	Less microbial contamination	Lubricant sensitivity

B. Wet Granulation:

wet granulation is a process of using a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed, and over wetting will cause the granules to be too hard and under wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvents.

- Procedure of Wet Granulation
- Step 1: Weighing and Blending - the active ingredient, filler, disintegration agents, are weighed and mixed.
- Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia and cellulose derivatives such as methyl cellulose, CMC, gelatin, and povidone. Ingredients are placed within a granulator which helps ensure correct density of the composition.
- Step 3: Screening the damp mass into pellets or granules
- Step 4: Drying the granulation
- Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity
- Step 6: Lubrication- A dry lubricant, antiadherent and glidant are added to the granules either by dusting over the spread-out granules or by blending with the granules. Its reduces friction between the tablet and the walls of the die cavity. Antiadherent reduces sticking of the tablet to the die and punch.
- Step7: liquid binder, but sometimes many actives are not compatible with water. Water mixed into the powder can form bonds between powder particles that are strong enough to lock them in together. However, once the water dries, the powders may fall apart and therefore might not be strong enough to create and hold a bond.

C. Dry Granulation:

This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification. However, the process may require repeated compaction steps to attain the proper granule end point. It requires drugs or excipients with cohesive properties.

- Some granular chemicals are suitable for direct compression (free flowing) e.g. potassium chloride.
- Tableting excipients with good flow characteristics and compressibility allow for direct compression of a variety of drugs.

D. Fluidized bed granulation:

It is a multiple step process performed in the same vessel to pre-heat, granulate and dry the powders. It is today a commonly used method in pharmaceuticals because it allows the individual company to more fully controls the powder preparation process. It requires only one piece of machinery that mixes all the powders and granules on a bed of air.

EXCIPIENTS USED IN TABLETS FORMULATION:[8]

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms which includes various sub- groups. Comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavours, fragrances and sweeteners.

Selection of excepients as follows:-

- They must be physiological inert.
- They must be acceptable to regulatory agencies
- They must be physiologically and chemically stable.
- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must be not interfering with the bioavailability of the drug.
- They must be commercially available in the form and purity commensurate to pharmaceutical standards.
- Cost must be relatively inexpensive.

To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and

must ascertain compliance of each ingredient with existing standards and regulations.The screening of drug-excipients and excipient-excipient interactions should be carried out routinely in preformulations studies

A. Lubricants:

Lubricants are used to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face.

In selecting a lubricant, the following should be considered:

- Lubricants markedly reduce the bonding properties of many excipients.
- Over blending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
- Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use.

B. Fillers (Diluents):

In order to facilitate tablet handling during manufacture and to achieve targeted content uniformity, the tablet size should be kept above 2-3 mm and weight of tablet above 50 mg. Many potent drugs have low dose (for e.g. Diazepam, Clonidine hydrochloride). In such cases diluents provide the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size. Usually the range of diluent may vary from 5-80%. Diluents are also synonymously known as “fillers”. Diluents are often added to tablet formulations for secondary reasons like to provide better tablet properties such as:

i. To provide improved cohesion

ii.To allow direct compression manufacturing

iii. To enhance flow

iv. To adjust weight of tablet as per die capacity

C. Disintegrants:

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

Examples

- Crospovidone: Crospovidone is disintegrant, crospovidone also enhances solubility.
- Sodium starch glycollate: sodium starch glycollate is widely used in oral pharmaceuticals and as a disintegrant in capsule.

D.Glidants :

Glidants are materials that improve the flow characteristics of granules by reducing the inter particulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times. Many of the excipients commonly used in tablet formulations are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chewabilty. In general; these fall into the sugar category, although a combination of excipients with artificial sweeteners may provide a satisfactory alternative.

EVALUATION OF THE PHARMACEUTICAL POWDERS:

a) Bulk Density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

Bulk density (BD) = Weight of the powder/ Volume of powder

$$BD = W/V_0 \ g/mL$$

Weighed quantity of the powder (W) was taken in a graduated measuring cylinder and volume (V_0) was measured and bulk density was calculated using the formula.

b) Tapped Density:

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 500 times using Tap Density tester USP I and the volume attained is the tapped volume. It is expressed in g/ml and is given by

$$\textbf{Tapped density } (\rho_t) = M/V_f$$

Weighed quantity of powder was taken in a graduated cylinder and the volume was measured (V_0). The graduated cylinder was fixed in the 'Tapped Densiometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f). The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

c) Angle of Repose

The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose , the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug and the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel.

Angle of repose was calculated using following equation.

Angle of Repose (θ) **= tan-1(h/r)**

Where, **h** = height of pile in cm, **r** = radius of pile in cm., θ = angle of repose

Table: 3 angle of repose limits

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

d)Carr's index:

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Table: 4 Carr's index and corresponding flow properties

Carr's Index (%)	***Flow***
5-15	Excellent
16-18	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Carr's index was calculated by using the formula:

$$\text{Carr's Index} = \frac{(\text{Tapped Density} - \text{Bulk Density})}{\text{Tapped Density}} \times 100$$

e) Hausner's ratio:

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property.

Table:5 Hausner's ratio and corresponding flow properties

Hausner's Ratio	**Property**
0-1.2	Free flowing
1.2-1.6	Cohesive Powder

Hausner ratio was calculated by using the formula.

$$\text{Hausner Ratio} = \text{Tapped density / Bulk density}$$

$$\text{Hausner Ratio} = V_f / V_0$$

Where V_0 = Initial volume

V_f = Final volume

EVALUATION OF TABLETS [9,10, 11]:

Physical appearance:

The general appearance of the tablet,its identity and general elegance is essential for consumer acceptance, for control of lot-to- lot uniformity and tablet to tablet uniformity.the control of general appearance involves the measurement of size,shape,colour,presence, or absence of odour, taste etc.

Weight variation test:

Twenty (20) tablets from each batch were individually weighed. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight .Weight Variation limits as per USP and the values were showed in the table-30.

Table: 6 Weight Variation that has be presented Solid dosage form

Average weight in mg	% ± deviation allowed
130 or less	10
130-324	7.5
More than 324	5

The content uniformity approach is preferred over the weight variation approach as it more precisely reflects the variation of the active ingredient from tablet to tablet.

The required specification for this test is that uniformity of dosage unit should be within a range of 85%–115% with a relative standard deviation of less than or equal to 6%.

Friability:

This test is intended to determine, under defined conditions, the friability of uncoated tablets, the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. Commercially available apparatus known as "friabilators" are used for the test. Basically, it consists of a drum with diameter between 283mm and 291mm and having width of 36 mm–40 mm, made of transparent plastic material. The drum is attached to the horizontal axis of a device that rotates at 25±1 rpm. The tablets are tumbled at each turn of the drum by a curve projection with an inside radius of 75.5 mm–85.5mm that extends from middle of the drum to outer wall. Thus, at each turn, the tablets roll or slide and fall onto the drum wall or onto each other. Usually, a sample of 10 tablets are tested at a time, unless tablet weight is 0.65 g or less, where 20 tablets are tested. After 100 turns, the tablet samples are evaluated by weighing. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test.

Generally, the test is done once. If cracked, cleaved, or broken tablets are obvious, then the sample also fails the test.

Thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliper's. The average thickness and standard deviation were reported in table-

Hardness testing:

A tablet requires a certain amount of mechanical strength to withstand the shocks of handling in its manufacturing, packing, shipping and dispensing. As discussed before, hardness and friability are most common measures used to evaluate tablet strength. If a tablet is more fragile than expected, then the friability test will detect its substandard quality. If the tablets are more robust than desired, then tablet hardness test that will detect the deficiency. The most widely used apparatus to measure tablet hardness is the Schleuniger apparatus. This, and other newer electrically operated test equipment, eliminates the

operator variability inherent in the measurement using older apparatuses. Generally, the force required to break a tablet may be expressed in either kilograms or pounds.

Disintegration test [5]:

A disintegration test is a test to establish how fast a tablet disintegrates into aggregates and/or finer particle, the test is conducted using a specially designed instrument known as disintegration apparatus. The apparatus employs a basket of six tubes with a base of metal sieve. A tablet is placed in each tube and is held in place by a plastic weight. The six-tube assembly, containing six tablets, is suspended using a hanger with a mechanism of vertical motion at a fixed speed of 28- 32 cycles/minute. While hanging the six-tube assembly on the hanger, the assembly is moved in vertical motion in water or a buffer solution. The time for disintegration of each tablet is recorded and should meet the required time specification.**Table: 7 The Pharmacopoeial specifications for disintegration testing**

Tablet Type	**Time limit and Specifications**
BP	
Uncoated	<15min
Coated Film	<30min
Sugar	<60min, repeat in 0.1MHCl
Gastro resistant, enteric	>120min in 0.1MHCl <60min in pH 6.8(Phosphate)
Effervescent	<5min in 200mL, water, 20°C
Soluble	<3min
Dispersible	<3min, 2 tablets in 100mL water dispersed, USP

Uncoated	<15min
Plain coated	<30 min
Enteric coated	Intact for 60min in simulated gastric fluid, disintegrated in simulated intestinal fluid<monograph time
Buccal	<4hours

Assay:

This test is a quantitative version of the identification test. Again, 10–20 tablets are ground and the active ingredient is dissolved or extracted in a suitable solvent using the standard procedure. The concentration of the extracted solution is determined using a specific and validated spectroscopic or chromatographic method against a solution of reference standard. These results are reported as percent of expected/labeled value. Although the specifications for assay results differ from product to product, generally the expected range for individual active ingredient is to be within 90%–110% of the labeled amount.

Dissolution [12,13]:

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

Dissolution is considered as one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence.

Dissolution behaviour of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between in- vitro dissolution rate of many drugs and their in-vivo bioavailability has been demonstrated and is generally referred to as in-vitro in-vivo correlation, IVIVC.

Dissolution Testing Conditions:

Apparatus:

The most commonly employed dissolution test methods are

The basket method (Apparatus 1) and

The paddle method (Apparatus 2)

The basket and the paddle methods are simple, robust, well standardized and used worldwide. These methods are flexible enough to allow dissolution testing for a variety of drug products. Apparatus 1 and Apparatus 2 should be used unless shown to be unsatisfactory. The in-vitro dissolution procedures, such as the reciprocating cylinder (Apparatus 3) and a flow-through cell system (Apparatus 4) described in the USP may be considered, if needed. These methodologies or other alternatives/modifications should be considered on the basis of their proven superiority for a particular product. Because of the diversity of biological and formulation variables and the evolving nature of understanding in this area, different experimental modifications may need to be carried out to obtain a suitable in-vivo correlation with in-vitro release data. Dissolution methodologies and apparatus described in the USP can generally be used either with manual sampling or with automated procedures.

Dissolution Medium:

Dissolution testing should be carried out under physiological conditions, if possible. This allows interpretation of dissolution data with regard to in-vivo performance of the product. However, strict

adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration.

The volume of the dissolution medium is generally 500, 900, or 1000 mL. Sink conditions are desirable but not mandatory. An aqueous medium with pH range 1.2 to 6.8 (ionic strength of buffers is given in USP) should be used.

To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0.

To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. Recent experience with elatin capsule products indicates the possible need for enzymes (pepsin with SGF and pancreatin with SIF) to dissolve pellicles, if formed, to permit the dissolution of the drug. Use of water as a dissolution medium also is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients. For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulfate is recommended. The need for and the amount of the surfactant should be justified. Use of a hydro alcoholic medium is discouraged.

All dissolution tests for IR dosage forms should be conducted at 37±0.5°C. The basket and paddle method can be used for performing dissolution tests under multimedia conditions (e.g., the initial dissolution test can be carried out at pH 1.2, and, after a suitable time interval, a small amount of buffer can

be added to raise pH to 6.8). Alternatively, if addition of an enzyme is desired, it can be added after initial studies (without enzymes).

Use of Apparatus 3 allows easy change of the medium. Apparatus 4 can also be adopted for a change in dissolution medium during the dissolution run. Certain drug products and formulations are sensitive to dissolved air in the dissolution medium and may need deaeration

PROBLEMS IN TABLET MANUFACTURING [2]

An ideal tablet should be free from any functional defect or visual defect. Functional defects are due to faulty formulation. Visual defect are either related to imperfections in any one or more of the following factors:

- Tableting Process
- Excipient
- Machine

The problems in manufacturing and their remedies are

A. Capping:

Definition:

‘ Capping’ is the term used, when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of a tablet and comes off as a cap, during ejection from the tablet press, or during subsequent handling.

Reason:

Capping is usually due to the air–entrapment in a compact during compression and subsequent expansion of tablet on ejection of a tablet from a die.

Remedies:

1. Remove some fines through 100 or 200 mesh.
2. Moisten the granules suitably. Add hygroscopic substance e.g.: sorbitol, methyl- cellulose
3. Increasing the amount of binder or Adding dry binder such as pre-gelatinized starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar.
4. Polish dies properly. Investigate other steels or other materials.
5. I Make proper setting of lower punch during ejection ncrease the amount of lubricant or change the type of lubricant.

B. Lamination:

Definition:

'Lamination' is the separation of a tablet into two or more distinct horizontal layers.

Reason:

Air-entrapment during compression and subsequent release on ejection. The condition is exaggerated by higher speed of turret Use flat punches.

REMEDIES:

- Use a less amount of lubricant or change the type of lubricant e.g.: Magnesium-stearate.
- Use tapered dies, i.e. upper part of the die bore has an outward taper of 3° to 5°.

C. Chipping:

Definition:

'Chipping' is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

Reason:

Incorrect machine settings, specially mis-set ejection take-off.

Remedies:

- Dry the granules properly or increase lubrication
- Moisten the granules to plasticize. Add hygroscopic substances
- Polish to open end, reverse or replace the die

D. Sticking / Filming:

Definition:

'Sticking' refers to the tablet material adhering to the die wall.

'Filming' is a slow form of sticking and is largely due to excess moisture in the granulation.

Reason:

Improperly dried or improperly lubricated granules

Remedies:

- Dry the granules properly. Make moisture analysis to determine limits
- Increase or change lubricant
- Increase pressure in machine
- Reduce speed

E. Binding:

Definition:

'Binding' in the die, is the term used when the tablets adhere, seize or tear in the die. A film is formed in the die and ejection of tablet is hindered. With excessive binding, the tablet sides are cracked and it may crumble apart.

Reason:

Binding is usually due to excessive amount of moisture in granules, lack of lubrication and/or use of worn dies.

Remedies:

- Dry the granules proper
- Increase the amount of lubricant or use a more effective lubricant
- Reduce granular size, add more fines, and increase the quantity of lubricant.
- If coarse granules, reduce its size. Use wear-resistant dies.

F. Mottling:

Definition:

'Mottling' is the term used to describe an unequal distribution of colour on a tablet, with light or dark spots standing out in an otherwise uniform surface.

Reason:

One cause of mottling may be a coloured drug, whose colour differs from the colour of excipients used for granulation of a tablet.

Remedies:

- Change the solvent system, Change the binder, Reduce drying temperature
- Incorporate dry colour additive during powder blending step, then add fine powdered adhesives such as acacia and tragacanth and mix well and finally add granulating liquid in case of improper mixing of colour.

G. Double impression:

Definition:

'Double Impression' involves only those punches, which have a monogram or other engraving on them.

Remedies:

- Use keying in tooling, i.e. inset a key alongside of the punch, so that it fits the punch and prevents punch rotation.
- Newer presses have anti-turning devices, which prevent punch rotation

TABLET COATING [14,15]:

Coating has an several functions .it strengthen the tablets,improve taste,colour,make easy to handle, package and control the release of tablets. all drug have thir own characterstics for example bitter in taste ,unpleasant odour, some are sensitive to light, hygroscopic, which are all can be altered by coating .

Tablet film coating is performed by two types:

One is aqueous fim coating generally water is used as an solvent and another is non aqueous film coating where non organic solvent is used.high quality of aqueous fim coating must be smooth, uniform, and adhere satisfactorily to the tablet surface and should be stable to drug.

Reason for tablet coating

A number of reasons can be suggested:

- The core contains a material which has a bitter taste in the mouth or has an unpleasant odour.
- Coating will protect the drug from the surroundings with a view to improve its stability.
- Coating will increase the ease by which a tablet can be ingested by the patient.

- Coating will develop the mechanical integrity; means coated products are more resistant to mishandling (abrasion, attrition etc.)
- The core contains a substance which is incompatible in the presence of light and
- Subject to atmospheric oxidation, i.e. A coating is added to improve stability.
- The core alone is inelegant.
- The active substance is coloured and migrates easily to stain hands and clothes.
- The coated tablets are packed on high-speed packaging machine. Coating reduces
- Friction and increases packaging rate.
- Coating can modify the drug release profile, e.g., enteric coating, osmotic pump,

- pulsatile delivery.

Types of coating

- Sugar coating
- Film coating
- Enteric coating
- Controlled release coating
- Specialized coating
- Compressed coating
- Electrostatic coating
- Dip coating
- Vacuum film coating

1. FILM COATING:

Film coating is the process whereby a tablet, capsule, or pellet is surrounded by a thin layer of polymeric material. Film coated tablets are compressed tablets with a thin layer of suitable polymer capable of forming a skin like film over the tablet. The polymeric substance most commonly used are hydroxyl propyl methyl cellulose, hydroxyl methyl cellulose, The film is usually colored and has the advantage over sugar coating in that it is more durable, less bulky, and less time consuming to apply. The film coating protects the medicament from the atmospheric effects. By its composition the coating is designed to rupture & expose the core tablet at the desired location within GIT.

