DEVELOPMENT AND EVALUATION OF MULTI-LAYER CONTROLLED RELEASE TABLET OF PENTOXIFYLLINE

A Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY,

Chennai-600 032

In partial fulfilment for the requirements for the award of the Degree of

MASTER IN PHARMACY

IN

BRANCH - I - PHARMACEUTICS

Submitted by

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THE CERTIFICATE

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DECLARATION

I hereby declare that the dissertation work entitled "**DEVELOPMENT AND EVALUATION OF MULTI-LAYER CONTROLLED RELEASE TABLET OF PENTOXIFYLLINE"** has been originally carried out by me under the guidance and supervision of **Dr. R. KUMARAVEL RAJAN, M. Pharm., Ph.D., Professor, Department of Pharmaceutics,** C.L. Baid Metha College of Pharmacy, and **Mr. P. MAHENDRAN, M.Pharm., Manager, Kausikh Therapeutics (P) Ltd,** Gerugambakam, Chennai – 600 128 during the academic year 2019-2021. This work has not been submitted in any other degree at any other university and that all the sources we have used or quoted have been indicated and acknowledged by complete reference.

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CONTENTS

LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
USP	United States Pharmacopoeia
CR	Controlled Release
ER	Extended Release
BCS	Biopharmaceutical Classification System
HEC	Hydroxyethyl Cellulose
HPMC	Hydroxy Propyl Methyl Cellulose
IPA	Isopropyl Alcohol
HCL	Hydrochloric Acid
MCC	Microcrystalline Cellulose
FTIR	Fourier Transform Infrared Spectroscopy
PEG	Poly Ethylene Glycol
MEC	Minimum Effective Concentration
HPLC	High Performance Liquid Chromatography
BP	British Pharmacopoeia
JP	Japanese Pharmacopoeia
Ph.Eur	European Pharmacopoeia
UV	Ultra Violet
ICH	International Conference On Harmonization
NMT	Not more than
NLT	Not less than

RT	Room temperature
AUC	Area under curve
V_d	Volume of distribution
SD	Standard deviation
Fig	Figure
Avg. wt	Average weight
%	Percentage
Conc	Concentration
hr	Hour
Rpm	revolution per minute
w/w	weight/weight
Kg/cm^2	Kilogram/square centimeter
µg/ml	microgram / milliliter
Sec	Seconds
g/ml	gram / milliliter
nm	Nanometer
mm	Millimeter

1. INTRODUCTION

Controlled release drug delivery systems are developed to moderate the drug release characteristics to achieve specific goals that cannot be accomplished with conventional drug delivery systems. Potential therapeutic benefits of an appropriately designed ER dosage form include improved efficacy, reduced adverse effects, low cost, flexible release characteristics, increased convenience and patient compliance. Pentoxifylline is a vasodilators (Hemorrheologic agent). It works by helping blood flow more easily through narrow arteries.

Over the past 30 years, as the expenses and complications involved in marketing a new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has focused on development of sustained or controlled release drug delivery systems.

The goal of designing sustained or controlled drug delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.[1]

1.1 Oral drug delivery:[2]

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

For the past decades, there has been enhanced demand for patient compliance dosage forms. As a result the demand for the technologies has been increased three fold annually. Since the development cost of new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.

Oral drug delivery is the most desirable and preferred method of administering 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 acceptance and convenience in administration. It has 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 difficult to solve.

1.2 Modified drug delivery system:[3,4]

Dosage forms can be designed to modify the release of drug over a given time or after the dosage form reaches the required location. Drug release acquire only after sometime of the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment or to increase patient compliance and convenience of administration.

1.3 Classification of drug delivery system:

- Extended release
- Sustained release
- Controlled release
- Delayed release
- Site specific targeting
- Receptor targeting

❖ **Delayed released drug delivery system:**

These systems are based on pH dependent drug release mechanism of similar to conventional enteric-coated formulations, but they differ in target site for delivery and therefore type of enteric polymers. Most commonly used polymers are derivatives of acrylic acid and cellulose. These polymers have ability to withstand from low pH end several hours.

❖ **Controlled released (Time control delivery system):**

The systems are useful for synchronous delivery of a drug either at pre selected times such that patient receives the drug when needed or at a pre selected site of the GI Tract.

These systems are particularly useful in the therapy of diseases, which depends on circadian rhythms.

- **Sustained released:**

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

- **Extended released:**

Pharmaceutical dosage forms that release the drug slower than the normal at predetermined rate and necessarily reduce the dosage frequency.

- **Site specific targeting:**

These systems refer to targeting of a drug directly to an certain biological system. In this case the target is adjacent to or in the diseased organ or tissue.

- **Receptor targeting :**

Site specific targeting and receptor targeting systems satisfy the aspect of drug delivery and are also considered to be controlled drug delivery systems.

1.4 Extended release drug therapy:[5,6]

The term controlled/extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue.

The oral route of administration for extended release systems has received greater attention because of more flexibility in dosage form design. The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Extended release denotes that the system is able to provide some actual therapeutic control whether be it of temporal or spatial nature or both. In other words, the system attempts to provide a constant drug concentration in the target tissue. It is this nature of this system that makes it different from sustained release systems.

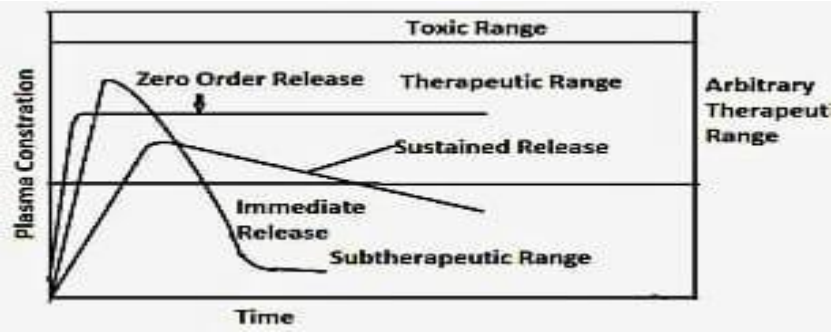


Fig 1: Plasma level versus time profile showing difference between controlled release, sustained release and release from conventional dosage forms.

1.4.1 Advantages of extended release dosage forms:[7]

- **Improved patient compliance** and convenience due to less frequent drug administration.
- **Reduction in fluctuation** in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- **Increased safety margin** of high potency drugs due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care costs** through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- **Attenuation of adverse effect** the use of extended release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, hemodynamic changes etc.

1.4.2 Disadvantages of extended release dosage form:

- Toxicity due to dose dumping.
- Increased cost.

- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.

1.4.3 Drug candidates suited for extended release dosage forms:

The drug and the therapeutic indication must be considered jointly in determining whether or not to develop an extended release dosage form. For a successful extended release product, drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.

- Drugs having short-biological half lives
- Drugs with fairly rapid rate of absorption and excretion
- Drugs which are uniformly absorbed in gastrointestinal tract.
- Drugs which require relatively smaller dosage for therapeutic effect.
- Drugs which are used for chronic rather than acute condition.
- Drugs which are having good margin of safety. The most widely used measure of the margin of a drug's safety is its therapeutic index. The larger the therapeutic index, the safer the drug.

1.4.4 Rationale for extended release pharmaceuticals:

These are some drugs which have long half life and hence are long lasting and they are required to be given one a day to system adequate blood levels and the desired therapeutic effects. There are on the other hand many drugs which are not long lasting and require multiple daily dosing to achieve the desired therapeutic levels. Multiple daily dosing is after is inconvenient for the patient and can result in missed doses, made up doses and patient non compliance with the therapeutic regimen. Another drawback of multiple dosing is that when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy and if the doses are administered too frequently minimum toxic concentrations may be recalled with toxic

side effects resulting. If doses are missed, periods of sub therapeutic blood levels or those below the minimum effective concentration may result, with no patient benefit.

1.4.5 Ideal candidate for Extended/controlled Release Drug Delivery systems:[8]

The desired biopharmaceutical characteristics of drugs to be used in the development of oral controlled release dosage forms are:

Table 1: Parameters for drug selection

Parameters for drug selection	
Parameter	**Preferred value**
Molecular weight	<1000
Solubility	>0.1mg/ml for pH 1to pH7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

- **Less protein binding :**

To evaluate whether a drug is viable candidate or not for the design of per oral CR formulation, one must consider the following pharmacokinetic parameters of the drug.