Table-8 Reasons for Film coating

Reasons for film coating include	
Appearance	To change the color, for branding purposes or other aesthetic reasons
Stability	To protect the active ingredient from moisture, light, and/or the acidic environment of the stomach
Taste/odor Masking	To provide an easy to swallow tablet without the bitter taste of many actives
Release characteristics	Many film coating materials have functional properties which enable the delayed (enteric) release of dosage forms

Film coating materials:

Usually spray process is employed in preparation of film coated tablet. Accelacota is the type of prototype of perforated cylindrical drum providing drying air capacity. Fluidized bed equipment has made considerable impact where tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column with a smaller cylindrical insert the stream of cores is rising in the centre of device together with spray mist applied in the middle of the bottom. For fluidized coating very hard tablet hardness above 20 N have to be used

Components required for film coating formulations:

1. Polymer:

Usually cellulose deraivatives , acrylic and copolymers are used

Non enteric polymers:

Eg: hypermellose , hydoxyethyl cellulose, polyethylene glycol,ethylcellulose, hydroxyl propyl cellulose.

Enteric polymers:

Cellulose acetate phthalate, polymethaacrylates, polyvinyl acetate phthalate.

2. Plasticizers:

Plasticizer are low molecular weight materials, which have tendency to alter physical properties of the polymer to render it more useful in function as film coating materil.it is of 3 types-Polyos type which contain glycerol,propylene glycol,polyethylene glycol, organic esters contain phthalate esters, dibutyl acetate, citrate esters. oils/glycerides contain castor oil, monoglycerides, coconut oil.

3. Solvents:

Its main function is to dissolve polymers and other additives.some of solvents are.,

- Water
- Alcohols
- Ketones
- Esters
- Chlorinated hydrocarbon

Among this water is a common solvent of choice, due to environmental and economic considerations.

4. colourants/opaquants:

These are the common materials used in film coating as an ingredient to contribute the visual appeal of the product.

Colorants can be classified into 3 classes:

Organic dyes example: Sunset yellow, tartrazine, erythrosine

Inorganic colours example: iron oxide red ,yellow, titanium dioxide,talc.

Natural colours example: riboflavin, carmine.

MISCELLANEOUS:

To provide dosage form with a single chractestic,special materials used to incorporate into a solution.

Flavors:

Flavors are added to tablet formulation in order to make them enough in case of chewable tablet by improving the taste. Flavours are commonly used to improve the taste of chewable tablets as well as mouth dissolved tablets. Flavours are incorporated either as solids (spray dried flavours) or oils or aqueous (water soluble) flavors.

Sweeteners:

Sweeteners are added to tablet formulation to improve the taste of chewable tablets. Sweeteners used in tablet formulation- Mannitol, Lactose, Sucrose, Dextrose, Saccharin, Cyclamate, Aspartame etc

Antioxidants:

Antioxidants are added in tablet formulation to protect drug from undergoing oxidation. Antioxidants undergo oxidation in place of drug or they block the oxidation reaction or they act as synergisys to other antioxidants.

Adsorbents:

Adsorbents are the agents that can retain large quantities of liquids. Therefore liquids like Vitamin E can be incorporated into tablets by addition of adsorbents. Most commonly used adsorbents in pharmaceuticals are anhydrous calicium phosphate, starch, magnesium carbonate, bentonite, kaoline, magnesium oxide. Generally the liquid to be adsorbed is first mixed with the adsorbent prior to incorporation into the formulation.

Wetting Agents:

Wetting Agents in tablet formulation aid water uptake and thereby enhancing disintegration and assisting in drug dissolution. Incorporation of anionic surfactant like Sodium Lauryl Sulphate (SLS) is

known to enchance the dissolution. It has been established that SLS improves permeation of drug biological membrane since it destroys the path through which drug has to pass and thus minimizing the path length for the drug to travel. Wetting agents are mainly added when hydrophobic drug is to be formulated into tablet. SLS, Sodium disobutylsulfosuccinate are used as wetting agent in tablet formulation

Coating process [15]:

Film coating of tablets is a multivariate processes,with many different factors,such as coating equipement, coating liquid, and processes parameters which affect the pharmaceutical quality of the final product. many film former have different chemical nature and different characterstics. percentage solid content present in coating liquid may affect tablet surface and coating efficacy. Processes parameters such as spray rate, atomizing air pressure, inlet air temperature, rotating speed of the fan influences coating. optimization of above parameters result in formation of a proper film, whereas improper spraying or aleterd airpressure, temperature, fan speed result in sticking of film, reduced tablet porosity, breakage.

Film Coatings for Every Application :

Colorcon offers a wide range of film coating products, many of which can be formulated specifically for your application and regulatory requirements. Whether the desired function for your tablet or particulate is immediate release, delayed (enteric) release and/or extended (controlled) release, the tablet film coating technology needed to enhance, protect, and modify the functionality of product.

Immediate Release

A distinctive product appearance offers many benefits to the producers and marketers of pharmaceutical tablets and nutritional supplements. Film coating is the most economical method of enhancing your product – improving visual appearance, as well as easing swallow ability, and enhancing the taste and masking objectionable odors. Colorcon film coatings can impart mechanical

integrity, color, gloss, pearlescence or moisture protection to create an immediate release tablet that is both memorable and effective.

Extended Release

The extensively used polymer for extended release coating was Ethyl cellulose.

Application of an ethyl cellulose film from aqueous dispersion or organic solution provides the formulator the means to control the release of drug from a tablet or multiparticulatevia diffusion of the drug through the ethyl cellulose film. Novel means of controlled release can also be achieved using a combination of Colorcon's modified release coating systems.

Delayed Release

The enteric/delayed release products can help the deliver of final product that saves you development, scale-up and production time while assuring the integrity of the coating for the safety and efficacy of your finished dosage form. Various systems are available based on a variety of delayed release polymers for aqueous or organic processing to provide targeted release at various pH conditions.

For the solid dosage manufacturer, tablet film coating technology conveys many benefits including improved packaging efficiency, prevention of cross contamination and reduced tablet breakage and chipping. A large variety of pigmented and non-pigmented tablet film coating systems available. Which is cost Effective, protect from light moisture and environmental gases.

Immediate Release Film Coating Systems for Tablets [15,16,17]

Colorcon, the innovator and industry standard for complete film coating systems, offers a range of custom pigmented and non-pigmented film coatings for immediate release solid dose applications. film coating formulas produce attractive, elegant coatings on even the most challenging tablet surfaces and

can be used in both aqueous and organic coating procedures.An extensive selection of polymer blend formulations provides the user with the ability to impart .

Benefits include:

- Reduced coating process time
- Superior adhesion on difficult to coat cores
- Less stressful processing conditions for heat sensitive, friable or high drug

  Content cores
- Sharper logo definition, even at higher weight gains
- Better gloss and smoothness compared to conventional film coatings
- Improvedcolor stability.

Aqueous film coating is the quickest and least expensive method for enhancing your tablet appearance and, unlike other methods, will not affect dissolution or disintegration profiles. dry-blend systems consist of polymers, plasticizers and pigments, combined in one, easy-to-use, dry powder system which is rehydrated quickly and simply with water. Colorcon also offers customized colour selection and colour matching of our immediate release tablet film coating products.

Celeron’s ongoing research of film coating polymers has produced many enhanced polymer combinations resulting in new tablet coating options for our customers. Our newly developed, dry coating technology provides benefits such as improved adhesion, reduced processing times, and application of the tablet coating at wider process parameters. Advances in our immediate release tablet film coating technology not only give a more elegant appearance to your solid oral dosage form, but provide unique.

Stability studies:

The purpose of at ability testing is to provide evidence of quality of the drug substance or drug product ,and how it varies with time under the influence of a variety of environmental condition(heat, humidity, light ,air)the final formlation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzes of their physical and chemical properties.

Table: 9 ICH guidelines for stability study.

study	**Storage conditions**	**Time period**
Long term	$25^0c \pm 2^0c/60\%RH \pm 5\%$ RH or $30^0c \pm 2^0c/65\%$ RH $\pm 5\%RH$	12 month
intermediate	$30^0C/65\%RH \pm 5\% \pm RH$	6 month
accelerated	$40^0C \pm 2^0C/75\%RH \pm 5\%RH$	6month

HYPERTENSION [18,19,20]

Introduction:

High blood pressure, also called hypertension, is elevated pressure of the blood in the arteries. Hypertension results from two major factors, which can be present independently or together:

•The heart pumps blood with excessive force.

•The body's smaller blood vessels (known as the arterioles) narrow, so that blood flow exerts more pressure against the vessels' walls.

Blood pressure is the force applied against the walls of the arteries as the heart pumps blood through the body. The pressure is determined by the force and amount of blood pumped and the size and flexibility of the arteries.

Two numbers are used to describe blood pressure: the systolic pressure (the higher and first number) and the diastolic pressure(the lower and second number). Health dangers from blood pressure may vary among different age groups and depending on whether systolic or diastolic pressure (or both) is elevated. A third measurement, pulse pressure, may also be important as an indicator of severity.

Systolic Blood Pressure.

The systolic pressure (the first and higher number) is the force that blood exerts on the artery walls as the heart contracts to pump out the blood. High systolic pressure is now known to be a greater risk factor than diastolic pressure for brain, heart, kidney, and circulatory complications and for death, particularly in middle-aged and elderly adults. The wider the spread between the systolic and diastolic measurements, the greater the danger.

Diastolic Blood Pressure.

The diastolic pressure (the second and lower number) is the measurement of force as the heart relaxes to allow the blood to flow into the heart. High diastolic pressure is a strong predictor of heart attack and stroke in young adults .There are a number of ways to categorize or describe hypertension.

Essential Hypertension. Essential hypertension is also known as primary or idiopathic hypertension. About 90% of all high blood pressure cases are this type. The causes of essential hypertension are unknown but are based on complex processes in all major organs and systems, including the heart, blood vessels, nerves, hormones, and the kidneys.

Secondary Hypertension. Secondary hypertension comprises about 5% of high blood pressure cases. In this condition, the cause has been identified.

Blood Pressure Guidelines

Blood pressure is measured in millimeters of mercury (mm Hg). According to current adult guidelines, blood pressure is categorized as normal, prehypertensive, and hypertensive (which is further divided into Stage 1 and 2, according to severity).

- Normal blood pressure is below 120/80 mm Hg.
- High blood pressure is greater than or equal to 140 mm Hg (systolic) or greater than or equal to 90 mm Hg (diastolic).

Blood pressure readings in the prehypertension category (120 -139 systolic or 80 - 89 diastolic) indicate an increased risk for developing hypertension.

Hypertension is defined as average systolic and diastolic readings that are greater than the 95th percentile for gender, age, and height on at least three occasions.

Pre-hypertension in children is diagnosed when average systolic or diastolic blood pressure levels are at least in the 90th percentile but less than the 95th percentile. For adolescents, as with adults, blood pressure readings greater than 120/80 are considered prehypertensive. Increasing rates of childhood obesity have led to increasing rates of hypertension and pre-hypertension among children and adolescents. Although more children are having high blood pressure, recent studies indicate that pediatric hypertension is frequently under diagnosed.

Table-10 ,blood pressure ranges

Blood Pressure Ranges	
Blood Pressure Category	**Ranges for Most Adults (systolic/diastolic)**
Normal Blood Pressure (systolic/diastolic)	Systolic below 120 mm Hg Diastolic below 80 mm Hg
Pre hypertension	Systolic 120 - 139 mm Hg Diastolic 80 - 89 mm Hg (NOTE: 139/89 or below should be the minimum goal for everyone. People with heart disease, peripheral artery disease, diabetes or chronic kidney disease should strive for 130/80 or less.)
Mild Hypertension (Stage 1)	Systolic 140 - 159 mm Hg Diastolic 90 - 99 mm Hg
Moderate-to-Severe Hypertension (Stage 2)	Systolic over 160 mm Hg or Diastolic over 100 mm Hg

Causes for hypertension

Blood pressure tends to rise as people get older and thus everyone's risk for hypertension increases with age. Behavior and lifestyle-related factors can put people at a higher risk for developing high blood pressure. This includes eating too much salt (sodium), not eating enough potassium (from fruits and

vegetables), being overweight, not getting enough exercise, as well as drinking too much alcohol and smoking.

About 60% of people who have diabetes also have high blood pressure.

Symptoms of hypertension:

High blood pressure is called the "silent killer" because it often has no warning signs or symptoms, and many people do not realize they have it; that is why it's important to get blood pressure checked regularly. Hypertension is usually without any symptoms, but could give rise to early-morning headache, nosebleed, irregular heartbeats and buzzing in the ears. Symptoms of severe hypertension include tiredness, nausea, vomiting, confusion, anxiety, chest pain and muscle tremors .The only way to detect high blood pressure is to have it measured by a doctor or a health professional. Measuring blood pressure is quick and painless.

Adverse health effects of hypertension

High blood pressure can cause serious damage to health. It can harden the arteries, decreasing the flow of blood and oxygen to the heart. This reduced flow can cause

Chest pain, also called angina. heart failure, which occurs when the heart cannot pump enough blood and oxygen to other organs. heart attack, which occurs when the blood supply to the heart is blocked and heart muscle cells die from lack of oxygen. The longer the blood flow is blocked, the greater the damage to the heart.High blood pressure can burst or block arteries that supply blood and oxygen to the brain causing stroke.

Prevent and control high blood pressure [21]

High blood pressure is largely preventable by adopting lifestyle modifications at early stages. Treating hypertension is associated with a reduction in cardiovascular complications. Below is a list of actions to prevent hypertension.Reduce and manage mental stress through yoga, meditation and other relaxing techniques Eat a healthy diet consisting of lots of fresh fruits and vegetables, which provides

nutrients such as potassium and fiber.Limit intake of sodium by reducing the amount of salt added to food. The total daily intake of salt or sodium chloride from all sources should be no more than 5 gm per day (1 tea spoon). Be aware that many processed foods are high in sodium. Avoid or reduce “pickles”, “papads”, “chutneys” and soy sauces which are high in sodium.Limit the intake of food high in saturated fats. Eliminate/reduce transfats in diet.Maintain a healthy weight. Being overweight can raise blood pressure. Losing weight can help lower blood pressure.Be physically active. Physical activity can help lower blood pressure. Adults should engage in moderate physical activity for at least 30 minutes on most days of the week.Do not use tobacco. Smoking injures blood vessels and speeds up the hardening of arteries. Smoking is a major risk factor for heart disease and stroke. If not using tobacco, do not start. If already using tobacco, quitting will lower the risk for heart disease and stroke.

Antihypertensive drugs [20,21]:

ACE inhibitors:

- Benazepril
- Captopril
- Enalapril
- Fosinopril
- Quinapril
- MoexiprilARBs

Angiotensin II receptor blocker:

- Losartan
- Valsartan
- Irbesartan
- Telmisartan
- Olmesartan

- Candesartan
- Eprosartan
- Potassium-sparing diuretics
- Amiloride

LITERATURE REVIEW

1. **Kannan et al (2012).,** Reported the Development and Evaluation of Valsartan Film Coated Tablets The aim of the present study is to formulate and evaluate immediate release tablets of Valsartan. Preformulation studies were performed prior to compression. Tablets were formulated by direct compression, wet granulation and slugging techniques. The fabricated tablets were evaluated for various pre compressional parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and post compressional parameters like average weight, thickness, hardness, friability, assay, disintegration time and dissolution studies. Comparatively, slugging technique exhibited the good flow property than direct compression technique. The stability studies were carried out for the optimized batch for six months. The results of the present study showed that among all the formulations, F8 was better in all terms of pre compression and post compression parameters and showed comparably a good dissolution profile with that of the innovator product .[22,23]

2. **Richa Sood et al (2012).,** Reported Immediate Release Antihypertensive Valsartan oral tablet. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after adminstration.[24]

3. **Pradeeep kumar et al(2012).,** aimed to develop pharmaceutical equivalent ,suitably and quality improved formulation of film coated ticlopidine hydrochloride. Immediate release tablet for direct

compression technique .the current study involves preparation and evaluation of ticlopidine hydrochloride .the three superdisintegrnts used.the study were crosscarmellose,microcrystalline cellulose and native starch.where these excipient combination shows good evaluations and best drug release.[25]

4. **Rajesh et al(2012).,** develop a stable formulation of antibiotic drug clarithromycin as an immediate- release tablet. The task of developing immediate release tablet is accomplished by using suitable diluents and superdisintegrants. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. . The formulated tablets were evaluated for various precompression parameters and post compression parameters like thickness, hardness, weight variation, friability, disintegration test, drug content uniformity and in vitro release studies. The formulation F8 showed satisfactory physical parameters, and it was found to be stable among other formulations. From this study, it was concluded that optimized clarithromycin tablet (OF7) containing croscarmellose sodium (3.029%) showed better characteristics of immediate release tablets**[26]**.
5. **SatyamPandey et al (2011).,** Developed and characterized valsartan and hydrochlorothiazide film coated tablet , They are solid, flat or biconvex disc in shape. They vary greatly in shape, size and weight which depend upon amount of medicament used and mode of administration. They also vary in hardness, thickness, disintegration and dissolution characteristics and in other aspects depending upon their intended use and method of manufacture.[27]
6. **Nataraj et al (2011).,** Simple precise accurate UV Spectroscopic method has been developed and validated for estimation of valsartan in pure and pharmaceutical dosage form. UV Spectroscopic method which is based on measurement of absorption of UV light, the spectra of valsartan in methanol showed maximum wave length at 250nm and calibration graphs were plotted over the concentrations ranging from 2-20µg/ml of valsartan with correlation coefficient 0.9968 validation

was performed as per ICH Q2 (R1) guidelines for linearity, accuracy, precision and recovery. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.15 and 0.449 respectively by simple UV Spectroscopy .The proposed method was validated.[28]