- **Elimination half-life :** Preferably between 0.5& 8 hours
- **Total body clearance :** Should not be dose dependent
- **Absolute bioavailability :** Should be 75% or more
- **Absorption rate :** Must be greater than release rate
- **Therapeutic concentration :** The lower the cssav and the smaller the vd ,the lesser is the amount required.
- **Apparent volume of distribution (Vd):**

The larger the vd and Minimum Effective Concentration (MEC), the larger will be the dose size required. The maximum dose to be incorporated in to a per oral Controlled release (CR) formulations is about 500mg. The smaller the v_d, the easier is incorporation of drug in to dosage form.

❖ **Minimum toxic concentration (MTC):**

Apart the values of MTC and MEC, safer the dosage form and also suitable for drugs with very short $t_{1/2}$.

1.4.6 Factors influencing oral extended release dosage design:[9,10]

❖ **Biological Factors**

A. Biological Half Life:

The usual goal of an oral extended release product is to maintain therapeutic blood levels over an extended period. Therapeutic compounds with short half-lives are excellent candidates for sustained release preparation, since this can reduce dosing frequency. However this is limited. In general, drugs with half-lives shorter than 2 hrs, such as furosemide or levodopa are most candidates for sustained release preparations. Compounds with long half-lives, more than 8hrs are also generally not used in sustained release forms, since their effect is already sustained. Digitoxin, warfarin, and phenytoin are some examples.

B. Absorption:

The characteristic of absorption of a drug can greatly affect its suitability as a extended-release product. Since the purpose of forming an extended- release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs and devices in the absorptive areas of GI tract is about 8-12hrs, the maximum half-life for absorption should be approximately 3-4hrs otherwise, the device will pass out of the potential region before absorption is complete. If a drug is absorbed by active transport or transport is limited to a specific region of the intestine, sustained release preparations may be disadvantageous to absorptions.

C. Metabolism:

Drugs that are significantly metabolized before absorption, either in the lumen or the tissue of the intestine can show decreased bioavailability from slower releasing dosage forms. Eg, Aloprenol was most extensively metabolized in the intestinal wall when given as a sustained release preparation. High concentration of dopa-decarboxylase in a

intestinal wall will result in a similar effect for levodopa. If levodopa is formulated in a dosage form with a drug compound that can inhibit the dopa-carboxylase enzyme, the amount of levodopa available for absorption increase and can sustain its therapeutic effects. Formulation of these enzymatic ally susceptible compounds as prod rugs is another viable solution.

- **Physiochemical Factors Influencing Oral Extended-Release Dosage Form Design:**

A. Dose size:

For orally administered system, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0gm is considered maximal for the conventional dosage form. This also holds for sustained release dosage form, those compound that require a large dosing size can sometimes can be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amounts of drug with narrow therapeutic range.

B. Ionization, pKa and Aqueous Solubility:

Most drugs are weak acids or bases. Since the unchanged form of drug preferentially permeates across lipid membrane, the drug in an unchanged form is advantageous for drug permeation. Consider a drug for which the highest solubility is in the stomach and is unchanged in the intestine. For conventional dosage form, the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of intestine. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form meaning that the solubility of the drug may change several orders of magnitude during its release. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained. The drugs that are limited in absorption by the dissolution rate are digoxin, griseofulvin and salicylamide. The lower limit has been reported to be 0.1mg/ml.

C. Partition coefficient:

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect these membranes are lipid in nature. Therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Compounds with a relatively high partition coefficient are predominantly lipid soluble and consequently, have very low aqueous solubility. Phenothiazine are representative of this type of compound.

D. Stability:

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage forms. This is because more drugs is delivered in the small intestine and hence it is subject to degradation. Propantheline, probanthine are representative examples of such drugs.

1.4.7 Physicochemical properties of the drug:[11]

Several physicochemical properties of the active drug can influence the choice of dosage form. This include aqueous solubility and stability, partition coefficient (or, more appropriately, permeability values) and salt form. The aqueous solubility and intestinal permeability of drug compounds are of paramount importance. A classification has been made whereby drugs can be considered to belong to one of four categories:

- High solubility and high permeability (best case)
- Low solubility and high permeability
- High solubility and low permeability
- Low solubility and low permeability (worst case).

This is now modified as the Biopharmaceutical Classification. Consider first the influence of solubility. A drug that is highly soluble at intestinal pH and absorbed by passive diffusion (i.e. not site-specific absorption) would probably present the ideal properties for inclusion in a modified release dosage form.

Drug compounds that satisfy the solubility and permeability requirements should also ideally have:

- A biological half-life of between two and six hours so that accumulation in the body does not occur a lack of capability to form pharmacologically active metabolites by, for example; first-pass metabolism.

- Modified release is actually used for drugs, which undergo first-pass metabolism but this should not be to such an extent that only inactive metabolites are left after absorption.

- A dosage not exceeding 125-325 mg in order to limit the size of the delivery system.

- The factors that influence the rate and extent of absorption depend upon the route of administration the intravenous route offers direct access to the systemic circulation and the total dose administered via this route is available in the plasma for distribution into other body tissues and the site(s) of action of the drug. Other routes will require an absorption step before the drug reaches the systemic circulation. Factors affecting this absorption will depend on the physiology of the administration site(s) and the membrane barriers present at those site(s) that the drug needs to cross in order to reach the systemic circulation.

1.4.8 Biopharmaceutical principles of drug delivery:[12]

The Rate and extent of drug absorption into the systemic circulation, a schematic illustration of the steps involved in the release and absorption of a drug from a tablet dosage form. It can be seen from this that the rate and extent of appearance of intact drug in the systemic circulation depends on a succession of kinetic processes. The slowest step in this series, which is known as the rate-limiting step controls the overall rate and extent of appearance of intact drug in the systemic circulation. The particular

rate-limiting step will vary from drug to drug. For a drug, which has a very poor aqueous solubility the rate at which it dissolves in the gastrointestinal fluids is often the slowest step, and the bioavailability of that drug is said to be dissolution-rate limited.
In contrast, for a drug that has a high aqueous solubility its dissolution will be rapid and the rate at which the drug crosses the gastrointestinal membrane may be the rate-limiting step (permeability limited). Other potential rate-limiting steps include the rate of release of the drug from the dosage form (this can be by design in the case of controlled- release dosage forms), the rate at which the stomach empties the drug into the small intestine, the rate at which the drug is metabolized by enzymes in the intestinal mucosal cells during its passage through them into the mesenteric blood vessels, and the rate of metabolism of drug during its initial passage through the liver, often termed the 'first-pass' effect.

1.4.8 Classification of extended release products:[13]

Extended release tablets are often classified according to the mechanism of drug release. The following are the most common means used to achieve a slow, control release of drug from tablets.

- Dissolution control
- Diffusion control
- Dissolution and diffusion control
- Erosion control
- Osmotic pump control & Ion exchange control

1) Dissolution controlled Release system:

Most of the products fall into two categories

a) Encapsulation dissolution controlled systems

Here the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes, etc. The resulting pellets may be filled as such in hard gelatin capsules (popularly called as spansules) or compressed into tablets. The dissolution rate of coat depends upon the solubility and thickness of the coating which may range from 1 to 200 microns.

b) Matrix dissolution controlled systems

Matrix systems are also called as monoliths since the drug is homogeneously dispersed throughout a rate-controlling medium. They are very common and employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, etc. which control drug dissolution by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The wax embedded drug is generally prepared by dispersing the drug in molten wax and congealing and granulating the same. The drug release is often firstorder from such matrices.

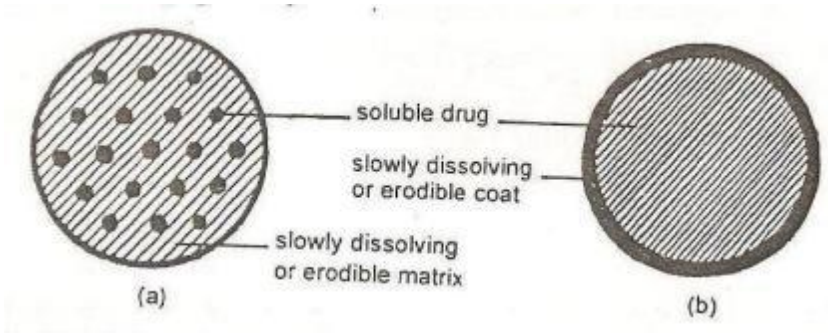


Fig.2: Dissolution Controlled Release Systems

a) Matrix system b) Coated/Encapsulated System

2) Diffusion controlled Release systems:

Diffusion of a drug molecule provides the movement from a zone of high concentration to that of low concentration. Here, the formulator relies on the diffusion of the drug through an inert membrane barrier to control the release rate of a drug. The drug release rate is never zero-order since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug.