7. **Soumya et al (2011).,** The purpose of the present investigation was to develop and optimize bilayered sustained release matrix tablets of Valsartan. The tablets contained an immediate releasing layer with the loading dose oThe drug polymer interaction was investigated by FTIR and DSC and their results directed further course of formulation. Valsartan tablets were evaluated for various post compression parameters like Tablet hardness, Friability, Weight variation, Drug content and In vitro dissolution. The results were found to be within the acceptable limits f the drug and a sustaining layer with maintenance dose of drug prepared by wet granulation method. The FT-IR Spectrum of pure valsartan drug was compared with the FT- IR spectrum of physical mixture of valsartan. The characteristic functional groups of the pure valsartan and physical mixtures of valsartan showed similar with minor changes **[29]**
8. **Srinivas et al (2010).,** formulate and evaluate of Valsartan film coated tablets. In order to obtain the best optimized product, eight different formulations were developed using diluents, binder, glidant, lubricant, and different concentrations of superdisintegrant. Tablets were formulated by direct compression, slugging and wet granulation techniques. Various pre-compressional parameters like bulk density, tapped density, compressibility index and Hausner's ratio and post compressional parameters like weight variation, thickness, hardness, friability, disintegration time, and drug release were studied. Comparatively granulation techniques exhibited the good powder flow than direct compression technique. Based on this investigation results, the drug release from tablets increased with increasing concentration of superdisintegrant. The formulation F-7 was showed good drug release and selected as an optimized formulation and it was concluded that

superdisintegrant concentration, granulation technique, binder, and lubricants plays a key role in the formulation development and optimizing the immediate release tablet of Valsartan formulation.[30]

9. **Nasiruddin Ahmad Farooqui et al (2010).,** aimed to formulate film coated tablets of secnidazole by wet granulation and the granules are compressed for tablets and they are coated with polymers for getting film coated tablets at specified conditions and the evaluation of film coated tablets for the following parameters as description, average weight, weight variation, hardness test, thickness, dissolution, related substances, disintegration time and assay of tablet for compliance with acceptance criteria, for formulation of secnidazole film coated tablets.[31]
10. **Abbaspour et al (2010).,** concluded that Hydrolysis is the dominant process in degradation of drugs, especially for esteric compounds e.g. aspirin. There are several methods for moisture protection of drugs including reduction of drug solubility, modification of chemical structure, moisture-resistant packaging and coating of solid dosage forms. Specific polymer coatings are used to protect moisture sensitive drugs. The aim of this study is to design and evaluate a moisture-resistant film formulation based on HPMC [32]
11. **Bhatia M. Sudesh et al(2010).,** Valsartan was subjected to different ICH prescribed stress studies. The stability-indicating assays were established by using isocratic RP-HPLC separation C18 column (250 mm length×4.6 mm internal diameterand 5 μm particle size) for both major degradants of valsartan by acid hydrolysis and by oxidation. The mobile phase comprising of methanol: water (70:30v/v, pH 7.2) was used in acid hydrolysis stability-indicating assay and the mobile phase comprising of methanol:water (60:40v/v, pH 7.2) was used in oxidation stability-indicating assay of valsartan. A simple, precise, and accurate isocratic reversed-phase stability-indicating high performance liquid chromatographic assay method was developed and validated for determination of valsartan.[33]
12. **Jain et al (2009).,** Reported the formulation and evaluation of fast dissolving tablets of valsartan, In this investigation fast dissolving tablets of valsartan were prepared using different super disintegrants by direct compression method. FDTs were evaluated for physicochemical properties and in vitro dissolution. Effect of disintegrant on disintegration behaviour of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration.[34]

13. **Agnivesh R shrivastava et al(2009)**., reported the Solubility and dissolution rate of valsartan a poorly water soluble antihypertensive was enhanced by preparation of solid dispersion granules which would additionally allow easy compression into tablets. The dispersion granules were prepared using a hot melt granulation technique which involved preparation of a homogenous dispersion of valsartan in gelucire-50/13 melt, followed by its adsorption on to the surface of aeroperl-300pharma®, an inert adsorbent. A two-factor, three-level (32) statistical design was implemented to quantitate the influence of gelucire-50/13 and aeroperl-300pharma on the dissolution profile and flow properties of the dispersion granules, where gelucire-50/13 and aeroperl-300pharma® were chosen as independent variables, while dissolution and flow properties were chosen as dependent variables. The dispersion granules were characterized for their *in-vitro* dissolution rate and flow properties. An appropriate statistical model was arrived at and a significantly enhanced dissolution rate and flow properties were exhibited with the optimized formulation.[35]
14. **Navin Sheth et al (2009).,** studied the aqueous-based film coating of tablets utilizing a laboratory scale side-vented perforated pan-coating apparatus. The process parameters of potential importance with respect to the final film quality were evaluated by using trial and error method. Tablets were evaluated for coating uniformity (mg), coating process efficiency (%), surface roughness, and %LOD (loss on drying). Spray rate and inlet air temperature both affect the all characteristic of coated tablets. Rotating speed of pan mainly affect the coating uniformity of tablets. % Solid content affects the surface of coated tablets and also creates a problem in spray flow. The process parameters relevant to a side vented perforated pan coating process can be identified and, consequently, optimized.[36]

15. **Praveen et al(2008).,** Oral controlled release matrix tablet formulations of isoniazid using hydroxylpropyl methylcellulose (HPMC) as a hydrophilic release retardant polymer and to study the influence of various formulation factors like proportion of the polymer, polymer viscosity grade, compression force, and release media on the *in-vitro* release characteristics of the drug. Finally the release rate of drug was highly influenced by above characters **[37]**

16. **Saishravan et al (2008) .,**reported the formulation and evaluation of valsartan film coated tablets. The present work was aimed at the formulation development and evaluation of Valsartan film coated tablets. Valsartan is used for the treatment of Hypertension and is an angiotensin II receptor blocker. Immediate release drug delivery is desired for drugs having long biological half life and poor bioavailability. Valsartan tablets are formulated as immediate release dosage forms. The tablets were formulated using direct compression, dry granulation and wet granulation techniques. In order to obtain the best optimized formula eight different formulations were developed using different binders, super disintegrants, diluents and glidants. The formulated tablets were evaluated for various tableting properties, like hardness, thickness, friability, weight variation, disintegration time and dissolution rate. Evaluating the results,it was determined that the drug release from the tablet was increased as the concentration of superdisintegrant was increased and the F8 formulation showed a good release pattern.[38]
17. **Bhalekar et al(2008).,**Hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet which can release the drug up to 24 hrs in predetermined rate. The *in-vitro* release rate profile should be higher concentration Gaur gum polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone.[39]

18. **Setty et al(2008).,**prepared aceclofenac fast dispersible tablets by direct compression method using superdisntegrants crosscarmellose,sodium starch glycolate and crospovidone and their effect on wetting time. disintegration ,dissolution shows best due to increased amount of sodium starch glycolate than crosscarmellose.[40]

19. **Babu et al(2007).,** prepared solid dispersions of piroxicam in five superdisintegrants are namely., microcrystalline cellulose,crosspovidone,crosscarmellose sodium and with water soluble carriers of polyvinylpyrrolidine.solid dipersion gave good drug release due to addition of superdiaintegrants.[41]

20. **Biraju patel et al(2001).,** developed fast dissolving tablets of glipizide by direct compression method with a view to enhance patient compliance. Two superdisintegrants viz, crospovidone and croscarmellose sodium (4%, 5%, 6%) with different binders viz, pvp k-30 and pregelatinized starch (3%) were used. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration, wetting time, drug content and in vitro dissolution studies. Based on evaluating parameters, Formulation prepared by using 5% croscarmellose sodium with 3% PVP K30 was selected as optimized formulation. Finally, the optimized formulation was compared with marketed conventional formulation. Stability studies were carried out at 25ºC / 60% RH and 40ºC / 75% RH for optimized formulation for 2 months. Stability studies on the optimized formulation indicated that there was no significant change found in physical appearance, disintegration time and wetting time of the tablets.[42]

AIM AND OBJECTIVE

AIM:

The aim of present work is to design and development of valsartan film coated tablets and its evaluation.

Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure.

Valsartan is rapidly absorbed from the gastrointestinal tract after oral administration and can be administered without regard to food intake. The peak effect of valsartan is evident in 2–4 h; the bioavailability is 25%. Valsartan has a half- life of 6–9 h and demonstrates antihypertensive effects for approximately 24 h. Less than 10% of an orally administered dose of valsartan undergoes biotransformation in the liver; the enzymes responsible for its metabolism are unknown, and no active metabolites have been identified.

The aim is to develop formulations of valsartan film coated tablet using different superdisintegrants (Croscarmellose, Crospovidone) by direct compression technique and the tablets were evaluated for various physiochemical properties. The effect of superdisintegrants on disintegration and dissolution of valsartan tablet were also studied extensively and compare with marketed product.

The present study objectives are…

- Preformulation studies: Compatability between drug and excipients
- Evaluation of powder blends like bulk density, tapped density, hausner's ratio, compressilbility index.
- Preparation of valsartan tablet
- Evaluation of tablets: thickness, disintegration, friability,hardness, weight variation, assay.
- Preparation of film Coating tablet
- Evaluation of film coating tablets:thickness,disintegration,friability, hardness,assay.
- In vitro dissolution studies
- To determine the best fit dissolution profile with marketed product
- Stability studies

PLAN OF WORK

The scheme of the entire work is listed as follows:

Active pharmaceutical ingredients characterization

- Physical observation
- Solubility
- Bulk density
- Tapped density
- Hausner's Ratio
- Compressibility Index

Preformulation studies

- Compatibility studies between drug with various excipients

Preparation and evaluation of powder blend.

- Angle of repose
- Bulk density and tapped density
- Compressibility index
- Hausner's Ratio

Preparation and evaluation of uncoated tablets

- Tablet appearance
- Hardness

- Weight Variation
- Friability
- Thickness
- Disintegration test
- Assay

Preparation and evaluation valsartan film coated tablets

- Tablet appearance
- Hardness
- Friability
- Thickness
- Disintegration test
- In vitro dissolution testing

Comparison of Invitro dissolution profile of optimized formulation with marketed product.

Stability Studies.

DRUG AND EXCEPIENT PROFILE:

VALSARTAN [43,44,45]

Chemical formula : $C_{24}H_{29}N_5O_3$

Molecular Weight : 435.518

Physical state : white or off white crystalline powder.

Melting point : 116-117^{0}c

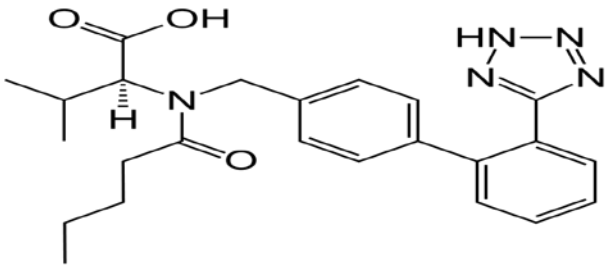
PHARMACOKINETIC DATA

Bioavaibility : 25%

Half life : 6-9 hours

Excretion : renal-3, Biliary-70%

Structural formula:



IUPAC name: (2S)-3-methyl-2-[N-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)pentanamido]butanoic acid

Categories: Antihypertensive Agents, Angiotensin II Receptor Antagonists

Dose: 40, 80, 160, 320 mg daily

Mechanism of action:

Valsartan is an ARB that selectively inhibits the binding of angiotensin II to AT1, which is found in many tissues such as vascular smooth muscle and the adrenal glands. This effectively inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure. Valsartan is selective for AT1 and has virtually no affinity for AT2. Inhibition of aldosterone secretion may inhibit sodium and water reabsorption in the kidneys while decreasing potassium excretion. The primary metabolite of valsartan, valeryl 4-hydroxy valsartan, has no pharmacological activity.

Metabolism:

Valsartan is excreted largely as unchanged drug (80%) and is minimally metabolized in humans. The primary circulating metabolite, 4-OH-valsartan, is pharmacologically inactive and produced CYP2C9. 4-OH-valsartan accounts for approximately 9% of the circulating dose of valsartan. Although valsartan is metabolized by CYP2C9, CYP-mediated drug-drug interactions between valsartan and other drugs is unlikely.

Side effect

•confusion, dizziness, light headedness or fainting spells

•decreased amount of urine passed

•difficulty breathing or swallowing, hoarseness, or tightening of the throat

•fast or irregular heart beat, palpitations, or chest pain

•skin rash, itching

•swelling of your face, lips, tongue, hands, or feet

Description &Applications:

Valsartan is an angiotensin II receptor blocker (ARB) that may be used to treat a variety of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Valsartan lowers blood pressure by antagonizing the renin- angiotensin- aldosterone system (RAAS); it competes with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II. Unlike angiotensin-converting enzyme (ACE) inhibitors, ARBs do not have the adverse effect of dry cough. Valsartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy and diabetic nephropathy. It may also be used as an alternative agent for the treatment of heart failure, systolic dysfunction, myocardial infarction and coronary artery disease.It ia mainly used hypertension, it can be used in combination like with hydrochlorthiazide,or in bilayer with ammlodipine.

Table: 11 Valsartan (80 mg) available in market:

s. no	**Brand name**	**manufacturer**
1	Diovan (80mg)	Novartis Indian ltd
2	Starval (80mg)	Ranbaxy laboratories
3	Valent (80mg)	Lupin laboratories ltd.
5	Valzaar (80mg)	Torrent pharmaceuticals pvt ltd.

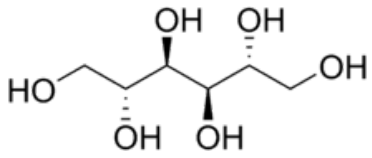
MANNITOL [46]

Synonyms: Cordycepic acid, Manna sugar, D-mannite, Mannitolum, Mannogem.

Chemical Name: D-Mannitol

Empirical Formula: $C_6H_{14}O_6$

Structural formula



Molecular Weight **:** 182.17

Functional Category **:** Plasticizer, sweetening agent, tablet and capsule.

Solubility:

Freely soluble in water, soluble in alkaline solutions, slightly soluble in pyridine, very slightly soluble in alcohol, practically insoluble in ether.

Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used as a diluent (10–90% w/w) and dissolution enhancer in tablet formulations, since it is not hygroscopic and may thus be used with moisture sensitive active ingredients. It may be used in direct compression tablet applications, for which the granular and spray dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. It is commonly used as an excipient in the manufacture of chewable tablet formulations and also used as a diluent in rapidly dispersing oral dosage forms.

Description

It occurs as a white, odourless, crystalline powder, or free flowing granules. It has a sweet taste and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

Incompatibilities

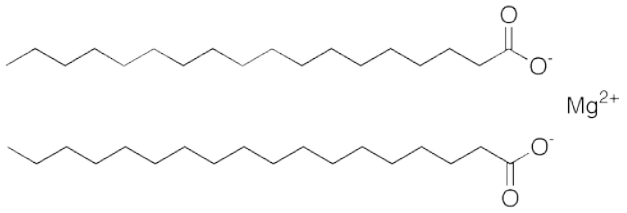
Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.(19) Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement ‘excessive consumption may have a laxative effect’.

MAGNESIUM STEARATE [47,48]

Structural formula :



Non-proprietary name :

- BP : magnesium stearate
- JP : magnesium stearate
- PHEUR : magnesiistearas
- USP : magnesium stearate

Synonym : magnesium octadeconate, magnesium salt.

Chemical name : octadecanoic acid, magnesium salt

Empirical formula : $C_{36}H_{70}O_4$

Molecular weight : 591.34

Physical state:

It is a fine,white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste

Functional category: tablet and capsule lubricant.

Typical properties:

- Density(bulk) : 0.159 g/cm^3
- Density(tapped) : 0.286 g/cm^3
- Density(true) : 1.092 g/cm^3
- Melting point : 117-150^{o}c

Solubility:

Practically insoluble in ethanol, ether, and water, slightly soluble in warm benzene and ethanol.

Stability & storage:

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

Incompatibilities:

It is incompatible with strong acids, alkalies, and iron salts. It cannot be used in products containing aspirin, vitamins and alkaloidal salts.

Applications:

It is widely used in cosmetics, food products and pharmaceutical formulations. It is used as a lubricant in capsule and tablet manufacture at concentration between 0.25-5.0 %.

TALC [49]

Synonyms **:** purified talc, talcum

Empirical formula **:** $Mg_3Si_4O_{10}(OH)_2$

Molecular weight **:** 379.266g/mol

Physical state:

It is a very fine, white to greyish – white colored, odorless, impalpable, unctuous crystalline powder. It adheres readily to skin, is soft to the touch and free from grittiness

Solubility:

Practically insoluble in dilute acids and alkalies, organic solvents, and water.

Typical properties **:** acidity/alkalinity: ph= 6.5-10 (20%w/v aqueous dispersion)

Density **:** $2.7g/cm^3$

Bulk density **:** 0.6

Tapped density **:** 1.1

Melting point **:** 150˚c

Stability and storage : stored in a well-closed container in a cool and dry place.

Incompatibility:

Incompatible with quaternary ammonium compounds.

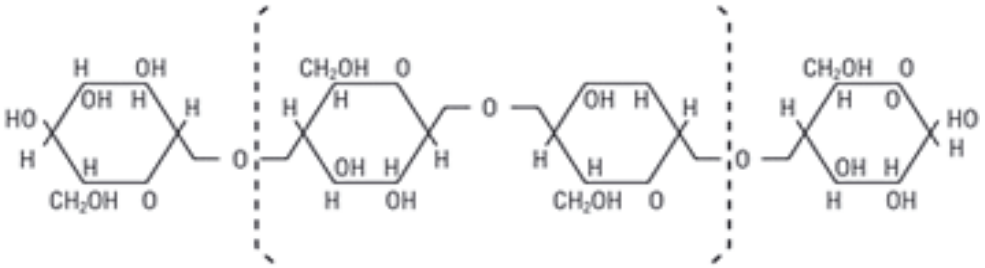
Application:

Tablet and capsule diluents, anticakingagent, glidant, tablet and capsule lubricant.

It is widely used in oral dusting powder. Talc is additionally used to clarify liquids.

MICROCRYSTALLINE CELLULOSE [50]

Structural formula :



Nonproprietary name

- **BP** **:** microcrystalline cellulose
- **JP** **:** microcrystalline cellulose
- **PHEUR :** cellulosum microcrystallinum
- **USPNF:** microcrystalline cellulose

Synonym:avicel; cellulosegel; tabulose crystalline cellulose; e460; emcocel Fibrocel; vivace

Chemical name : cellulose

Empirical formula : $(C_6H_{10}O_5)_n$

Molecular weight : 246.98

Functional category :

Adsorbent; suspending agent; capsule and tablet diluents; tablet disintegrant**.**

Physical state

It is purified, partially depolymerised cellulose that occurs white odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size and moisture grades which have different properties and applications.

Typical properties

Density (bulk) : 0.337 g/cm^3

Density (tapped) : 0.478 g/cm^3

Density (true) : 1.512-1.668 g/cm^3

Melting point : chars at 260-270^{o}c

Moisture content : less than 5% w/w

Solubility:

Slightly soluble in 5%w/v sodium hydroxide solution, practically insoluble in water, diluteacids, and most organic solvents.

Stability & storage condition:

Microcrystalline cellulose is a stable, though hygroscopic material. The bulk material should be stored in a well closed container in a cool, dry, place.

Incompatibilities:

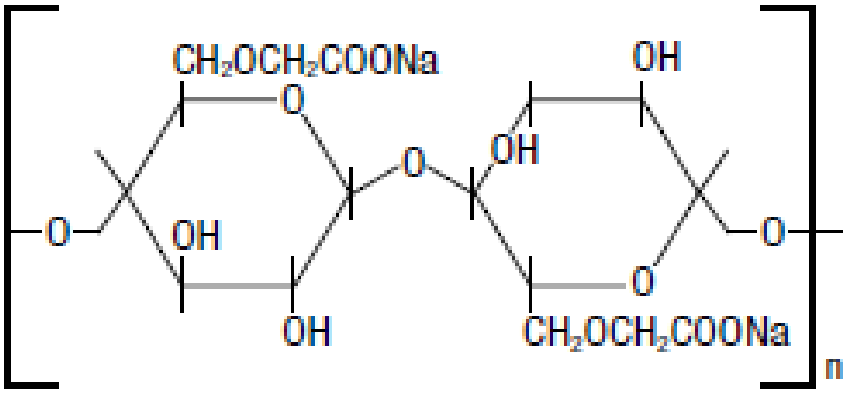
Incompatible with strong oxidizing agents.

Applications:

it is widely used in pharmaceuticals, primarily as a binder/ diluents in oral tablet and capsule formulations. where it is used in both wet granulation and direct compression processes. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. It is also used in cosmetics and food products.

CROSCARMELLOSE SODIUM [51]

Structural formula



Non-proprietary name:

- BP : Croscarmellose sodium
- USP : Croscarmellose sodium

Synonym **:** Ac-Di-Sol, Solute, Primellose, Pharmacel XL

Chemical name **:** Cellulose, carboxy methyl ether,

Molecular weight : 90,000-7, 00,000**.**

Physical state:

crosscarmellose sodium occurs as an odourless, white coloured powder.

Functional category: tablet and capsule disintegrant

Typical properties:

- **Density (bulk)** **:** 0.529 g/cm^3
- **Density (tapped)** **:** 0.819 g/cm^3
- **Density (true)** **:** 1.543 g/

Solubility:

Insoluble in water, rapidly swells to 4-8 times of its original volume on contact with water.

pH : the pH of a 1% w/v dispersion is 5.0 to 7.0

Stability & storage condition:

croscarmellose sodium is a stable though hygroscopic material. It should be stored In well closed container.,in cool dry place.

Incompatibilities:

The efficacy of croscarmellosesodium, may be slightly reduced in tablet formulations prepared by either wet granulation or direct compression process which contains hygroscopic excipients such as sorbitol.

Applications:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for tablet, capsules and granules. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet granulation processes.

COLLOIDAL SILICON DIOXIDE [52]

Nonproprietary Names: Colloidal Silicone Dioxide (Aerosil)

BP: Colloidal anhydrous silica

PHEUR: Silica colloidalis anhydrica

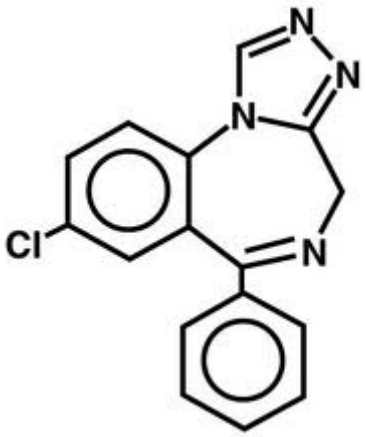
USPNF: Colloidal silicon dioxide

Synonyms: colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride and silicon dioxide fumed

Chemical Name: Silica

Molecular Weight: 60.08

Structural Formula



Functional Category:

Adsorbent, anticakingagent, emulsion stabilizer, glident, suspending agent, tabletdisintegrant, thermal stabilizer, and viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area gives desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting.

Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, and non-gritty amorphous powder.

Stability and Storage Conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0-7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

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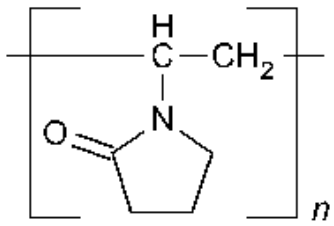
CROSPOVIDONE [53]

Structural formula:



Synonyms:crosslinkedpovidone,kollidoncl-m,polyplasdonexl,polyplasdonexl-10,

polyvinylpolypyrolidone, PVP, 1-vinyl-2-pyrrolidinonehomopolymer.

Non-proprietary names:

BP **:** crospovidone

PHEUR **:** crospovidonum

USPNF **:** crospovidone

Chemical name : 1-ethenyl-2-pyrrolidinone homopolymer

Empirical formula: $(C_6H_9O)_n$

Molecular weight : >1000000

Physical state:

crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odourless, hygroscopic powder.

Solubility: partially insoluble in water and most common organic solvents.

Bulk density **:** 0.323 g/cm3

Tapped density **:** 0.461 g/cm3

Acidity/alkalinity **:** pH=5.0-8.0

Moisture content **:** 60%

Application:

crospovidone is a water- insoluble tablet disintegrate and dissolution agent use at 2- 5% concentration in tablet prepared by direct compression or wet and dry granulation method. It is rapidly exhibits high capillary activity. Crospovidone can also be used as a solubility enhancer. With the techniques of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is absorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Stability: it is a hygroscopic material. The bulk material

Storage: should be stored in a well- closed container in a cool, dry place.

Incompatibilities:

crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. when exposed to a high water level, crospovidone may form molecular adduct with some materials.

Handling precaution : handling with eye protection, gloves and dust mask

Safety: it is widely used in oral pharmaceutical preparation and food products.

Hydroxyl propl methyl cellulose [54,55]

IUPAC name: hydroxyl propyl methyl cellulose

Non-proprietory name

IP : hydroxy propyl methyl cellulose

PHUR : methylhydroxy propyl cellulosum

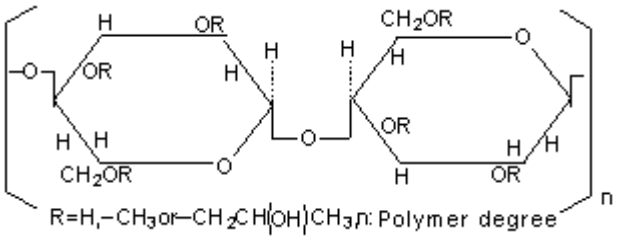
BP : hypromellose

USP : hypromellose

Chemical name: cellulose,hydroxyl propyl methyl ether

Synonyms: methyl hydroxyl propyl cellulose,propylene glycol ether of methylcellulose.

Structural formula:



Physical and chemical properties:

Molecular weight: 10,000-15,000

Colour **:** white to creamy white

Nature **:** granular powder

Odor **:** odorless

Taste **:** tasteless

Solubility: soluble in cold water,insoluble in chloroform,ethanol(95%) andether,but soluble in ethanol and dichloromethane mixture

Melting point: browns at190-200,chars at225-230,glass transistion at170-180

Functional category:

Used as coating,film forming,rate controlling polymer for sustained release andtablet binder,suspending agent.

Applications:

Hpmc widely used in topical and oral fprmulation.in oral products hpmc is primarily used as tablet binder.conentration between 2-5%w/w used as wet or dry granulation.hpmc used as adhesive in plastic bandages and as wetting agenr for hard contact lenses,it is widely used in cosmetics and food products.

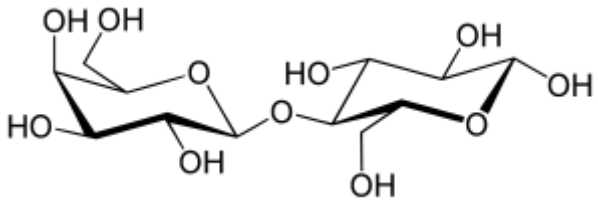
Safety: it is generally regarded as non toxic, nonirritant, so it is widely used in oral and topical pharmaceutical formulation.

Lactose[56]

IUPAC name:beta-d-galactopyranosyl-(1 ⟶ 4)-d-glucose

Other name: milk sugar

Structural name:



Molecular formula : $C_{12}H_{22}O_{11}$

Density **:** 1.525 g/cm^3

Appearance **:** white solid

Melting point **:** 202.8^{0}c

Boiling point **:** 668.9^{0}c

Colour **:** white or off white crystalline powder

Odour : odourless.

Application and safety:

Its bland flavor has lent to its use as a carrier and stabiliser of aromas and pharmaceutical products. Lactose is not added directly too many foods, because it is not sweet and its solubility is less than other sugars commonly used in food. Infant formula is a notable exception where the addition of lactose is necessary to match the composition of human milk.

lactose is not fermented by yeast during brewing, which may be used to advantage.for example, lactose may be used to sweeten stout beer; the resulting beer is usually called a milk stout or a cream stout.

Another major use of lactose is in the pharmaceutical industry. lactose is added to pills as a filler because of its physical properties (i.e., compressibility) and low price. for similar reasons it can be used to dilute heroin.

Polyvinylpyrrolidine [57]

IUPAC name:poly[1-(2-oxo-1-pyrrolidinyl)ethylene]1-ethenyl-2-pyrrolidone homopolymer 1-vinyl-2-pyrrolidone-polymere copovidone.

Molecular formula: $(C_6H_9NO)_n$

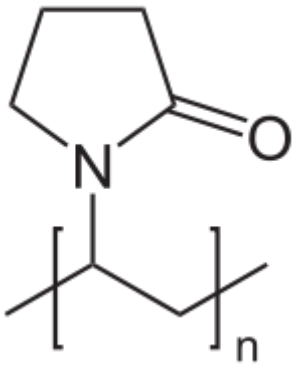
Other name : povidone,polyvidone

Density :1.2 g/cm^3

Appearance : white to light yellow,hygroscopic.

Melting point : 150-180^{0}c

Structural formula:



Properties :

PVP is soluble in water and other polar solvents. When dry it is a light flaky powder, which readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

Application:

It is used as a binder in many pharmaceutical tablets;it simply passes through the body when taken orally. However, autopsies have found that crospovidone does contribute to pulmonary vascular injury in substance abusers who have injected pharmaceutical tablets intended for oral consumption. The long-term effects of crospovidone within the lung are unknown. Pvp added to iodine forms a complex called povidone-iodine that possesses disinfectant properties.this complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs. It is known under the trade name betadine and pyodine.

It is used in pleurodesis (fusion of the pleura because of incessant pleural effusions). For this purpose, povidone iodine is equally effective and safe astalc, and may be preferred because of easy availability and low cost.

Safety:

The U.S. Food and drug administration (fda) has approved this chemical for many uses,and it is generally considered safe. However, there have been documented cases of allergic reactions to pvp/povidone, particularly regarding subcutaneous (applied under the skin) use and situations where the pvp has come in contact with autologous serum (internal blood fluids) and mucous membranes. For example, a boy having an anaphylactic response after application of pvp-iodine for treatment of impetigo was found to be allergic to the pvp component of the solution.a woman, who had previously

experienced urticaria (hives) from various hair products, later found to contain pvp, had an anaphylactic response after povidone-iodine solution was applied internally. She was found to be allergic to pvp. In another case, a man experiencing anaphylaxis after taking acetaminophen tablets orally was found to be allergic to PVP

Titanium-di-oxide [58]

IUPAC name **:** titanium di oxide,titanium oxide.

Molecular formula : TiO_2

Other name **:** Titania.Rutile,Anatase.

Appearance **:** white solid.

Melting point **:** 1843^0c.

Application:

Titanium dioxide is the most widely used white pigment because of its brightness and very high refractive index, in which it is surpassed only by a few other materials. Approximately 4.6 million tons of pigmentary tio_2 are consumed annually worldwide, and this number is expected to increase as consumption continues to rise. when deposited as a thin film, its refractive index and colour make it an excellent reflective optical coating for dielectric mirrors and some gemstones like "mystic fire topaz". Tio_2 is also an effective opacifier in powder form, where it is employed as a pigment to provide whiteness and opacity to products such as paints, coatings, plastics, papers, inks, foods, medicines (i.e. Pills and tablets) as well as most toothpastes. In paint, it is often referred to offhandedly as "the perfect white", "the whitest white", or other similar terms. Opacity is improved by optimal sizing of the titanium dioxide particles.

In ceramic glazes titanium dioxide acts as an opacifier and seeds crystal formation.

Titanium dioxide has been shown statistically to increase skimmed milk's whiteness, increasing skimmed milk's sensory acceptance score.

Safety:

Titanium dioxide is incompatible with strong reducing agents and strong acids. Violent or incandescent reactions occur with molten metal's that are very electropositive, e.g. Aluminium, calcium, magnesium, potassium, sodium, zinc and lithium.

Titanium dioxide accounts for 70% of the total production volume of pigments worldwide. It is widely used to provide whiteness and opacity to products such as paints, plastics, papers, inks, foods, and toothpastes. It is also used in cosmetic and skin care products, and it is present in almost every sunblock, where it helps protect the skin from ultraviolet light.

Many sunscreens use nanoparticle titanium dioxide (along with nanoparticle zinc oxide) which, despite reports of potential health risks, is not actually absorbed through the skin. Other effects of titanium dioxide nanoparticles on human health are not well understood. Nevertheless, allergy to topical application has been confirmed.

Iron oxide red [59]

Molecular formula : Fe_2O_3

Other names : Ferric oxide,Ferric iron,Red iron oxide .

Appearance : Red brown solid

Odour : odourless.

Density : $5.242 g/cm^3$

Melting point : 1566^0c.

Applications:

A very fine powder of ferric oxide is known as "jeweler's rouge", "red rouge", or simply rouge. It is used to put the final polish on metallic jewelry and lenses, and historically as a cosmetic.. Other polishing compounds are also often called "rouge", even when they do not contain iron oxide. Jewelers remove the residual rouge on jewelry by use of ultrasonic cleaning. Products sold asstropping compound are often applied to a leather strop to assist in getting a razor edge on knives, straight razors, or any other edged tool.

Castor oil [60,61]

Castor oil is a vegetable oil obtained from the castor bean (technically castor seed as the castor plant, Ricinus communis (Euphorbiaceae), is not a member of the bean family). The common name "castor oil" probably comes from its use as a replacement for castoreum, a perfume base made from the dried perineal glands of the beaver .

Colour **:** clourless to pale yellow liquid.

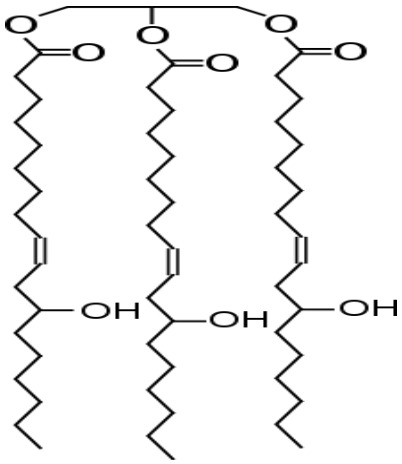
Odour **:** mild odor or odorless

Taste **:** tasteless

Density **:** 961 kg/m^3

Boiling point **:** 313 °C

Structural formula:



Application:

Castor oil used as a laxative with its major site of action the small intestine. Castor oil is a stimulant and lubricating laxative .It is not a preferred treatment, because it can produce painful cramps, fecal incontinence and explosive diarrhea. Its action can go on for hours, sometimes unpredictably and powerfully causing an involuntary bowel movement at inconvenient locations and during sleep.

Undecylenic acid, a castor oil derivative, is also FDA-approved for over-the-counter use on skin disorders or skin problems. Castor isostearate succinate is a polymeric mixture of esters with isostearic acid and succinic acid used for skin conditioning, such as in shampoo, lipstick and lip balm. Ricinoleic acid is the main component of castor oil, and it exerts anti-inflammatory effects. It is believed that the antibacterial properties of the castor oil are mainly due to its high ricinoleic acid content.

Therapeutically, modern drugs are rarely given in a pure chemical state, so most active ingredients are combined with excipients or additives. Castor oil, or a castor oil derivative such as Kolliphor EL (polyethoxylated castor oil, a nonionic surfactant), is added to many modern drugs, including:

- Miconazole, an antifungal agent
- Paclitaxel, a mitotic inhibitor used in cancer chemotherapy;

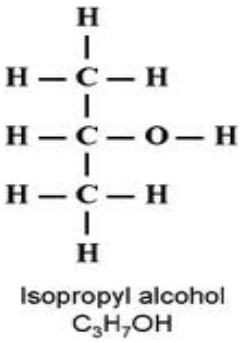
- Sandimmune (cyclosporine injection, USP), an immunosuppressant drug widely used in connection with organ transplant to reduce the activity of the patient's immune system;

Isopropyl alcohol [62]

Isopropyl alcohol is miscible in water, alcohol, ether and chloroform. It will dissolve ethyl cellulose, polyvinyl butyral, many oils, alkaloids, gums and natural resins. It is insoluble in salt solutions.
Unlike ethanol or methanol, isopropyl alcohol can be separated from aqueous solutions by adding a salt such as sodium chloride, sodium sulfate, or any of several other inorganic salts, since the alcohol is much less soluble in saline solutions than in salt-free water. The process is colloquially called salting out, and causes concentrated isopropyl alcohol to separate into a distinct layer.