The two types of diffusion controlled systems.

a) Matrix diffusion controlled systems

The drug is dispersed in an insoluble matrix of rigid non-swellable hydrophobic materials or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as PVC and fatty materials like stearic acid, bees wax, etc.

Swellable matrix systems are popular for sustaining the release of highly watersoluble drugs. The material for such matrices are generally hydrophilic gums and may be of natural origin (Guar gum, Tracaganth), semi synthetic (HPMC,CMC, Xanthan gum) or synthetic (Poly acrylamides)

The release of drug from such matrix systems involve simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug via a swelling controlled diffusion mechanism. As the gum swells and the drug diffuses out of it, the swollen mass, devoid of drug appears transparent.

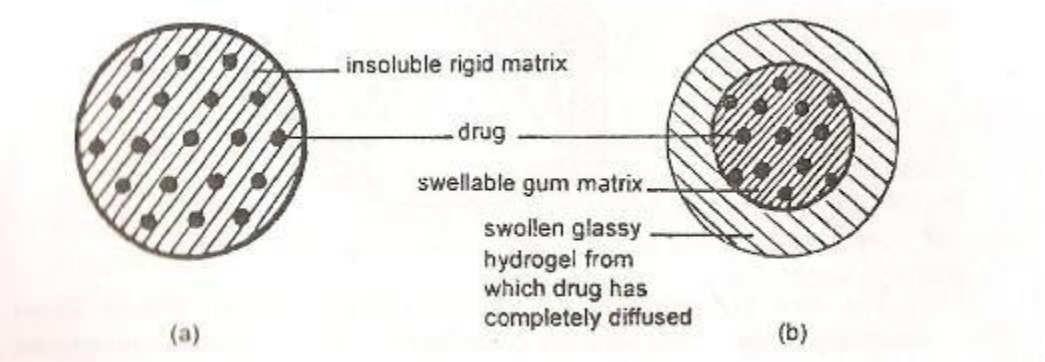


Fig.3: Diffusion Controlled Systems

a) Rigid matrix b) Swellable matrix

b) Reservoir diffusion controlled systems

These systems are hollow containing an inner core of drug surrounded in a water &insoluble polymer membrane. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are HPC, Ethyl cellulose and polyvinyl acetate.

A disadvantage of all such microencapsulated drug release systems is a chance of sudden drug dumping which is not common with matrix devices.

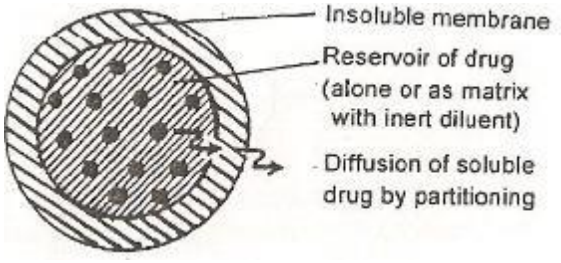


Fig.4: Drug release by diffusion across the insoluble membrane

3) Dissolution and diffusion controlled release systems:

A combined dissolution and diffusion control of drug release can be accomplished by coating a drug core with a partially soluble membrane. Usually this membrane contains a combination of hydrophobic and hydrophilic polymers.

Eg., a mixture of ethyl cellulose and pvp.

The dissolution of the hydrophilic polymer causes the formation of pores through the membrane

-Permit the entry of aq. medium into the core and hence drug dissolution

-Allow diffusion of dissolved drug out of the system

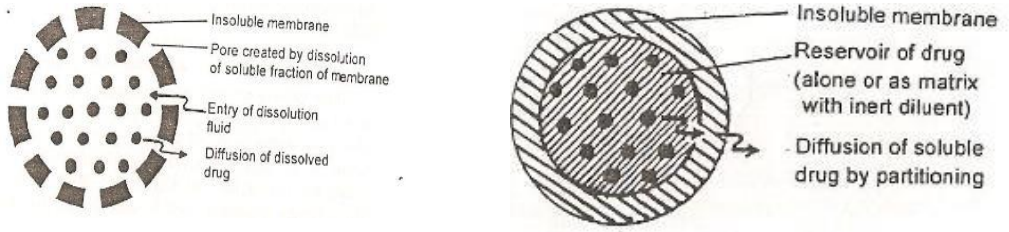


Fig.5: Dissolution and diffusion controlled release system

1.5 Tablet formulation design:[14]

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

1) **Diluents**: Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. Also used to improve cohesion, to permit use of direct compression.

2) **Binders**: To form cohesive compacts for directly compressed tablet.

3) **Lubricants**: Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

4) **Glidants**: Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.

5) **Anti–adherents:** Anti-adherents are added to the tablet formulations to prevent the material from sticking to the walls of the tablet press.

6) **Disintegrates**: Added to a tablet formulation to facilitate its breaking or disintegration when it contact in water in the GIT.

7) **Coloring Agents**: The use of colors and dyes in a tablet has three purposes: (A) Masking of off color drugs (B) Product Identification (C) Production of more elegant product.

8) **Flavoring Agents**: Flavoring oils are needed for chewable tablets. The oil is generally added in a dry form such as spray-dried beadlets.

9) **Absorbents**: The inclusion of absorbents in a tablet formulation is necessary if the product contains a substance with a high affinity to water. Hygroscopic materials, if present, render the blend wet and difficult to handle during manufacture.

Table 2: Tablet formulation design

S.no.	Ingredients	Examples
1.	Diluents	Calcium Phosphate; Carboxymethylcellulose Calcium; Cellulose; Dextrin; Lactose; Microcrystalline Cellulose; PR gelatinized Starch; Sorbitol; Starch
2.	Binders	Acacia; Alginic Acid; Carboxymethylcellulose; Cellulose; Dextrin; Gelatin; Liquid Glucose; Magnesium Aluminum Silicate; Maltodextrin; Methylcellulose; Povidone; Sodium Alginate; Starch; Zein.
3.	Lubricants	Calcium Stearate; Glyceryl Palmitostearate; Magnesium Oxide; Poloxamer; Polyvinyl Alcohol; Sodium Benzoate; Sodium Lauryl Sulfate; Sodium Stearyl Sulfate; Stearic Acid; Talc; Zinc Stearate
4.	Glidants	Magnesium Trisilicate; Cellulose; Starch; Talc; Tribasic Calcium Phosphate
5.	Anti – adherents	Corn Starch; Metallic Stearate; Talc

6.	Disintegrants	Alginic Acid; Carboxymethylcellulose; Cellulose; Colloidal Silicon Dioxide; Croscarmellose Sodium; Crospovidone; Potassium Polacrilin; Povidone
7.	Coloring agents	FD&C or D&C Dyes or Lake Pigments
8.	Flavoring agents	Ethyl Maltol; Ethyl Vanillin; Menthol; Vanillin
9.	Absorbents	Kaolin; Magnesium Aluminum Silicate; Tricalcium Phosphate

1.6 Manufacturing methods:[15]

There are four general methods of tablet preparation.

1. Direct compression
2. Wet granulation method
3. Dry granulation method

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.

1) Wet granulation method:

It is the most common and widely used method. This method involves various steps like weighing of ingredients, mixing, granulation, and screening of damp pass, drying, lubrication and compression of tablets. The main active ingredient, diluent, disintegrant are blended together, and then it is allowed to pass through the sieve (sifting). Solutions of the binding agent are added to the initial mixture with stirring. The amount of binding agent added should be sufficient, in order to avoid over wetting of the tablet. If the powder is not wetted properly, the granules will be too soft and can be broken down during lubrication, which is difficult during compression of tablet. Tray drying is most common method of drying the tablet granules, Tray drying was the most widely used method of drying tablet granulations in the past, which might be replaced by fluid –bed dryers as a novel approach. After drying the granules, they are allowed to pass through the screen; usually 60-100 mesh nylon cloth is used. After dry granulation, lubricant is added as fine powder, which is required for proper filling of the die cavity.

2) Dry granulation method:

This method is used for tablet preparation, in case tablet ingredients are highly sensitive to moisture, or unable to with stand elevated temperatures during drying, slugging may be used to form the granules. Dry granulation or double compression, usually eliminates various steps, which involves slugging of the powder mass.The active ingredient, diluent and lubricant are blended together, to form the slug. Thus, the compressed slug is passed through the mesh or through the mill, and the remaining lubricant is added to the granulation, blended properly and compressed to form the tablets.

3) Direct compression:

Direct compression involves direct compressing the powdered material into tablets. Direct compression is adopted, if drug constitutes major portion of tablet total weight. Tablets containing 25% or less of drug substances can be formulated, with a suitable diluent which acts as a carrier or vehicle for the drug. Tablets prepared by above method are subjected to compression machine which may be single station or multiple stations.