IUPAC name **:** propane-2-ol

Structural formula :



Other names **:** 2- propanol,isopropanol,isopropyl alcohol.

Molecular formula **:** C_3H_8O

Density **:** 0.786 g/cm^3

Appearance **:** colourles solid

Majority of isopropyl alcohol was used as a solvent for coatings or for industrial processes. Isopropyl alcohol in particular is popular for pharmaceutical applications, presumably due to the low toxicity of any

residues. Some isopropyl alcohol is used as a chemical intermediate. Isopropyl alcohol may be converted to acetone, but the cumene process is more significant. In that year, a tiny fraction (5.4 tonnes) was consumed for household use and in personal care products. It is also used as a gasoline additive

Safety:

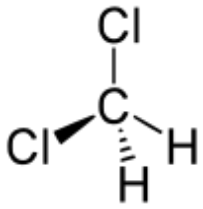
Isopropyl alcohol vapor is denser than air and is flammable with a combustible range between 2 and 12.7% in air. It should be kept away from heat and open flame. Isopropyl alcohol has also been reported to form peroxides, which may explode upon concentration. Isopropyl alcohol is a skin irritant.

Methylene chloride [63]

IUPAC names **:** Dichloromethane.

Other names **:** methylene chloride,methylene di chloride,narkotil,solaesthin.

Structural formula :



Density **:** 1.33 g/cm^3

Appearance **:** colourless liquid.

Melting point **:** -96.7^{0}c

Taste **:** sweet aroma.

Application:

DCM's volatility and ability to dissolve a wide range of organic compounds makes it a useful solvent for many chemical processes. Concerns about its health effects have led to a search for alternatives in many of these applications

- Paint stripping
- Pharmaceutical manufacturing
- Metal cleaning and degreasing
- Paint remover

MATERIAL AND METHODS:

List of materials used

Table:12

S.no	Materials	Source
1	Valsartan	Paxmy speciality chemicals, Mumbai
2	Microcrystalline cellulose	Welming chemicals, india
3	Lactose	S.d.fine-chem.,pvt ltd
4	Crospovidone	Nanhany industrial &co, china
5	Polyvinyl pyrrolidine	Welming chemicals,india
6	Colloidal silicon dioxide	Amaratal &co.,cennai
7	Mannitol	S.d.fine-chem.,pvt ltd Mumbai
8	Magnesium stearate	Loba chemie.,pvt ltd, Mumbai
9	Talc	Loba chemie,.pvt ltd Mumbai
10	Crosscarmellose	S.d. Fine-chemi., pvt ltd Mumbai

List of materials used for film coating

Table: 13

s.no	Materials	Source
1	Hydroxyl propyl methyl cellulose	Loba chemie., pvt ltd,. Mumbai
2	Titanium di oxide	amaratal&co., chennai
3	Castor oil	Tablets pvt ltd., chennai
4	Iron oxide red	Signet chemical ., Chennai
5	Iso propyl alcohol	Loba chemie.,pvt ltd,. Mumbai
6	Methylene chloride	Paxmy speciality chemicals., mumbai

List of equipments used

Table:14

S.no	Equipment	company
1	Electronic balance	Melter Toledo,Mumbai
2	Bulk density apparatus	Electrolab,mumbai
3	Double cone blender	Erweka
4	Rotary tablet punching machine	Rimek., chennai
5	Friability test apparatus	Electrolab., Mumbai
6	Tablet hardness tester	Schleuniger hardness tester.,
7	Digital vernier caliper	Mitutiyo.,japan
8	Stability chamber	Servewell instruments pvt ltd.,banglore
9	UV-visible spectrophotometer	Shimadzu corporation.,japan
10	FTIR	Shimadzu corporation.,japan
11	HPLC	Shimadzu coporation., japan
12	USP dissolution apparatus	Electrolab.,mumbai

Experimental investigation

Market sample details

Product name : Diovan-80mg

Label claim : Each tablet contain 80mg of valsartan

Manufactured by : Novartis pharmaceuticals Pvt ltd .

Description : Pale pink in colour, round flat shaped concave, film coated tablet

Thickness : 4.23mm

Storage : Store at 25 °c, protect from light and

Dissolution apparatus : Paddle type (USP apparatus)

Dissolution medium : Phosphate buffer solution ph-6.8bufer.

Dissolution medium volume : 900 ml

Time points : 10, 20, 30, 45minutes

Speed : 50 rpm

Active Pharmaceutical Ingredient characterization [64]:

Physical appearance:

The Valsartan powder was examined for its organoleptic properties like colour and odour.

Valsartan is white or off white crystalline powder and it is found odour less.

Bulk density:

Active pharmaceutical ingredient valsartan sample powder was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below

Bulk density (ρ_0) = M/Vo

Where, M = mass of the powder

Vo = volume of the powder

Tapped Density:

The valsartan sample was screened through sieve no. 18 and the weight of sample equivalent to 10 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted. The tapped density was calculated in gm/ cm^3 by the formula,

Tapped density (ρ_t) = M/V_f

Where, M = weight of sample powder taken

V_f = tapped volume

Hausner Ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner Ratio = Tapped density / Bulk density

Compressibility index (Carr's index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$\text{Compressibility index} = \frac{100\,(V_0 - V_f)}{V_0}$$

Table No: 15 Compressibility index specifications

% Comp. Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Solubility study:

The valsartan sample was qualitatively tested for its solubility in various solvents. It was determined by taking 10 mg of valsartan drug sample in 10 ml of solvent as water, methanol, ethanol, acetonitrile, pH buffer 6.8 in small test tubes and well solubilized by shaking.

Table-16 Solubility of valsartan:

S.no	Solvent	Solubility
1	Phosphate buffer 6.8	Soluble
2	Methanol	Freely Soluble
3	Ethanol	Freely soluble
4.	Acetonitrile	Soluble

Melting point determination:

The Melting point was determined by the capillary method using Digital Melting point apparatus. The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.

Meting point of valsartan found to be **116°C.**

Calibration for pure drug valsartan:

Preparation of standard stock solution:

Standard drug solution of valsartan was prepared by dissolving 50mg pure valsartan in methanol and transferred into 100ml volumetric flask to obtain 500µg/ml of stock solution from which desired concentrations of solutions were prepared.

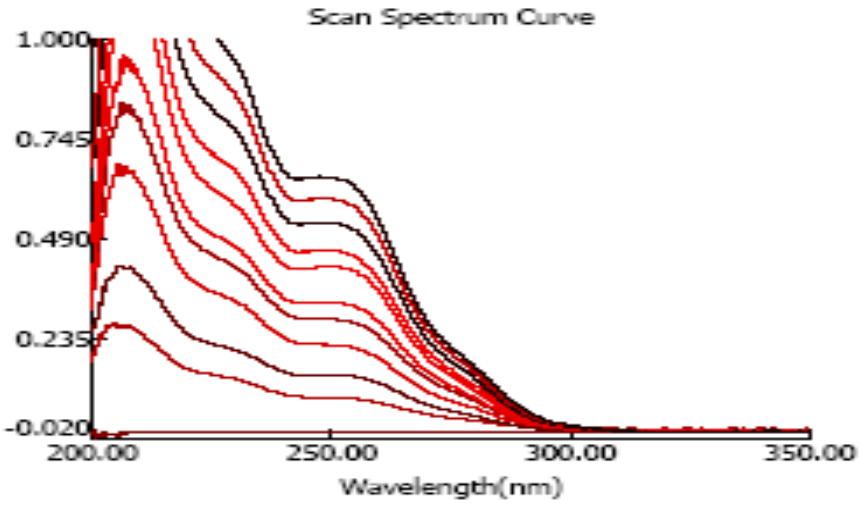
Preparation of test solution:

10 Tablets were weighed and its average weight was determined. An accurately weighed tablet power equivalent to 25 mg of valsartan transferred into 50 ml volumetric flask dissolved in 25 ml of methanol and sonicated for 10 min and volume was made upto the mark and solution was filtered using whattman filter paper to obtain 500µg/ml stock solution .

Determination of λ max:

10 µg/ml solution of valsartan was prepared and scanned in UV range of 200-400nm and spectrum was obtained. The **λ max** was found to be at 250nm wave length where absorbance was maximum at this wavelength. Hence this is considered as absorbance maxima (λ max) shown in fig-2

Fig-2 λ max of valsartan:



Preparation of calibration curve:

Standard stock solution was suitably diluted with methanol to obtain concentrations ranging from 2-20 µg/ml. Absorbance of these solutions was measured at 250nm (λ max valsartan) using UV, calibration curve was obtained by plotting graph between concentration and absorbance shown in **fig-3**

Linearity:

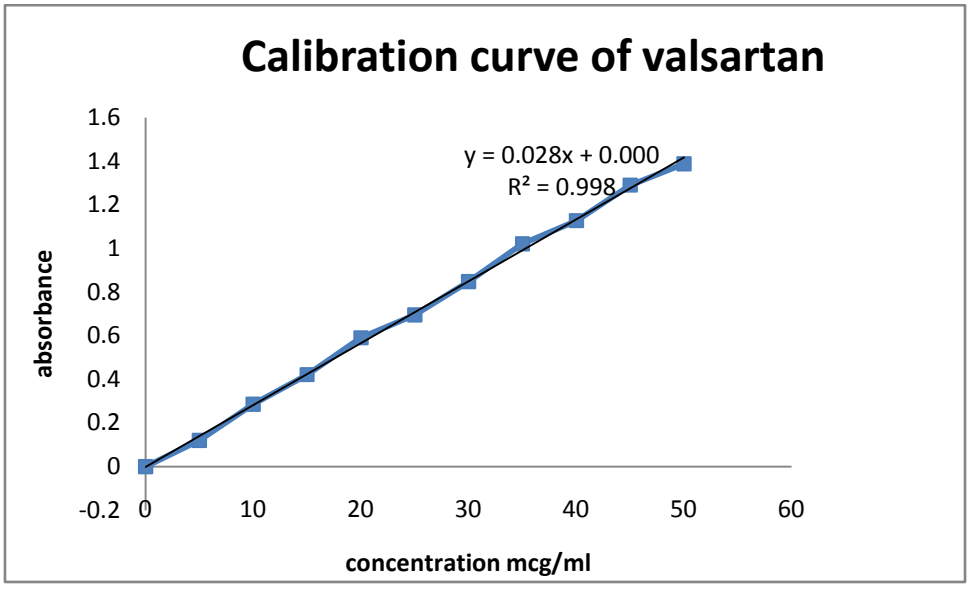
Linearity was obtained between2-20µg/ml concentration. Graph was plotted for concentration and absorbance. The equation of calibration curve obtained was Y=0.028x+0.00. The correlation coefficient (R^2) was 0.998 shown in fig-3

Calibration of valsratan in methanol at250nm

Table:17

S.no	Concentration(µ g/ml)	Absorbance
1	5	0.121
2	10	0.286
3	15	0.422
4	20	0.591
5	25	0.696
6	30	0.849
7	35	1.022
8	40	1.128
9	45	1.291
10	50	1.389

Fig-3 Calibration of valsartan:



Preformulation

Compatibility Studies between drug and excipients :

Fourier Transform Infrared Spectrophotometry (FTIR):

Compatibility study of valsartan with the excipients was determined by I.R. Spectroscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using potassium bromide and the ratio of sample to potassium bromide is 1:100.The pellets thus prepared were examined and the spectra of valsartan and other ingredients in the formulations were recorded in the region of 4000 to 400cm^{-1}. compared with that of the original spectra of valsartan .

TABLE: 18. Composition of valsartan tablets

INGREDIENTS	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8* (mg)**
Valsartan	80	80	80	80	80	80	80	80
Microcrystalline Cellulose	90	88	88	85	88	90	85	85
Lactose	70	70	67	65	70	65	65	65
Mannitol	20	20	20	20	20	20	20	20
Poly vinyl pyrrolidine	3	3	3	3	3	3	3	3
Cross povidone	-	2	5	10	-	-	-	5
Colloidal silicon dioxide	4	4	4	4	4	4	4	4
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5	5
Crosscarmellose	_	-	-	-	2	5	10	5
Total(mg)	275 mg	275 mg	275 mg	275 mg	275 mg	275 mg	275 mg	275 mg

F8*-optimized formulation

Table:19, composition of coating valsartan

S. no	Coating ingredients	Weight For 1000 tablets
1.	Hydroxy propyl methyl cellulose	5gm
2.	Titanium di oxide	1gm
3.	Castor oil	1gm
4.	Iron oxide red	1gm
5.	Iso propyl alcohol	100ml
6.	Methylene chloride	150ml

2. Preparation of powder blend:

Dispensing of materials

All the solid raw materials are dispensed and packed in a individual clean Poly bags and label.

Sifting

Separately valsaratan drug, micrcrystallinecellulose, crosspovidone,mannitol,lactose,colloidal silicon dioxide, polyvinyl pyrrolidine are all passed through 40# mesh and magnesium stearate and talc passed through 60#mesh

Collect all the above sifted materials individually into a double lined poly ethylene bag.

Mixing

Load sifted valsartan drugs, mannitol, microcrystalline cellulose,lactose, polyvinylpyrrolidine, colloidal silicon dioxide, , crospovidone, crosscarmellose into blender and mix for 10 mnutes.

Lubrication

Lubricate the above blend with magnesium stearate and talc blend for 3-5minutes.

Evaluation of Blend characteristics :

Bulk density:

Bleneded drug and excipients sample powder has to be introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below;

Bulk density (ρ_0) = M/Vo

Where, M = mass of the powder

Vo = volume of the powder

Tapped Density:

Blended drug and excipients powder sample has to be screened through sieve no. 18 and the weight of sample equivalent to 10 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted.

The tapped density was calculated in gm/ cm^3 by the formula,

Tapped density (ρ_t) = M/V_f

Where, M = weight of sample powder taken

Vf = tapped volume

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Compressibility index (Carr's indices)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$C_I = 100 \frac{(V_O - V_f)}{V_0}$$

Angle of repose:

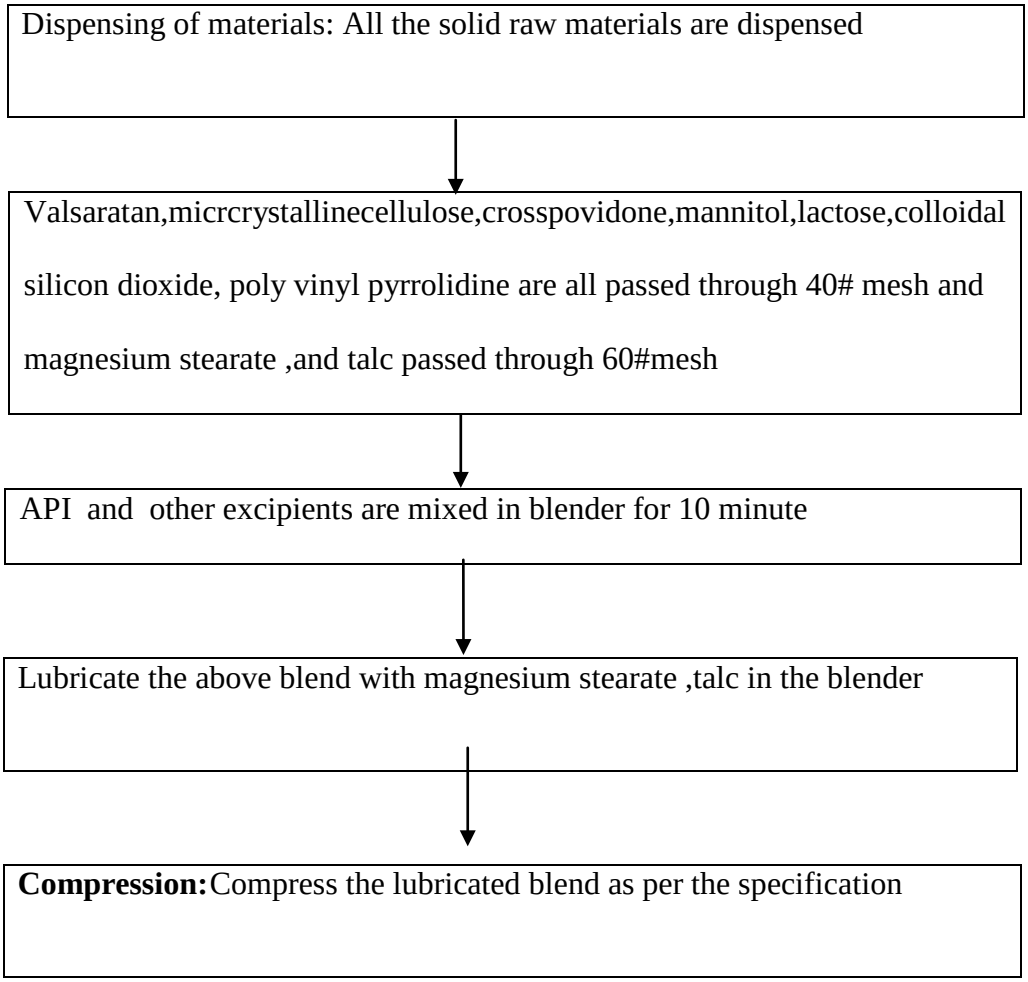
For determination of angle of repose , the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug and the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel.

Angle of repose was calculated using following equation.