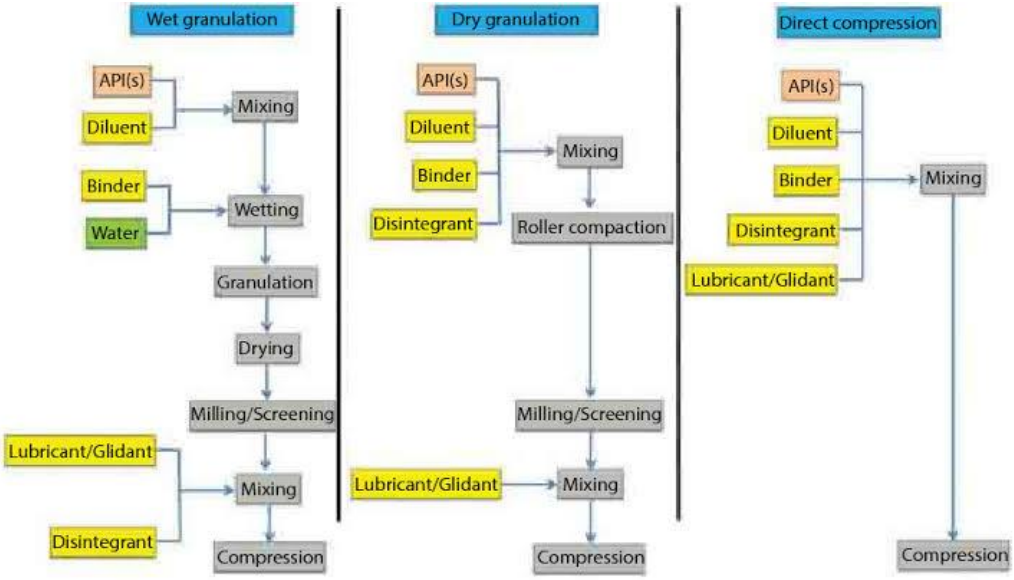


Fig. 6: Processing steps in wet granulation, dry granulation and direct granulation.

1.7 Compression:[16,17]

After the preparation of lubricated granules they are compressed to get the final product. The compression is done either by single punch machine (Stamping press) or by multi station machine (Rotary press). The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams-an upper cam and a lower cam. The punch head (top of the upper punch) sits on the upper cam edge. The bottom of the lower punch sits on the lower cam edge. The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed.

1.7.1 The principle of tablet compression machine:

The basic principle behind the tablet compression machine is hydraulic pressure. This pressure is transmitted unreduced through the static fluid. Any externally applied pressure is transmitted via static fluid to all the directions in the same proportion. It also makes it possible to multiply the force as needed.

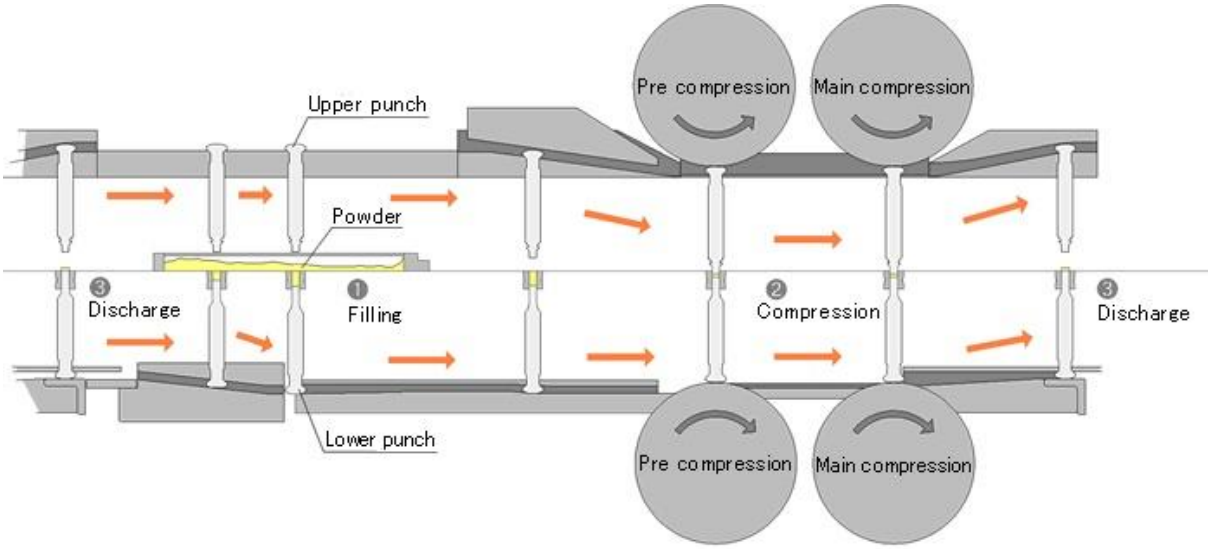


Fig. 7: Tablet compression machine

1.8 Tablet coating:[18]

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 their own characterstics for example bitter in taste ,unpleasant odour, some are sensitive to light, hygroscopic, which are all can be altered by coating .

1.8.1 Tablet film coating is performed by two types:

One is aqueous film 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 film coating must be smooth, uniform, and adhere satisfactorily to the tablet surface and should be stable to drug.

1.8.2 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
- Coating can modify the drug release profile, e.g., enteric coating, osmotic pump, pulsatile delivery.

1.8.3 Types of coating:

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

1.8.4 Coating equipment:[19]

Most of the coating processes use one of the three general types of equipments.

1. The standard pan.
2. The perforated pan.
3. The fluidized bed coater.

1. Conventional pan system:

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.

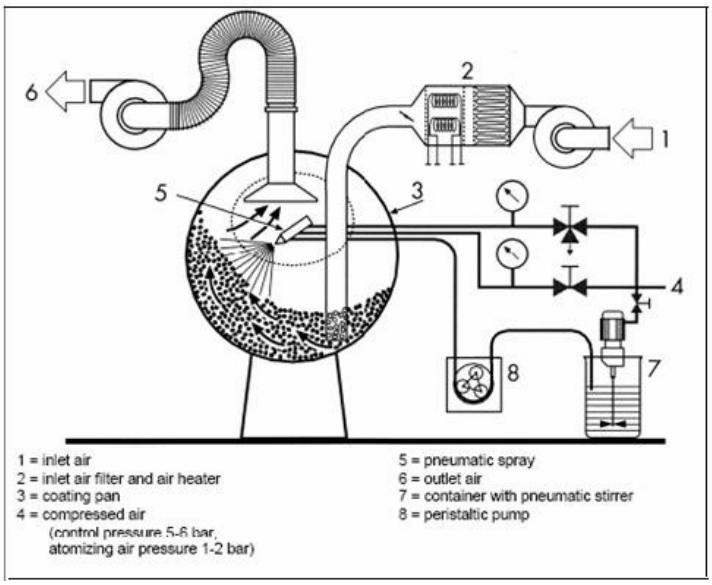


Fig. 8: Conventional coating pan

2. The perforated coating pan:

Neocota is an automatic coating system for tablets and pellets. Neocota is a completely updated automatic coating system having a batch capacity of 500 gm to 1 kg. This model efficiently carries out the following operations: aqueous film coating of tablets/pellets; Non-aqueous organic solvent based film coating of tablets/pellets; and enteric film coating of tablets/pellets. The basic system are has coating pan with perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, exhaust unit and an air fitter. Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun and interconnecting flexible hoses.

3. The fluidized bed coater:

The fluid fed technology offers a very efficient coating technique. The major advantage of the Fluid Bed Systems is that it is as per GMP standards and a closed system. The second advantage of the Fluid Bed Systems is that not only coating but granulation and

pellet formation is also possible in the same machine. Fluidized bed coating is a process that takes place inside a fluidized bed where by a coat is introduced to cover the intended object in order to protect it or modify its behavior. Particulate coating is a form of fluidized bed coating involving the coating of solid particles inside the bed. In this process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also use to dry the deposited solution to form a coat on the surface of the particle. There is considerable diversity in methods of using fluidized bed technology. For e.g. liquids can be applied to fluidized particles in a variety of ways, including top, bottom and tangential spraying. For a given product, each method can offer markedly different finished product characteristics. Fluidized beds are used for coating because of their high energy and mass transfer. Fluidized beds for film coating can be divided into three groups

1. Top-spray.
2. Bottom-spray equipment.
3. Tangential-spray.

1.9 Multilayered tablets for controlled drug delivery:[20-22]

Multilayered systems (bilayered, triple-layered, quadruple-layered, *etc*.) are becoming increasingly recognized as controlled-release drug delivery systems. These systems have been shown to be advantageous over typical tablet systems as depicted. Namdeo expressed that multi-layered tablets have demonstrated promise, possessing various benefits, namely the ability to prevent interactions between drugs and excipients; and by providing an array of release profiles in one delivery system of either the same or different drugs, treatment for conditions that require a regimen of more than one drug, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release using an eroding monolithic matrix which may deliver another active drug to a different part of the gastrointestinal tract, providing controlled drug release instituting a swellable monolithic matrix and better control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics. It would be beneficial if research focused on further modification of these systems for improved and comprehensive drug release capabilities that enable a larger scope of application in drug delivery.

Controlled-release multilayered tablets typically involve a drug core layer that is surrounded by barrier layers that may be made up of hydrophilic swellable polymers such as hydroxypropylmethylcellulose (HPMC) and poly(ethylene oxide) (PEO) or hydrophobic polymers such as ethylcellulose (EC). The barrier layers minimize and therefore delay the interaction of the gastrointestinal environment with the active core, by decreasing the surface area available for drug release or by controlling the rate at which the solvent penetrates the layers. This allows the initial burst release to be minimized and therefore the drug release can be controlled at a near constant level while the barrier layers undergo erosion or swelling. The swollen barrier layers undergo erosion as time goes on, thus increasing the surface area which ultimately allows more drug to be released. Following the same principle, it is possible to obtain a constant release profile as well as other types of dissolution patterns such as pulsatile or delayed delivery as well as extended drug delivery depending on the characteristics of the polymers employed. In either case the system should ideally erode completely.

1. Spheroidal Oral Drug Absorption System (SODAS),
2. Intestinal Protective Drug Absorption System (IPDAS),
3. Chronotherapeutic Oral Drug Absorption System (CODAS),
4. Programmable Oral Drug Absorption System (PRODAS)

SODAS or Spheroidal Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug-delivery technology and consists of controlled-release beads that can be produced in the range from 1 to 2 mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the in vivo dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form.

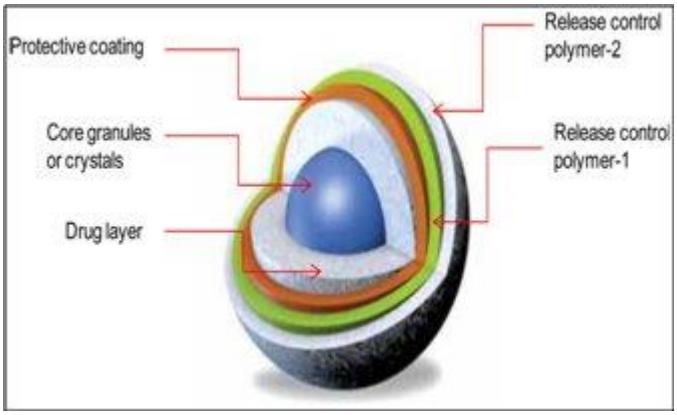


Fig. 9: Sodas® multilayer tablet technology

Benefits offered by the SODAS technology include:

- controlled absorption with resultant reduction in peak to trough ratios
- targeted release of the drug to specific areas within the gastrointestinal tract
- absorption independent of the feeding state
- suitability for use with one or more active drug candidate
- facility to produce combination dosage forms
- "sprinkle dosing" by administrating the capsule contents with soft food
- once or twice daily dose resembling multiple daily dose profiles

1.10 Peripheral Artery Disease:[23]

Peripheral artery disease (PAD) is damage or disease of the arteries outside of the heart and brain. Blood carries oxygen and nutrients to organs and tissues. Problems with the arteries can affect the health of tissue in the arms, legs, and body core.

If PAD isn't treated, it can lead to problems like tissue death, infection, and amputation. Things that cause PAD can also harm blood vessels in the heart and brain. This means people with PAD are at risk for heart attack and stroke.

1.10.1 Causes:

Atherosclerosis is the most common cause of PAD. This is a build-up of plaque on the walls of the vessels. Plaque is a waxy matter made of fats and other matter in the blood. It sticks to the walls. It can also be made of scar tissue or fibers used to fix damage to the walls. Overtime, plaque grows by trapping other matter in the blood, such as bad

cholesterol and blood sugar. As the it grows, the blood vessel gets narrow and makes it harder for blood to flow.

Things that can lead to atherosclerosis are:

- Smoking —can bother vessel walls and make deposits on them
- High cholesterol —bad cholesterol can stick to and bother the walls of the vessels
- High blood pressure —causes strong blood flow that can injure the walls of vessels
- Diabetes —too much sugar in the blood can lead to plaque build up
- Radiation therapy

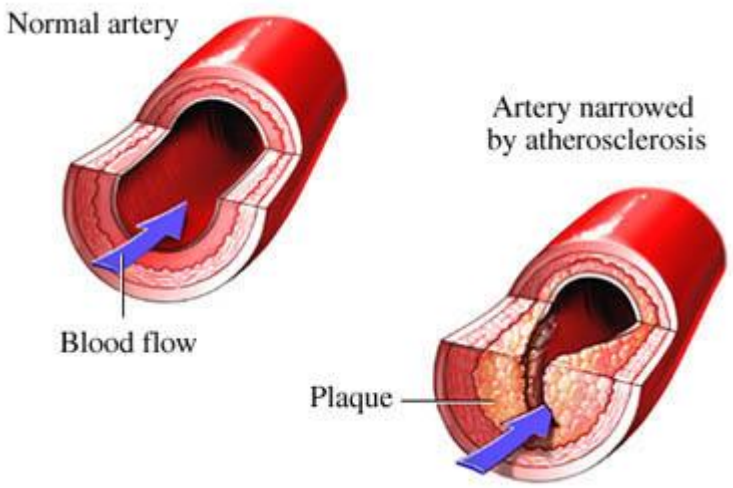


Fig. 10: Atherosclerosis

1.10.2 Risk Factors:

a) Smoking:

Smoking makes blood vessels narrow. It also builds up plaque in the arteries and raises your pulse and blood pressure. The risk of PAD is four times higher in smokers and former smokers. It can also happen up to 10 years earlier in smokers.

b) High cholesterol:

Cholesterol is a waxy matter used by the body. The body makes it and some also comes from the foods you eat. High levels of certain cholesterol in blood can lead to atherosclerosis. This is the main cause of PAD.

c) **High blood pressure:**

Blood pressure is the force of blood on the walls of arteries. It can cause too much stress and force on blood vessel walls when it is too high. Over time, this causes damage. It also raises the risk of PAD.

d) Glucose Intolerance:

Glucose intolerance and diabetes happen when the body does not make insulin or does not use it well. Insulin is a hormone that helps pull sugar out of the blood and into cells for use. High levels of it can lead to atherosclerosis and blood vessel damage. Controlling blood sugar can help lower the risk of diseases like PAD.

e) Metabolic Syndrome:

Metabolic syndrome is high blood pressure, cholesterol, blood sugar, and body weight, mainly around the midsection. People with this health problem have an greater risk of PAD because of too much stress on their heart.

1.10.3 Symptoms:

- A numb feeling in your legs or feet when you are resting
- Cold legs or feet
- Muscle pain in the thighs, calves, or feet
- Loss of hair on the lower limbs
- Poorly growing or thick toenails
- Pale or blue legs or feet
- Foot wounds that heal slowly

1.10.4 Diagnosis:

- The **ankle/brachial index (ABI)** is a measurement of the blood pressure in the lower legs compared to the blood pressure in the arms.
- A **pulse volume recording (PVR**) is a noninvasive test that measures the blood volume changes that occur in the legs.
- A **vascular ultrasound** is a noninvasive test used to examine blood circulation.

2. Literature Review

Jayakar .B et al.,(2010)[24] reported the study of controlled or sustained release dosage form was formulated and evaluated the extended release tablets of Pentoxifylline by using polymers HPMC-K100M and HPC in different ratios as matrix. Pentoxifylline was prescribed to patients who are suffering from chronic peripheral heart diseases. Pentoxifylline in the Extended release may be used to improve the bioavailablity and to improve the Patient non -compliance.

Dey NS et al.,(2008)[25] reported this research work deals with the development of multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations. The release of drug from microparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations.

Kiattisak saeio et al.,(2007)[26] this work was to investigated the factors influencing the dissolution characteristics of drug substances from hydrophilic polymer matrix tablets. Various kinds of cellulose derivative polymers were used for matrix formation. Their swelling properties were measured. The effects on drug release were studied in comparison with lactose. Results also indicate that PVP K30 supports cellulose polymers so as to improve the release behavior in order to better keep drug release constant in each time interval.