Angle of Repose (θ) **= $\tan^{-1}(h/r)$.**

Preparation of tablets:

Fig-4, flow chart for preparation of uncoated tablets



Evaluation of Uncoated tablets:

Physical appearance:

The general appearance of the valsartan uncoated tablet ,its identity and general elegance is essential for consumer acceptance,for control of lot-to- lot uniformity and tablet to tablet uniformity.the control of general appearance involves the measurement as follows

Size and Shape - Round flat faced concave shape

Colour - white

Odour - odour less

taste - tasteless

Weight variation test:

Twenty (20) valsartan uncoated tablets from each batch were individually weighed. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight

Weight Variation limits as per USP and the values were showed in the table-6

The content uniformity approach is preferred over the weight variation approach as it more precisely reflects the variation of the active ingredient from tablet to tablet.

The required specification for this test is that uniformity of dosage unit should be within a range of 85%–115% with a relative standard deviation of less than or equal to 6%.

Friability:

A sample of valsartan uncoated 10 tablets are tested at a time, unless tablet weight is 0.65 g or less, where 20 tablets are tested. After 100 turns, the tablet samples are evaluated by weighing. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test.

Thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliper's.

Hardness testing:

The most widely used apparatus to measure tablet hardness is the Schleuniger apparatus. Generally, the force required to break a valsartan uncoated tablet may be expressed in either kilograms or pounds.

Disintegration test:

The apparatus employs a basket of six tubes with a base of metal sieve. A valsartan uncoated tablet is placed in each tube and is held in place by a plastic weight. The six-tube assembly, containing six valsartan tablets, is suspended using a hanger with a mechanism of vertical motion at a fixed speed of 28-32 cycles/minute. While hanging the six-tube assembly on the hanger, the assembly is moved in vertical motion in water or a buffer solution. The time for disintegration of each tablet is recorded and should meet the required time specification

Assay of valartan [11]:

The valsartan content in each tablet is assayed by HPLC method using X-terra RP-18 column(100 x4.6mm,5µm)by injecting20µL of sample with a flow rate of 2.0mL/min and a run time of 15min at an ambient temperature using a uv detector at273 nm

Preparations:

Mobile phase preparation :

A mixture of 50volumes of water,50 volumes of acetonitrile and 0.1volume of glacial acetic acid.

Reference solution:

0.005% w/v solution of valsartan RS in mobile phase.

Test solution preparation:

Weigh and powder 20tablets.weigh accurately a quantity of powder containing 50mg of valsartan, disperse in 25ml of mobile phase and dilute to 100ml with Mobile phase and filter. dilute 5.0ml of this solution to 50ml with the mobile phase.

Chromatographic system:

A stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica(5µm). Flow rate .1ml per minute, spectrophotometer set at 273nm,injection volume.10µl.Inject the reference solution .the test is not valid unless the tailing factor is not more than2.0 and the relative standard deviation for replicate injections is not more than 2.0percent.inject the test solution and reference solution. Calculate the content of valsartan in tablets.

System suitability:

Chromatograph standard preparations (five relicate injection)measure the peak area responses for the analyte peak evaluate the system suitability parameters as directed.

Acceptance criteria:

%RSD for replicate injection of peak area response of the valsartan peak from the standard preparation should not be more than 2.06

The tailing factor for valsartan peak should be not more than 2.0

The number of theoretical plate for valsartan peak should not be less than 2000

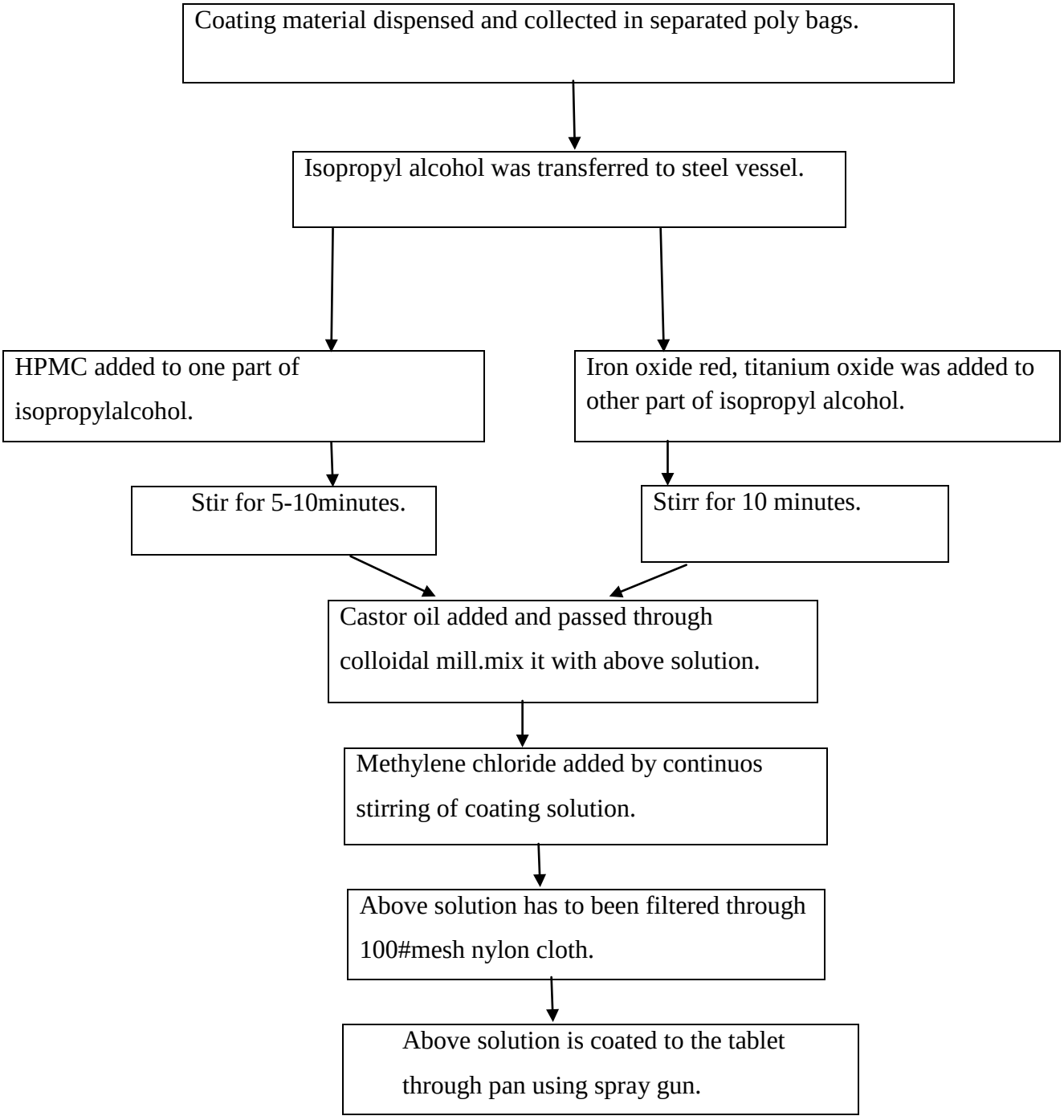
Assay formula:

$$\frac{\text{Sample area}}{} \times \frac{\text{std. weight}}{} \times \frac{1}{} \times \frac{100}{} \times \frac{50}{} \times \frac{\text{std. purity}}{} \times 275.9$$

Std. area	50	100	spl.weight	5	10

Preparation of coating tablets:

Fig :5 flow chart for preparation of coating tablets



Evaluation of Coated tablets:

Physical appearance:

The general appearance of the valsartan coated tablet,its identity and general elegance is essential for consumer acceptance, for control of lot-to- lot uniformity and tablet to tablet uniformity. the control of general appearance involves the measurement as follows

Colour -pale reddish in colour

Odour -odourless

Taste -tasteless

Friability:

A sample of valsartan coated 10 tablets are tested at a time, unless tablet weight is 0.65 g or less, where 20 tablets are tested. After 100 turns, the tablet samples are evaluated by weighing. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test.

No cracked, cleaved, or broken tablets are seen.

Thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliper's. The average thickness and standard deviation were reported in table-

Hardness testing:

The most widely used apparatus to measure tablet hardness is the Schleuniger apparatus.

Generally, the force required to break a valsartan coated tablet may be expressed in either kilograms or pounds

Disintegration test:

The apparatus employs a basket of six tubes with a base of metal sieve. A valsartan tablet is placed in each tube and is held in place by a plastic weight. The six-tube assembly, containing six tablets, is suspended using a hanger with a mechanism of vertical motion at a fixed speed of 28- 32 cycles/minute. While hanging the six-tube assembly on the hanger, the assembly is moved in vertical motion in water or a buffer solution. The time for disintegration of each tablet is recorded and should meet the required time specification

Dissolution of valsartan tablets

Apparatus:

The paddle method (USP Apparatus 2)

Dissolution medium:

Dissolution testing should be carried out under physiological conditions, if possible. This allows interpretation of dissolution data with regard to in-vivo performance of the product. However, strict adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration

To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0.

Standard solution:

50 mg of valsartan drug has been taken and made uto 100 ml with methanol then pipette out 2ml from above solution and make upto 100ml with phosphate buffer pH6.8.

Buffer preparation:

pH-6.8 phosphate buffer is prepared by taking 40.8 gm of potassium dihydrogen phosphate. and 5.376gm of sodium hydroxide was added and made upto 6000ml with water.

Sample preparation:

1.Transfer 900 ml of dissolution media into each dissolution vessel.

2.Weigh six tablets randomly chosen and transfer one tablet into the each dissolution vessel.

3.Withdraw suitable volume of sample from the solution from the above vessel at the sampling time pointsrespectively.

4. Replace aliquots withdrawn for analysis with equal volumes of dissolution medium which is maintained at 37.0 ± 0.5°C.

Formula for dissolution:

$$\frac{\text{sample .absorbence} \times \text{std.weight} \times 2 \times 900 \times 10 \times 98.81(\text{std.purity})}{\text{Std. absorbence} \quad 100 \quad 100 \quad 1 \quad 1 \quad 100}$$

In vitro dissoluton studies:

The dissolution conditions used for invitro drug release.

APPARATUS : USP apparatus II (paddle)

AGITATION SPEED : 50 rpm

MEDIUM : 37.0 ± 0.5°C 6.8 phosphate buffer

VOLUME : 900 ml

TEMPERATURE : 37.0 ± 0.5°C

TIME :10min, 20min,30min,and 45min

Stability data:

The optimized tablets from batch f 7 were charged for stability studies at 40^0c and 75%rh.there was no change in physical appearance , colour. Optimized formulation were analyzed at the end of 3 months for general tablet properties like hardness, friability, disintegration and dissolution studies. Tables have shown that there is no much deviation in friability and hardness values. And in vitro dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablet at the end of 3months.

RESULT AND DISCUSSION:

Table-20 Active Pharmaceutical Ingredient Characterization:

Ingredient	Buk density(gm/cm^3)	Tapped density(gm/cm^3)	Angle of repose	Compressibility index%	Hausner's ratio
Valsartan	0.31	0.34	19.2	8.82%	1.09

Inference: Result indicates bulk density, tapped density , angle of repose, compressibility index, hausner's ratio for API is found within the limits.

Preformulation studies:

Compatibility Studies between drug and excipients:

Fig-6 FTIR spectrum of valsartan

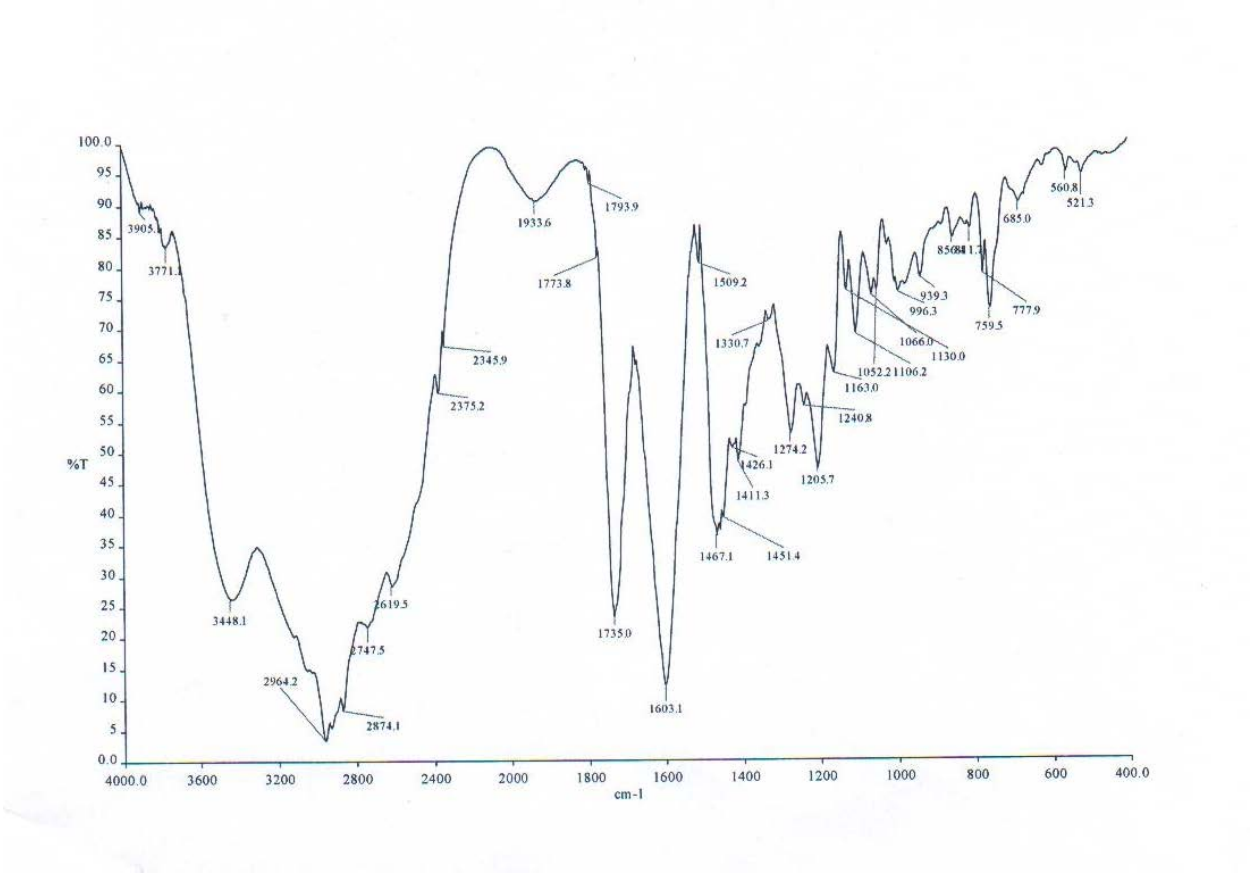


Fig-7 FTIR spectrum of valsartan & excipients

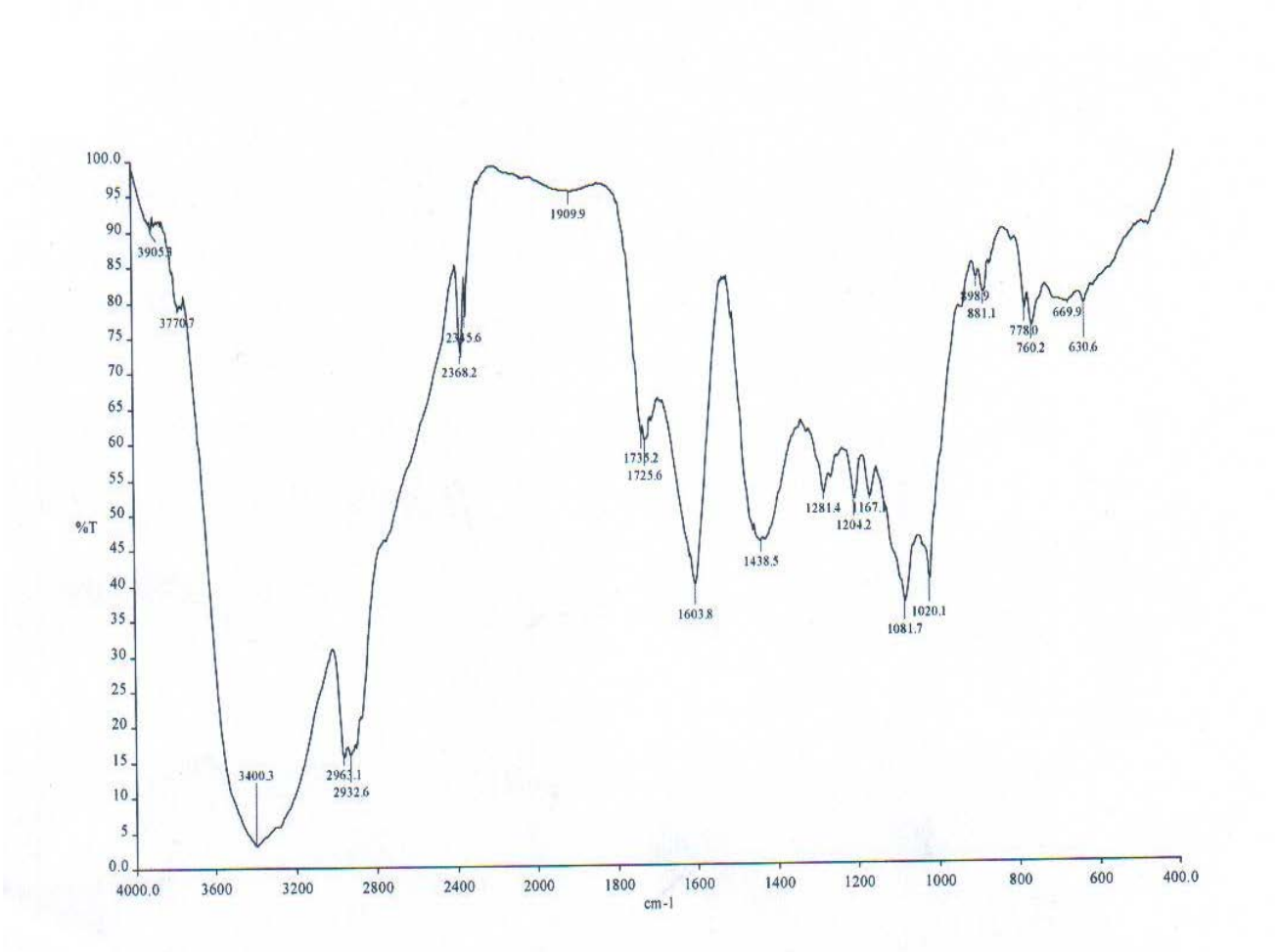


Table: 21 Interpretation of FTIR spectrum of valsartan (fig-6)

S.NO	WAVENUMBER(cm^{-1})	VIBRATIONS
1.	3448.1	CH- stretching (aliphatic)
2.	2964.2	Aromatic.CH- streching
3.	759.5	Aromatic.CH-bending
4.	1426.1	N=N. streching
5.	1735.0	C=O. stretching (ke stretching(ketone)
6.	1274.2	O-H bending(aromatic)

Table: 22 Interpretation of FTIR spectrum of valsartan & excipients (fig-7)

S.NO	WAVENUMBER(cm^{-1})	VIBRATIONS
1.	3400.30	CH- stretching (aliphatic)
2.	2963.1	CH- stretching (aromatic)
3.	778.0	CH-bending(aromatic)
4.	1438.5	N=N streching
5.	1725.6	C=O stretching (ketone)
6.	1281.4	O-H bending (alcohol)

Inference: Results indicates that there is no extra peak found in the sample (drug and excipients) when compared with pure drug spectrum.