Lakshmana Rao. Potti et al.,(2013)[27] this research work deals with the method was developed for the estimation of Pentoxyphylline in bulk drug and its pharmaceutical formulation by using water and 0.1N NaOH as a solvent. Pentoxyphylline show absorbance maxima at 275nm and 271 nm for water and 0.1N NaOH respectively. This method can be used for the routine quantitative analysis of Pentoxyphylline in bulk drug and its pharmaceutical formulation.

Eleonora Mircia et al.,(2008)[28] this experimental study observed the influence of temperature and humidity on the stability of pentoxifylline from the proposed formulations. This paper described the HPLC determination of pentoxifylline from new controlled release tablets with hydrophilic matrix (HPMC, HPC, HEC). The studied

tablets were kept in the stability chamber at a temperature of 40±20C and a relative humidity of 75±5 %. At different time intervals, the dissolution test and the quantitative determination of pentoxifylline.

Viswanathan M B et al., (2008)[29] the objective of this work was two retardant polymers were employed with varying concentrations and also in combination in different ratio to get promising concentration for controlled release matrix tablets. Matrix tablets of pentoxifylline were formulated using hydrophilic swellable polymers hydroxyl propyl methyl cellulose and guar gum with lactose as diluent.

Eleonora Mircia et al.,(2010)[30] formulated and evaluated modified release tablet of pentoxifylline 400 mg. Hydroxypropylcellulose (HPC) in different ratios was used as hydrophilic matrix agent. The pentoxifylline inclusion in the matrix has been carried out by water granulation, using PEG 6000 as binder. The determination was performed by spectrofotometric as say in UV at 274 nm. The analysis of dissolution profiles showed that all formulations exhibit slow release.

Prashant Malik et al.,(2013)[31] the objective of the study involved design, development, and characterization of pentoxifylline loaded floating microballoons to prolong their gastric residence time. Pentoxifylline (trisubstituted xanthine derivative) loaded microballoons were prepared by the solvent evaporation technique using different concentrations of polymers like HPMC K4M and ethyl cellulose (EC) in ethyl alcohol and dichloromethane organic solvent system.

Amal Ali Elkordy et al.,(2017)[32] this study was to designed and evaluated effervescent floating tablets with sustained release behaviour. Pentoxifylline is a water-soluble model drug with a short half-life,consequently developing sustained release preparations would be beneficial. A binary (1:1) mixture of sodium alginate and hydroxyethyl cellulose containing pentoxifylline, with either 10% or 20% calcium carbonate or sodium carbonate, was used to prepare floating tablets.

Rahman BM et al.,(2009)[33] formulated and evaluated Methocel K15M Controlled release matrix tablets of pentoxifylline using microcrystalline cellulose, starch and lactose were prepared by wet granulation process. There was no significant difference in drug release between the hydrophilic matrices when the Methocel K15M CR concentration was modified in low percentage. The release of pentoxifylline was

influenced by the presence of microcrystalline cellulose, and by the different concentrations of starch and lactose.

Zeynep S. Teksin et al.,(2009)[34] investigated the feasibility of enhancement of oral bioavailability of Pentoxifylline using Chitosan. Pentoxifylline is a highly water-soluble, hemorheologic drug that undergoes first-pass effect with 20 % bioavailability. Chitosan, a biocompatible and biodegradable natural polymer, is used to increase drug bioavailability, as well as prolonging release. Chitosan as an absorption enhancer for preparing the matrix tablet.

Georgeta ionica et al.,(2009)[35] studied the results of a pharmacokinetics study concerning pentoxifylline and its main metabolites after administration of extended release formulation and correlation of this pharmacokinetics with in vitro dissolution test results of parent drug. Correlation was linear and very good. Generalization of correlation to rate of appearance of metabolites in plasma proved that this process could be well correlated with dissolution.

Safwan Abdel Rahim et al.,(2015)[36] designed and evaluated effervescent floating gastro-retentive drug delivery matrix tablets with sustained-release behavior using a binary mixture of hydroxyethyl cellulose and sodium alginate. Pentoxifylline was used as a highly water-soluble, short half-life model drug with a high density. The effect of different formulation variables was investigated, such as wet granulation, sodium bicarbonate gas-forming agent level, and tablet hardness properties.

Omaima N. El-Gazayerly et al.,(2003)[37] hvae prepared pentoxifylline-controlled release tablets using xanthan gum. The effects of polymer concentration, rotation speed, ionic strength, and pH of the dissolution medium on the release of the water-soluble pentoxifylline were studied. The release rate decreased with increasing polymer concentration in the tablet, which was reflected in the increase in the mean dissolution time. A higher rotation speed and increased ionic strength of the dissolution medium resulted in a higher rate of drug release of xanthan-based tablets.

Rajasekhar .P et al.,(2015)[38] have prepared and evaluated of controlled release matrix tablets of pentoxifylline. The formulation of tablets was done by using wet granulation technique which was found acceptable. All the formulations were subjected to various

evaluation studies. A different method of graphical evaluation was used for evaluation of in-vitro dissolution data.

Stanislav Tzankov et al.,(2019)[39] reported the possibilities for correction of the rate of pentoxifylline – extended release tablets were explored. Correction was made by addition of different quantity of HPMC K4M to a granulating solution of PEG 6000. The swelling of the hydrogel tablets in water was determined in order more information on the release process to be obtained.

Chinmaya Keshari Sahoo et al.,(2015)[40] have reported HPMC is a polymer selected by most formulators as a hydrophilic matrix system probably due to the claim that it gives fast gel formation to control initial drug release. It is nontoxic, ease of compression and high drug loading capacity. It provides the release of drug in a controlled manner and giving maximum utilization of drug.

Zema .L et al.,(2006)[41] have reported release-controlling coating agents for tableted core-based delivery systems, three different hydroxypropyl methylcellulose (HPMC) grades, Methocell E5, E50, and K4M, provided lag phases of varying duration. The polymers were evaluated for dissolution and swelling, while the finished systems were concomitantly evaluated for drug release and polymer dissolution. This polymer indeed proved to yield higher viscosity and slower dissolving gel layer.

Stephen A. Martellucci et al.,(2002)[42] concluded that effect of different grades of hydroxyethyl cellulose (HEC) and hydroxypropyl methylcellulose (HPMC) on the film-formation and taste-masking ability for ibuprofen granules was evaluated. . Two grades of HEC were combined with three different grades of HPMC to prepare the coating solutions. These data suggested that the molecular weight of the HEC affects the taste-masking ability of the resultant polymer film.

3. Aim and Objective

Controlled release drug delivery systems are developed to moderate the drug release characteristics to achieve specific goals that cannot be accomplished with conventional drug delivery systems. Potential therapeutic benefits of an appropriately designed Multilayered dosage form include improved efficacy, reduced adverse effects, low cost, flexible release characteristics, increased convenience and patient compliance. Pentoxifylline is a vasodilator (Hemorrheologic agent). It works by helping blood flow more easily through narrow arteries.

Controlled-release Multilayered tablets prepared here which involve a Pentoxifylline core layer that is surrounded by barrier layers that may be made up of hydrophilic swellable polymers such as Hydroxypropyl Methylcellulose (HPMC K4 M for inner layer) and hydrophobic polymers such as Hydroxy Ethylcellulose (HEC for outermost layer). In view of fact that HEC layers minimize and therefore delay the interaction of the gastrointestinal environment with the active core, by decreasing the surface area available for Pentoxifylline to release or by controlling the rate at which the solvent penetrates the layers. This allows the initial burst release to be minimized and therefore the drug release can be controlled at a near constant level while the barrier layers undergo erosion or swelling. The swollen barrier layers undergo erosion as time goes on, thus increasing the surface area which ultimately allows more Pentoxifylline to be released. Coating of drug core carried out in conventional coating pan and, to be continued to achieve weight increases by 4%, 6% and 8% w/w of total tablet weight. Therefore, nine batch to be prepared with various weight gain of both barrier polymer and optimized for further characterisation through *in vitro* dissolution, swelling indexes, and short-term stability studies.

4. Plan of Work

1. Literature Review
2. Preformulation studies of drug and excipients
3. Rationalize the selection of excipients on the available information
4. Evaluation of lubricated granules (Pre-compression parameters)
    a. Angle of repose
    b. Bulk density
    c. Tapped density
    d. Carr's compressibility index
    e. Hausner's ratio
5. Formulation of pentoxifylline core tablet
6. Preparation of coating solution
7. Formulation of pentoxifylline coated tablets
8. Evaluation of formulation (Post-compression parameters)
    a. Physical appearance
    b. Thickness
    c. Hardness
    d. Weight variation
    e. Friability
    f. Assay
9. Swelling index
10. In-vitro dissolution studies
11. Comparision of optimized formula with marketed product.
12. Drug release kinetic studies
13. Stability studies as per ICH guidelines

5. Drug Profile

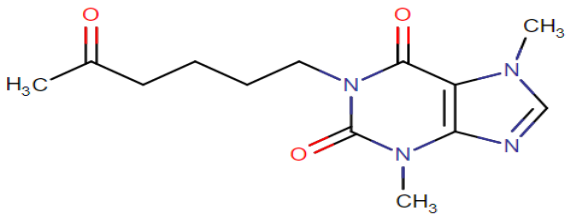
5.1 Pentoxifylline :[43-45]

Drug : Pentoxifylline

Category : Vascular disease

Class : Hemorrheologic agents

Structure :



Chemical Name : 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione.

Molecular formula : C13H18N4O3

Molecular weight : 278.307 g/mol

Dose : Therapy usually is initiated with 400mg orally thrice a day.

Description : Pentoxifylline is a white powder.

Solubility : It is soluble in water and ethanol,and sperinly soluble in toluene.

PHARMACOLOGY

Therapeutic category : Hemorrheologic agents

Mechanism of action : The actions of pentoxifylline include increased erythrocyte flexibility and decreased blood viscosity. The mechanism of action for increasing erythrocyte flexibility is unknown, but the drug's actions appear to be related to inhibition of erythrocyte phosphodiesterase, which causes an increase in erythrocyte cAMP activity. This increase allows the erythrocyte membrane to maintain its integrity and become more resistant to deformity. Pentoxifylline's effect on blood viscosity is

attributed to its reduction in plasma fibrinogen concentrations and an increase in fibrinolytic activity, as well as to its effects on erythrocytes. Improvement in blood viscosity results in increased blood flow to the microcirculation and enhanced tissue oxygenation. Unlike theophylline, pentoxifylline does not possess any bronchodilatory actions. Although pentoxifylline does not possess any direct anti-sickling properties, its actions on erythrocyte flexibility make it potentially beneficial in sickle cell disease.

PHARMACOKINETICS

Absorption and Distribution:

Pentoxifylline is rapidly and completely absorbed in the gastrointestinal tract after oral administration. It is usually recommended with meals (food or milk) to minimize gastrointestinal irritation. It is usually sustained releasing tablets with an early peak plasma pentoxifylline concentration two to three hours of post-administration.

Bioavailability	**:**	20-30%,because of a high first-pass clearance.
Plasma protein binding	**:**	45%
Volume of distribution	**:**	4.15 L/kg
Biological half life	**:**	0.4-0.8 hours
Tmax	**:**	2-4 hours

Metabolism and Elimination:

Erythrocytes and liver extensively metabolize pentoxifylline to its active metabolites (M1). Pentoxifylline and its metabolites are primarily eliminated by the kidneys and less than 5% by feces.

Availability:

Oral tablets	:	400 mg
Injectable solution	:	20mg/mL

Posology and method of administration:

Adults: The usual oral dose of Pentoxifylline for adults is 400 mg administered at, three times daily. If side effects are particularly disturbing, the dose may be reduced to 400 mg two times daily. The total dose within 24 hours should not exceed 1.2 gm.

Paediatric: Safety and effectiveness have not been established in pediatric patients (less than 18 years of age)

Elderly: Clinical studies of pentoxifylline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Contraindication: Pentoxifylline should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

Drug interaction:

❖ **Drug-Drug Interaction:**

Pentoxifylline may interact with blood thinners (warfarin, clopidogrel, aspirin), antibiotics (ciprofloxacin), pain relievers (ketorolac, diclofenac, indomethacin), antihypertensive (metoprolol, atenolol, propranolol, prazosin), antidiabetics (metformin, alogliptin, linagliptin, saxagliptin, sitagliptin, canagliflozin), a drug used to treat lung diseases (theophylline), diuretics (furosemide, chlorothiazide, indapamide, metolazone).

Adverse effect:

- **Cardiovascular -** dyspnea, edema, hypotension.
- **Digestive -** anorexia, cholecystitis, constipation, dry mouth/thirst.
- **Nervous -** anxiety, confusion, depression, seizures, aseptic meningitis.
- **Respiratory -** epistaxis, flu-like symptoms, laryngitis, nasal congestion.
- **Skin and Appendages -** brittle fingernails, pruritus, rash, urticaria, angioedema.
- **Special Senses -** blurred vision, conjunctivitis, earache, scotoma.
- **Miscellaneous -** bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

Therapeutic use:

Pentoxifylline is a prescription drug used to improve the symptoms of a certain blood flow problem in the legs/arms (intermittent claudication due to occlusive artery disease). Pentoxifylline can decrease the muscle aching/pain/cramps during exercise, including walking, that occurs with intermittent claudication. Pentoxifylline belongs to a class of drugs known as hemorheological agents. It works by helping blood flow more easily through narrowed arteries. This increases the amount of oxygen that can be delivered by the blood when the muscles need more (such as during exercise) thereby increasing walking distance and duration.

Excipients Profile:

5.2 Hydroxy Propyl Methyl Cellulose:[46]

Synonyms:

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose;MHPC

Official Status:

BP : Hypromellose
JP : Hypromellose
PhEur : Hypromellose
USP : Hypromellose

Functional Category:

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent;tablet binder; thickening agent; viscosityincreasing agent.

Description:

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder. HPMC K 15M can successfully be used in mortars and plasters which are manually applied. The product imparts good workability to mortars and plasters and enhances water retention. HPMC 15CPS and HPMC K 4M cellulose derivatives also been used as in these formulation. Solubility Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of Hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol.

Grades:

Higher viscosity grades leading to greater diffusional resistance to water. This directly reduces the diffusion of drug out of the matrix and indirectly affects the state of hydration within the gel, thus affecting that component of drug release due to erosion of the dosage form. Methocel K 4M (4000 Cps), K 15M (15000 Cps) and K 100M (100000 Cps) were similar despite differences in viscosities. Methocel K 100M>Methocel K 15M>Methocel K 4M based on viscosities.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Storage:

Hydroxy Propyl Methyl Cellulose powder should be stored in a well-closed container, in a cool, dry place.

5.3 Hydroxyethyl CellulosE:[47]

Nonproprietary Names

BP : Hydroxyethylcellulose

PhEur : Hydroxyethylcellulose

USP-NF : Hydroxyethyl Cellulose

Synonyms:

Cellosize HEC; cellulose hydroxyethyl ether; cellulose 2-hydroxyethyl ether; cellulose hydroxyethylate; ethylhydroxy cellulose; ethylose; HEC; HE cellulose; hetastarch; 2 hydroxyethyl cellulose ether; hydroxyethylcellulosum; hydroxyethyl ether cellulose; hydroxyethyl starch; hyetellose; Natrosol; oxycellulose; Tylose H; Tylose PHA.

Chemical Name and CAS Registry Number

Cellulose, 2-hydroxyethyl ether [9004-62-0]

Molecular Weight: 806.93

Functional Category:

Coating agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical:

Formulation or Technology Hydroxyethyl cellulose is a nonionic, water-soluble polymer widely used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic and topical formulations, although it is also used as a binder and film-coating agent for tablets. It is present in lubricant preparations for dry eye, contact lens care, and dry mouth. The concentration of hydroxyethyl cellulose used in a formulation is dependent upon the solvent and the molecular weight of the grade. Hydroxyethyl cellulose is also widely used in cosmetics.

Description:

Hydroxyethyl cellulose occurs as a white, yellowish-white or grayish-white, odorless and tasteless, hygroscopic powder.

Acidity/alkalinity: pH = 5.5–8.5 for a 1% w/v aqueous solution.

Ash:

2.5% w/w for Cellosize;

3.5% w/w for Natrosol.

Autoignition temperature: 420°C

Density (bulk):

0.35–0.61 g/cm3 for Cellosize;

0.60 g/cm3 for Natrosol.

Melting point: Softens at 135–140°C; decomposes at about 280°C

Stability and Storage Conditions:

Hydroxyethyl cellulose powder is a stable though hygroscopic material. Aqueous solutions of hydroxyethyl cellulose are relatively stable at pH 2–12 with the viscosity of solutions being largely unaffected. However, solutions are less stable below pH 5 owing to hydrolysis. At high pH, oxidation may occur.

Safety:

Hydroxyethyl cellulose is primarily used in ophthalmic and topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material. Acute and subacute oral toxicity studies in rats have shown no toxic effects attributable to hydroxyethyl cellulose consumption, the hydroxyethyl cellulose being neither absorbed nor hydrolyzed in the rat gastrointestinal tract.