Evaluation of Blends:

Table: 23

S.No	Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of repose	Compressibility Index(%)	Hausners ratio
1.	F-1	0.482	0.576	33.4	15.78	1.19
2.	F-2	0.357	0.419	31.6	14.63	1.11
3.	F-3	0.605	0.710	29.3	15.49	1.18
4.	F-4	0.584	0.685	31.9	14.71	1.17
5.	F-5	0.354	0.418	32.1	14.63	1.16
6.	F-6	0.434	0.507	30.5	13.66	1.15
8.	F-7	0.452	0.527	31.5	14.25	1.16
7.	F-8	0.465	0.538	29.1	13.52	1.15

Inference: Result indicates that Bulk density, tapped density , angle of repose, compressibility index, hausner's ratio of powder blend is found within the limits.

Evaluation of uncoated tablets:

Table-24 physiochemical properties of uncoated tablet

S.No	Formulations	Thickness (mm)	Hardness Kg/cm^2	Disintegration Time(mins)	Friability (%)	Assay %
1.	F-1	4.18	7.8	13min 12 sec	0.14	93.2
2.	F-2	4.15	6.2	8 min 40 sec	0.12	93.6
3.	F-3	4.13	7.5	7 min 17 sec	0.16	98.2
4.	F-4	4.21	5.5	4 min 52 sec	0.08	96.5
5.	F- 5	4.16	6.0	7 min25 sec	0.18	94.8
6.	F-6	4.22	5.4	5 min 56sec	0.09	97.1
7.	F-7	4.19	4.5	3 min 23 sec	0.15	98.8
8.	F-8	4.32	4.6	2 min32 sec	0.12	96.9

Table-25, Weight variation:

	F1	F2	F3	F4	F5	F6	F7	F8
AVG WT(20 TAB)	275.35	270.49	278.87	268.06	283.80	272.15	277.82	275.66
% max positive deviation	+2.89	+1.98	+2.5	+1.62	+2.42	+2.63	+1.98	+2.14
% min negative deviation	-2.13	-2.56	-1.89	-1.56	-2.63	-2.96	-1.68	-2.21

Inference: Result Indicates thickness, hardness, friability, disintegration, weight variation , assay are within the pharmacopeial limits.

Evaluation of Film Coated Tablets:

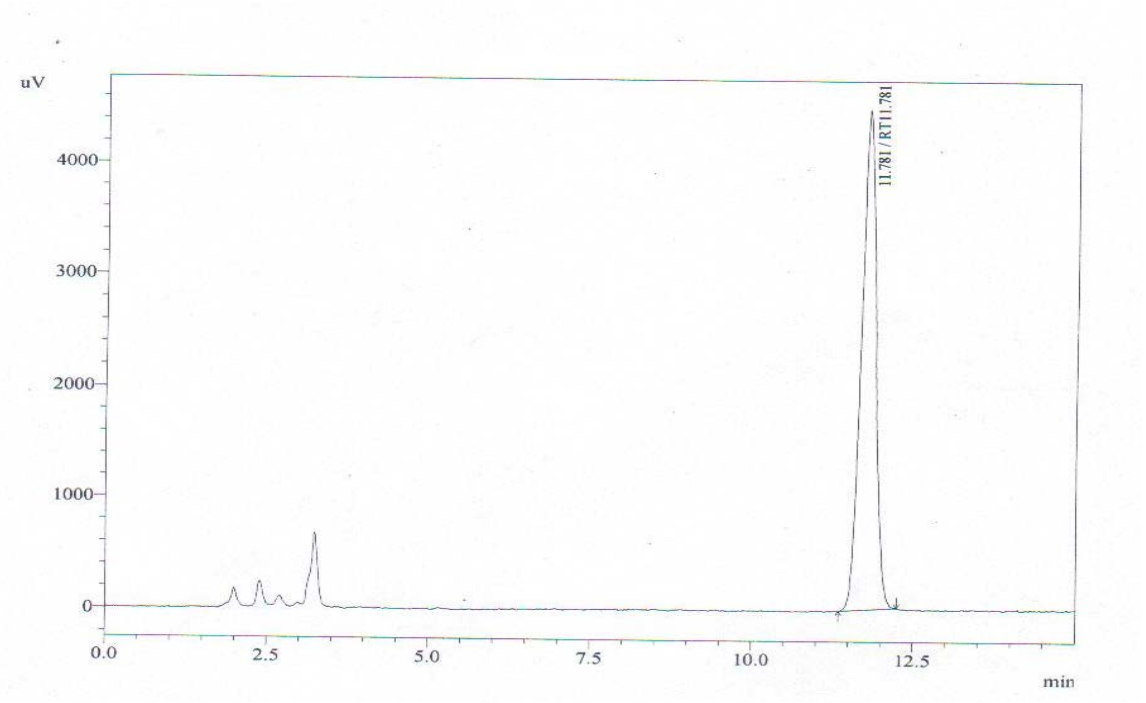
Table:26 phsiochemical properties of film coated tablets.

S.No	Formulations	Thickness (mm)	Hardness Kg/cm^2	Disintegration Time(mins)	Friability (%)	Assay %
1.	F-1	4.28	7.8	13 min 42 sec	0.14	93.2
2.	F-2	4.21	6.5	10 min 58sec	0.10	93.6
3.	F-3	4.24	7.5	8 min 37 sec	0.16	98.4
4.	F-4	4.40	5.8	7 min 8 sec	0.08	96.5
5.	F- 5	4.23	6.0	9 min47 sec	0.18	94.8
6.	F-6	4.42	5.4	8 min 15 sec	0.09	97.1
7.	F-7	4.25	4.5	5 min 28 sec	0.15	98.7
8.	F-8	4.32	4.8	2 min 41 sec	0.15	96.9
9.	Marketed product	4.23	4.7	3 min 12sec	0.12	94.4

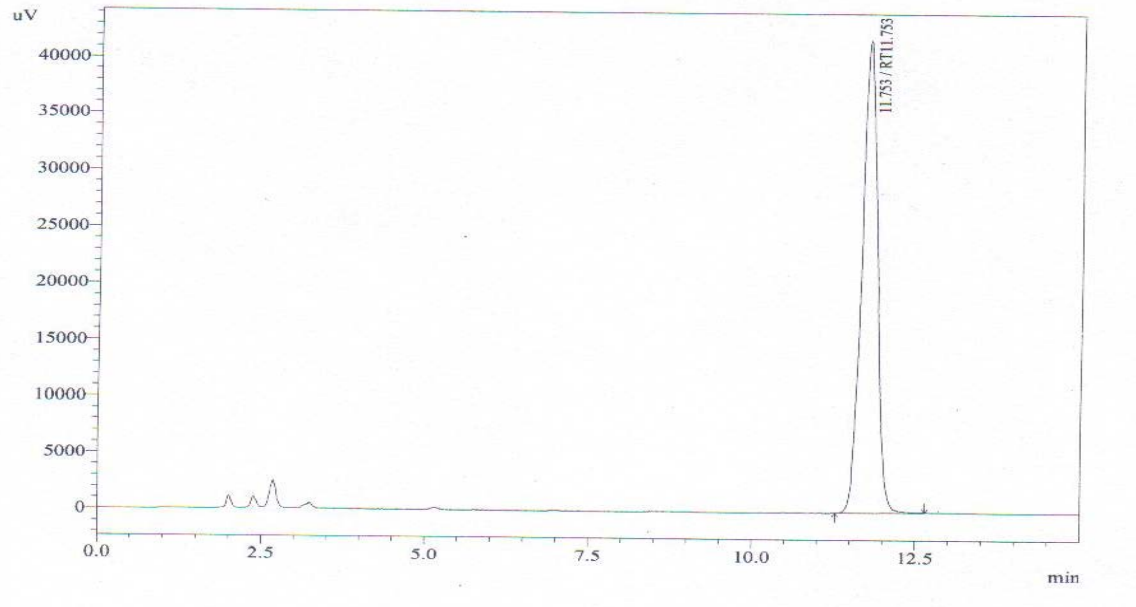
Inference: Result indicates thickness, hardness, friability, disintegration , assay of valsartan tablet is found to be within the limit.

Assay: typical chromatogram of valsartan

1.Fig-8 chromatogram of pure valsartan drug



2. Fig-9 chromatogram of sample valsartan:



In-vitro dissolution studies:

The dissolution conditions used for in vitro drug release ..

APPARATUS : USP apparatus II (paddle type)

AGITATION SPEED : 50 rpm

MEDIUM : pH 6.8 phosphate buffer

VOLUME : 900ml

TEMPERATURE : 37.0 ± 0.5°C

TIME : 10min, 20min, 30min and 45min

Results of dissolution profile:

Table: 27 Invitro dissolution profile of all the formulation

S.No	Time (min)	F1 %	F2 %	F3 %	F4 %	F5 %	F6 %	F7 %	F8 %	Market Sample
1.	10	32.18	48.28	52.5	65.72	53.03	61.53	70.23	76.62	72.12
2.	20	48.32	61.67	69.92	76.83	68.46	74.15	81.66	84.03	80.96
3.	30	59.51	72.14	79.64	84.36	76.22	82.41	86.77	90.56	86.74
4.	45	68.77	80.50	83.98	86.6	82.87	86.26	88.43	96.74	90.56

Inference: Result indicates formulation 8 showed good drug release profile. when compared with the marketed product .

Invitro dissolution studies:

Fig-10 Invitro dissolution profile of formulation (F1):

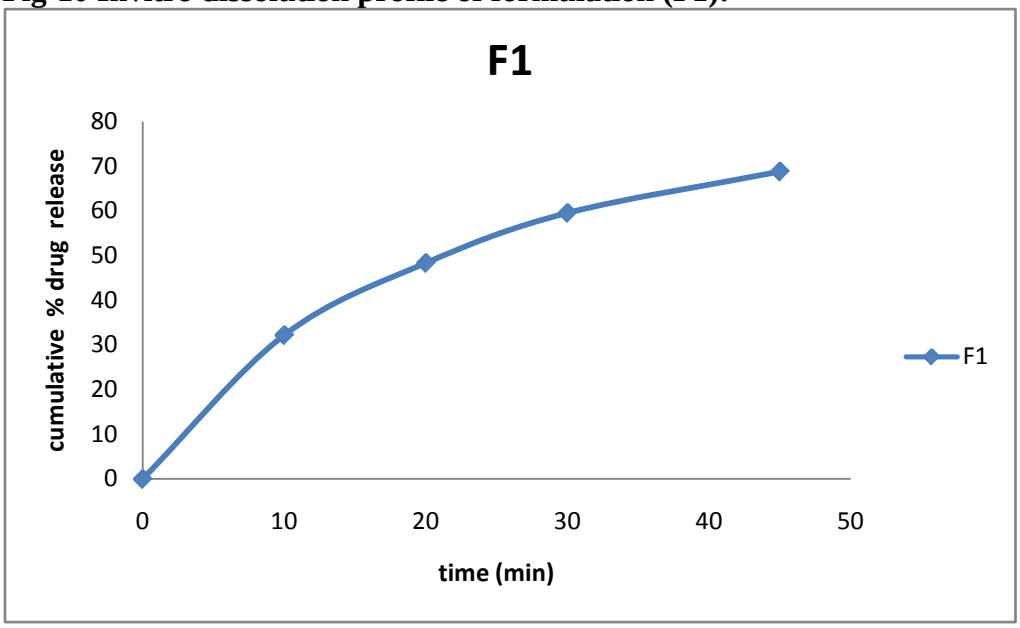


Fig-11, Invitro dissolution profile of formulation (F2-F4)

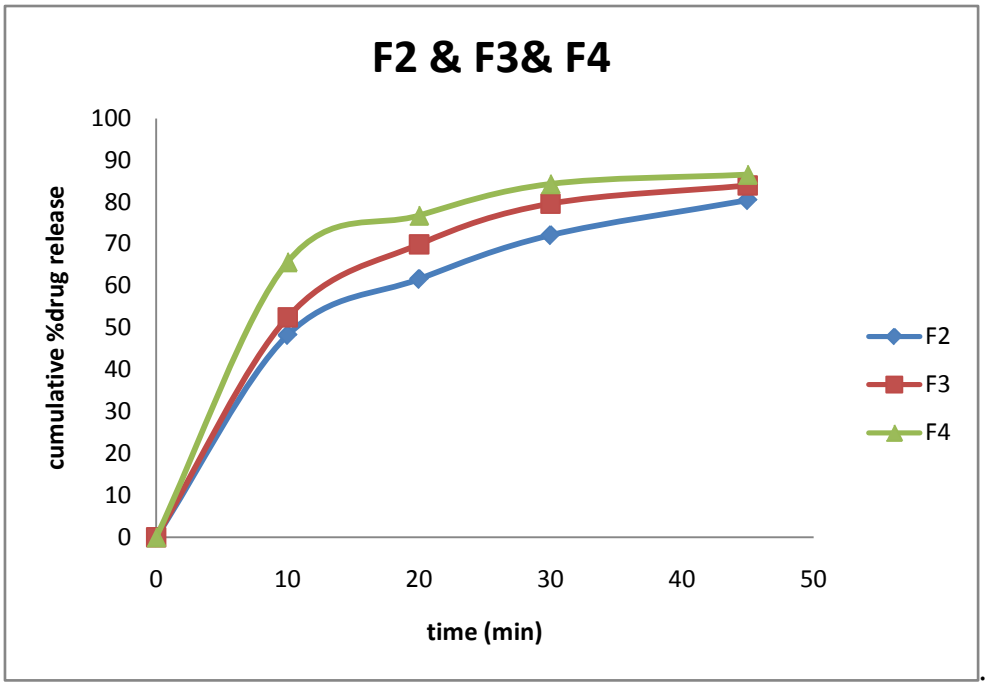


Fig-12 Invitro dissolution profile of formulation (F5-F7)

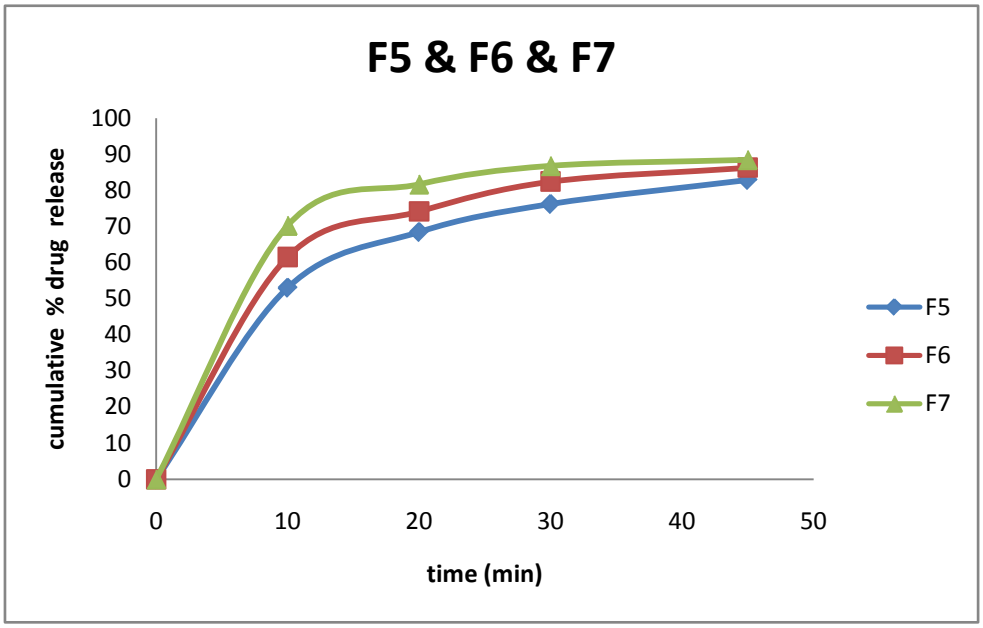


Fig-13 Invitro dissolution profile of formulation (F8)

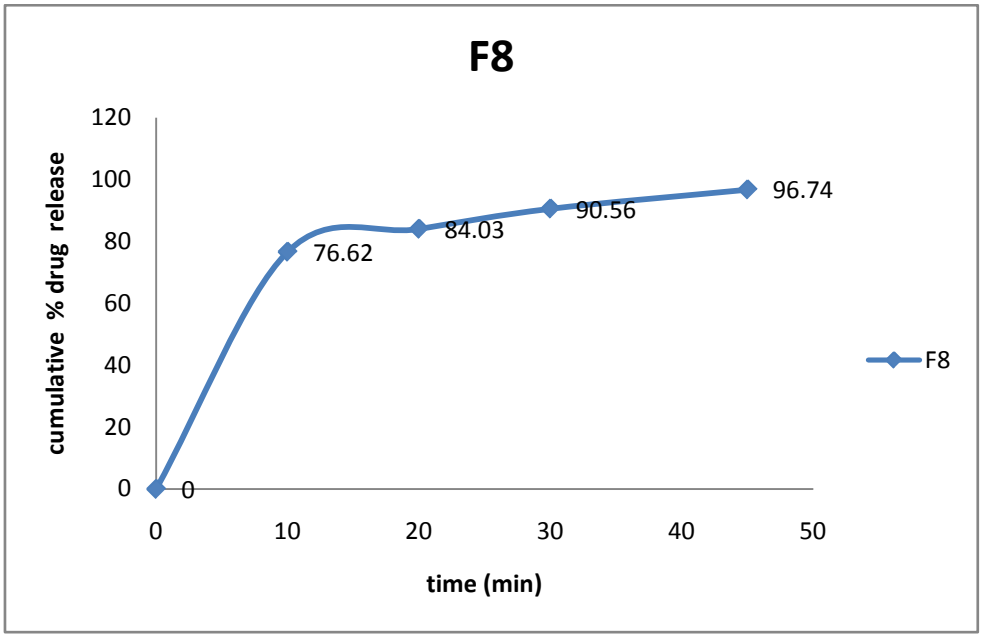
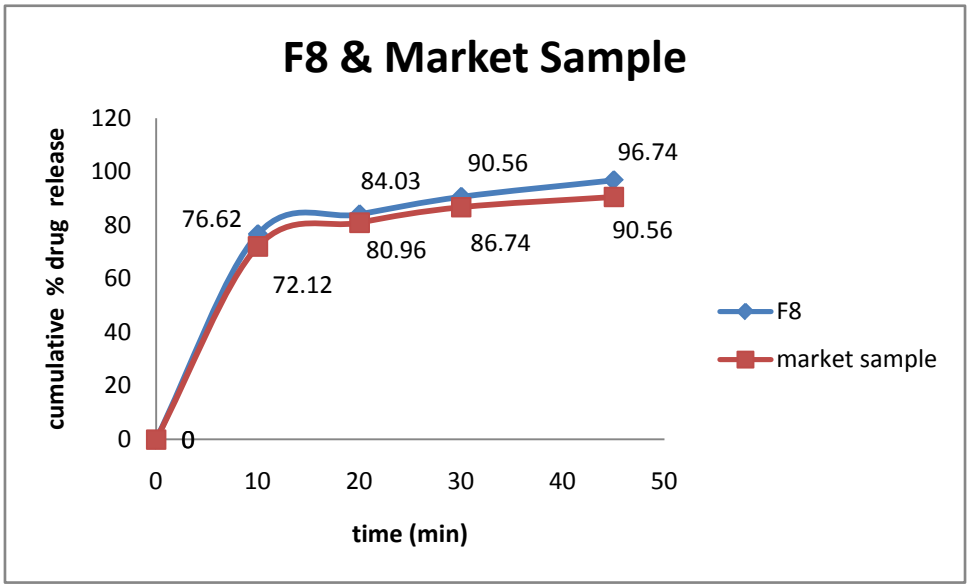


Fig-14 Invitro dissolution profile comparison between formulation (F8) and marketed product



Inference:

- Invitro dissolution release of all the formulation were showed in **fig:10-14**
- The formulation 8 showed best fit of dissolution profile when compared with marketed product.
- Formulation 1,showed very low drug release due to absence of disintegrant in the formulation.
- The drug release was increased in formulation F2, F3, F4 due to addition of superdisintegrant crospovidone in the formulation. But the release profile was not matched with marketed product .
- The drug release was increased in the formulation F5, F6, F7 due to addition of superdisintegrant crosscarmellose in the formulation .but the drug release was not fit with marketed product.
- So the formulation F8 consist of combination of superdisintegrant crospovidone and croscarmellose , showed best match release profile with marketed product.The result attributed that , they wetting and swelling property was significantly increased in combination of super disintegration.

Stability studies:

Table: 28 Accelerated stability studies for 3 months: 40^0c and 75%RH

Characteristics	**Initial**	**1st month**	**2nd month**	**3rd month**
Hardness	4.6	4.6	4.6	4.6
%friability	0.15	0.15	0.15	0.15
Disintegration	2min32 sec	2 min 37sec	2min 41sec	2 min 4 sec
Assay (LIMIT-90-110%)	98.8%	96.5%	95.9%	93.2%
Dissolution(NLT 70%)	96.23%	94.68%	93.93%	93.21%
Moisture content (NMT-5.0%)	1.826%	1.953%	1.987%	2.028%
Description (pale reddish colour,round shaped concave film coated tablet)	Comply	Comply	Comply	Comply

Inference: Stability studies for the optimized tablets were carried out at $40^0C \pm 2^0C$, 75%±5%RH for a period of three months .Tablets were evaluated for physical appearance , colour, hardness, friability, disintegration and dissolution studies. Tablets have not shown any significant changes during the study period .

Conclusion:

The valsartan film coated tablets have been developed with direct compression method and it was compared with that of marketed product. The powder blend were subject to various physical characteristics tests such as bulk density, tapped density, Hausners ratio, compressibility index and core tablets were evaluated for weight variation, hardness, thickness, disintegration time and the results were within specification. In-vitro dissolution profile of developed formula was compared with marketed product and drug release profile of formula 8 was found to be matched with marketed product. The combination of superdisintegrants, crosscarmellose and cropovidone was shown faster disintegration rate. The optimized batch tablets were packed in HDPE bottle and performed stability studies at 40°C/75%RH. Stability samples were evaluated initially and upto three months. All the results were found to be satisfactory. Hence the designed and developed formula was stable. Valsartan film coated tablet developed in the present work was found to be pharmaceutically equivalent to marketed product.

Reference:

1. Dr. Sahoo P.K. Pharmaceutical Technology, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi: Pg no 1-3
2. Lachman L, Liberman HA, Schwartz JB. Pharmaceutical dosage forms Tablet. (3):225-39.
3. James Swarbrick, Encyclopedia of Pharmaceutical Technololgy, Volume 2, Third edition, Informa healthcare,2007:1242,1248,3707-3709.
4. Syed,Azeem.,Shaweta ,Sharma., 2011. 'Immediate release drug deliverysystems.' Int. J. Biopharm. Toxicolg. R., 1(1): 24-46
5. Shangraw RF, Mitrevej A, Shah M. 1980 . "A new era of tablet disintegrates. Pharm. Technol".; 4(10):49-57
6. http://www.pharmapedia.com/
7. Gilbert S.Banker Christopher T.Rhodes, Modern Pharmaceutics, 2nd edition, 1990: pg.402-405, 416 & 417
8. Aulton M.E, Pharmaceutics, The science of dosage form design, 2nd edition:398 & 404-409
9. Rawlins EA. Tablets and Capsules. In: Bentleys. Text book of pharmaceutics. New Delhi: All India Traveller Publishers; 2006; pp 234-310
10. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Ed 3. New Delhi: CBS publishers and distributors; 2009; pp 171-196, 293-345.
11. Indian pharmacopeia vol:3(2010)pp:170,454,2287
12. Chowhan ZT, Chi LH. Drug–excipient interactions resulting from powder mixing III: solid state properties and their effect on drug dissolution. J Pharm Sci 1986; 75: 534–541.

13. Chowhan ZT, Chi LH. Drug–excipient interactions resulting from powder mixing IV: role of lubricants and their effect on in vitro dissolution. J Pharm Sci 1986; 75: 542–545.

14. Martin's, P.S.Patrick, Physical Pharmacy, 5th edition, 2006,337-353.

15. Tobiska S, peter K,coating uniformity and coating efficiency in a bohle lab coater using oval tablets.Eur J Biopharm2003;56(1):3-9

16. Abhay Gupta, Robert L. Hunt, Rakhi B. Shah, Vilayat A. Sayeed and Mansoor A. Khan. Disintegration of Highly Soluble Immediate Release Tablets: A Surrogate for Dissolution,APSPharmSciTech, 2009; 10(2):495-499.

17. Sabah Souliman, Stéphanie Blanquet, Eric Beyssac, Jean-Michel Cardot.A level a in vitro/in vivo correlation in fasted and fed states using different methods: Applied to solid immediate release oral dosage form ,European Journal of Pharmaceutical Sciences, 2006;27(1):72-79.

18. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011 Feb;42:517-84.

19. Kaplan NM. Systemic hypertension: Treatment. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia, Pa: Saunders Elsevier; 2011:chap 46.

20. http://www.searo.who.int/linkfiles/non_communicable_diseases_hypertension-fs.pdf

21. Mancia G, Grassi G. Improving the management of hypertension reconsidering efficacy assessment. Medicographia. 2010; 32(3):221-329

22. Kannan K, ramya krishna, manikandan M., selvamuthukumar S., manavalan R.. Development and evaluation of valsartan film coated tablets . Journal of pharmaceutical sciene and research vol.4(6), 2012, 1866 - 1871

23. http://www.readperiodicals.com.

24. Richa Sood , MS Rathore, Anil Sharma, Richa Thakur, Jayesh Chaudhari, Vijay Soni2 Immediate Release Antihypertensive Valsartan oral tablet Journal of Scientific Research in Pharmacy 2012 vol-5;(4).

25. Pradeep kumar T, chandra S, sivakumar N.R, kanthal S.Kjayasekar R.S.formulation and evaluation of film coated ticlopidine hydrochloride immediate release tablets. international journal of pharmacy(2012)3(5)pp-324-329.

26. Rajesh M, kamarapu nagaraju and seyed mohamed buhary S.H. formulation and evaluation of clarithromycin immediate release film Coated tablets, International Journal of Pharmacy and Pharmaceutical Sciences2012 vol-4;(5)pp-154-158

27. Satyam Pandey, Int. J. of Pharm. & Life Sci. (IJPLS), Vol. 2, Issue 7-Suppl: July: 2011, 963-969.

28. Nataraj K.S., Ramakrishnama Charya S.V , Swathi Goud E., Saigeethika S. And Ramanjineyulu K . simple quantitative method development and validation of valsartan in pureform and pharmaceutical dosage forms by uv –spectroscopy. International Journal of Pharmacy and Biological Sciences .vol:1 ,223 229.

29. Soumya M., Saritha M, Preparation And Optimisation Of Valsartan Bilayered Sustained Release Matrix Tablets, International Journal of Pharmaceutical & Biological Archives, 2011; 2(3):914-920.

30. Srinivas D, Subal Debnath, S.Y. Manjunath , Chowdary T.R.S, Formulation and evaluation of Valsartan film coated tablets Journal of Chemical and Pharmaceutical Research J. Chem. Pharm. Res., 2010, 2(5):534-540.

31. Nasiruddin Ahmad Farooqui, A.Anton Smith, H.K.Sharma and R.Manavalan. Formulation and Evaluatio of Secnidazole Film Coated Tablets. Journal of Pharmaceutical Science and Technology Vol. 3 (2), 2011, 555-558.

32. Abbaspour MR, Jalali, Sharif Makhmalzadeh , Study of free films and coated tablets based on HPMC and Microcrystalline cellulose aimed to improve the stability of moisture sensitive drugs Jundishapur Journal of Natural Pharmaceutical Products 2010; 5(1): 6- 17

33. Bhatia M. Sudesh and Kokil S, Uttamrao Saishravan, determination and validation of valsartan and its degradation products by isocratic HPLC .journal of chemical methodology,2010.vol3(1),1-12.

34. Jain C. P , and naruka P.S. International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 1, Issue 1, July-Sep. 2009

35. Agnivesh R. Shrivastava, Bhalchandra Ursekar and Chhanda J. Kapadia Design, Optimization, Preparation and Evaluation of Dispersion Granules of Valsartan and Formulation into Tablets.Current Drug Delivery, 2009, 6, 28-37

36. Navin Sheth , Sunny Shah, Arti Potdar and Anand Shah. Studies in Optimization of Aqueous Film Coating Parameters. International Journal of Pharmaceutical Sciences and Nanotechnology, , October – December 2009, Volume 2, Issue 3.

37. Praveen S, Hiremath, Rajendra NS. Controlled release hydrophilic matrix tablet formulations of isoniazid:Design and in-vitro studies. Aaps Pharm Sci Tech. 2008;9(4):1171-8.

38. Saishravan K ,_Satyanarayana T ,Belsen David J , YalakarajulaBhagath Singh . formulation and evaluatio of valsartan film coated tablets.journal of pharmaceutcal science and technology.2008,5(2).

39. Bhalekar M R,Lakade S H,. Formulation and evaluation of sustained release matrix tablet of anti-anginal drug, influence of combination of hydrophobic and hydrophilic matrix former. Research Journal of Pharmacy and Technology. 2008;1(4):410-13.

40. Setty C.M,prasad d,gupta V,development of fast dispersible aceclofenac tablet;effect of functionality of super disintegrants : ind J pharm sci 2008;70(2)180-185

41. Babu P, ramu A, sasidhar R, vidhyadhara. enhancement of dissolution ratepiroxicam by solid dispersion using new carrier .the pharma review 2007;1(3);163-66

42. Biraju Patel ,Priyal R "Development and invitro Evaluation of fast dissolving tablets of Glipizide".Int J Pharmacy and Pharm Sci. ,2001 1(1): 145-49

43. Bader M. Renin-angiotensin-aldosterone system. In S. Offermanns, & W. Rosenthal (Eds.). Encyclopedic reference of molecular pharmacology (pp. 810-814) (2004).

44. http://www.drugbank.com,rl:www.drug bank.ca/drugs/valsartan.com

45. http://www.chemicalland21.com/drug/valsartan.com

46. Mannitol. Paul.J.Sheskey and Sian.C.Owen, Raymond.C.Owen. Hand Book of pharmaceutical Excipients 6theditonpp:424-427

47. Steele.G- Pre-formulation as an aid to product design in early drug development. In Gibson M, editor, pharmaceutical pre-formulation and formulation: A practical guide from candidate drug selection to commercial dosage for: CRC press. P-175.

48. Lerk CF, Bolhuis GK, Smallenbroek AJ, Zuurman K. Interaction of tablet disintegrants and magnesium stearate during mixing II:effect on dissolution rate. Pharm Acta Helv 1982; 57: 282–286

49. Levy G, Gumtow RH. Effect of certain formulation factors on dissolution rate of the active ingredient III: tablet lubricants.J Pharm Sci 1963; 52: 1139–1144

50. Cellulose, Microcrystalline Paul.J.sheskey and Sian.C.Owen, Raymond.C.Owen. Hand Book of pharmaceutical excipients pp: 486-493

51. Croscarmellose .Raymond CR,Paul S,and Sian CO.owen Hand book of pharmaceutical Excipients 6th edition American Pharmacists association , printed in royal pharmaceutical press.2006,pp.206-208

52. Colloidal Silicon dioxide. R.C.Rowe, P.J.Sheskey, M.E.Quinn Hand Book of Pharmaceutical excipient. 6thed. London: Pharmaceutical presspp:185-188

53. Crospovidone.Raymond CR,Paul S,and Sian CO. Hand book of pharmaceutical Excipients 6th edition American Pharmacists association , printed in royal pharmaceutical press.2006,pp.208,209,210

54. Siepman J and peppas NA.modeling of drug release and delivery systems,based on HPMC.adv.drug deliv rev2001;48:139-157.

55. Hypromellose.Raymond CR,PaulJS,and Sian CO. Hand book of pharmaceutical Excipients 6th edition American Pharmacists association , printed in royal pharmaceutical press.2006,pp.326-328

56. Linko, P (1982), "Lactose and Lactitol", in Birch, G.G. & Parker, K.J, Nutritive Sweeteners, London & New Jersey: Applied Science Publishers, pp. 109–132

57. Bühler, Volker (2005). Excipients for Pharmaceuticals - Povidone, Crospovidone and Copovidone. Berlin, Heidelberg, New York: Springer. pp. 1–254

58. Phillips, Lance G. and Barbano, David M.. "The Influence of Fat Substitutes Based on Protein and Titanium Dioxide on the Sensory Properties of Lowfat Milk". Journal of Dairy Science 80(11): 2726

59. Catherine E. Housecroft; Alan G. Sharpe (2008). "Chapter 22: d-block metal chemistry: the first row elements". Inorganic Chemistry, 3rd Edition. Pearson. p. 716

60. Use of castor oil in pregnancies at term. Garry D. Figueroa R. Guillaume J. Cucco V. Alternative Therapies in Health & Medicine. 6(1):77-9, 2000 Jan

61. Castor oil.Raymond CR,PaulJS,and Sian CO. Hand book of pharmaceutical Excipients 5th edition American Pharmacists association , printed in royal pharmaceutical press.2006,pp.126,127,128

62. Logsden, John E.; Loke, Richard A (1999). "Propyl Alcohols". In Jacqueline I., Kroschwitz.Kirk-Othmer Concise Encylclopedia of Chemical Technology, (4th ed.). New York: John Wiley & Sons, Inc.. pp. 1654–1656

63. Remington Pharmaceutical Sciences, 28th edition, pg.860-870.

64. Cooper, J., Gunn, C., “Powder flow and compaction”, In: Carter SJ, eds. Tutorial Pharmacy. CBS Publishers and Distributors, New Delhi, India 1986, pp.211-233.