However, although used in oral pharmaceutical formulations, hydroxyethyl cellulose has not been approved for direct use in food products. Glyoxal-treated hydroxyethyl cellulose is not recommended for use in oral pharmaceutical formulations or topical preparations that may be used on mucous membranes. Hydroxyethyl cellulose is also not recommended for use in parenteral products.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxyethyl cellulose dust may be irritant to the eyes, and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hydroxyethyl cellulose is combustible.

When heated to decomposition, hydroxyethyl cellulose emits acrid smoke and irritating vapors, in which case a ventilator is recommended.

5.4 Microcrystalline Cellulose:[48]

Nonproprietary Name:

BP : Microcrystalline cellulose

JP : Microcrystalline cellulose

PhEur : Cellulosum microcristallinum

USP : Microcrystalline cellulose

Synonyms:

Avicel PH; Celex; cellulose gel; Celphere; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; abulose; Vivapur.

Chemical Name and CAS Registry Number: Cellulose [9004-34-6]

Empirical Formula: $(C_6H_{10}O_5)_n$ where n = 220.

Molecular weight : 36000

Functional Category:

Adsorbent, suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications:

Microcrystalline cellulose is primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet- granulation and direct-compression processes. In addition to its used as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting. Microcrystalline cellulose is also used in cosmetics and food product.

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Typical Properties

Bulk density :
0.337g/cm3
0.32g/cm3Avicel pH-101
Density (tapped) :
0.478g/cm3;
0.45g/cm3 for Avicel pH-101
Density (true) : 1.512–1.668 g/cm3

Flowability : 1.41g/s for Emcocel 90M (9)

Moisture content:

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Stability and Storage Conditions:

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:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

5.5 Lactose Monohydrate:[49]

Synonyms:

CapsuLac; GranuLac; Lactochem; lactosum monohydricum; Monohydrate; Pharmatose;PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.

Official Status:

BP : Lactose

PhEur : Lactose Monohydrate

JP : Lactose Hydrate

USP-NF : Lactose Monohydrate

Structural Formula: C12H22O11.H2O

Functional Category:

Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

Description:

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. lactose monohydrate, b-lactose anhydrous, and lactose anhydrous. The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous, and stable a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet.

Handling Precautions:

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

5.6 Povidone (PVP K-30):[50]

Synonyms:

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

Official Status:

BP : Povidone

JP : Povidone

PhEur : Povidone

USP : Povidone

Functional Category:

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Structural Formula:

Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder. Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water, practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K30 value.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Storage:

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

5.7 Colloidal Silicon Dioxide:[51]

Synonyms:

Aerosil; Cab-O-Sil; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed.

Official Status:

BP : Colloidal Anhydrous Silica

JP : Light Anhydrous Silicic Acid

PhEur : Silica, Colloidal Anhydrous

USP-NF : Colloidal Silicon Dioxide

Structural Formula: SiO2

Functional Category:

Adsorbent; anti caking agent; emulsion stabilizer; glidant; Suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Description:

Colloidal silicon dioxide is sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish white- coloured, odourless, tasteless, non gritty amorphous powder.

Solubility:

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Handling Precautions:

Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. In the absence of suitable containment facilities, a dust mask should be worn when handling small quantities of material. For larger quantities, a dust respirator is recommended.

5.8 Magnesium Stearate:[52]

Synonyms:

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Structural Formula : [CH3 (CH2)16COO] 2Mg

Official Status:

BP : Magnesium Stearate

JP : Magnesium Stearate

PhEur : Magnesium Stearate

USP-NF : Magnesium Stearate

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functional Category:

Tablet and capsule lubricant

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

Storage:

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

5.9 Croscarmellose Sodium:[53]

Nonproprietary Names:

BP : Croscarmellose sodium

PhEur : Carmellosum natricum conexum

USPNF : Croscarmellose sodium

Synonyms :

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name : Cellulose, carboxymethyl ether, sodium salt, crosslinked

Functional Category : Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet granulation process.

Description:

Croscarmellose sodium occurs as an odorless, white or greyish white powder.

Stability and Storage Conditions:

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 300C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

5.10 Isopropyl Alcohol:

Nonproprietary Names

Isopropyl Alcohol (BP, JP, PhEur, USP)

Synonyms:

Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2-propanol, sec-propyl.

Chemical Name : Propan-2-ol

Empirical Formula : C3H8O

Molecular Weight : 60.1

Description:

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor and it has a slightly bitter taste.

Typical Properties:

Boiling point : 82.40C

Flammability : Flammable.

Viscosity (dynamic) : 2.43mPasat200C

Specific gravity : 0.786

Functional Category:

Disinfectant, solvent.

Solubility:

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

Applications in Pharmaceutical Formulation or Technology:

Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It

has also been shown to significantly increase the skin permeability of nimesulide. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Storage Conditions:

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

Safety:

Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

5.11 Methylene Chloride:

Chemical Name : Dichloromethane

Other Names : Methylene chloride, methlene dichloride, narkotil, solaesthin.

Appearance : Colourless liquid

Melting point : -96.7˚C

Taste : Sweet aroma

Applications:

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.

Pharmaceutical manufacturing, Paint stripping, Metal cleaning, Paint remover.etc

6. Materials and Methods

Table 3 : Materials used in the study

S.No	Materials	Source
1.	Pentoxifylline	Reine Life Science, Gujarat.
2.	Microcrystalline Cellulose	Ankit pulps chemicals pvt, Maharashtra.
3.	Lactose Monohydrate	Zytex biotech pvt limited, Gujarat.
4.	Croscarmellose Sodium	Remedy labs, Ahmedabad.
5.	Povidone K-30	Akhil healthcare pvt limited, Gujarat.
6.	Colloidal silicon dioxide	SBF pharma pvt limited, Ahmedabad.
7.	Magnesium stearate	Remedy labs, Ahmedabad.
8.	Water	In- House
9.	Hydroxy Propyl Methyl Cellulose K4M	Sakshi chem sciences pvt limited, Nagpur.
10.	Hydroxyethyl cellulose	Sakshi chem sciences pvt limited, Nagpur.
11.	PEG 6000	Akhil healthcare pvt limited, Gujarat.
12.	Isopropyl alcohol	Antares chem pvt limited, Mumbai.
13.	Methylene Chloride	Antares chem pvt limited, Mumbai.

Table 4 : Equipments used in the study

S. No	Equipments	Manufacturers/ Suppliers
1.	Digital Weighing balance	Essae, Banglore
2.	Vernier caliper (digital)	Mitutoyo corps, japan
3.	Hardness tester.	Pharmatest PTB-311E
4.	Friability apparatus, ET-2	Electrolab, Mumbai
5.	Tap density apparatus, ETD-1020	Electrolab, Mumbai
6.	PH meter	Thermolab, Mumbai
7.	Dissolution test apparatus.	Elecctro lab USP XXII
8.	Homogenizer.	Chamunda pharma machinery pvt. Ltd.
9.	Disintegration tester	Electro lab ED-2L
10.	Conventional coating pan GMP-CP-60	Gansons
11.	Rotary Tablet compression machine, CMP210	Elit pilot press
12.	UV-Visible Spectrophotometer	Shimadzu UV 1800, Japan
13.	FTIR Spectrometer	ABB Bomem 104 MB, Canada

Experimental Methods

6.1 Preformulation Studies:

Preformulation studies can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipient. Preformulation investigations are designed to identify those physiochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. It is the first step in the rational development of dosage forms.

6.1.1 Preparation of standard calibration curve of pentoxifylline:

25 mg of pentoxifylline was accurately weighed and dissolved in 25 ml of distilled water in 100 ml volumetric flask and make up the volume using distilled water, to make (250 µg/ml) standard stock solution. From the standard solution pipette out 1,2,3,4, and 5 ml into 50 ml volumetric flask and dilute them up to 50 ml with distilled water to produce concentration as 5,10,15,20, and 25 µg/ml respectively. The absorbance of standard solution was determined using UV/VIS spectrophotometer at 274 nm and distilled water as blank. Values were shown in **table 13 and Fig 11.**

6.1.2 Drug- Excipient Interaction Studies:[54,55]

The compatibility of drug and excipient is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipient under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

FT-IR Analysis:

Potassium Bromide Pellet (KBr) method was used in the study. Test samples were prepared by physical mixing of pentoxifylline and exicipients in ratios of 1:1. Initially 100 mg of Potassium Bromide powder was mixed with 2mg of each sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of Bruker FT-IR spectrophotometer. The spectra were recorded in the wave number region of 2000-600cm^{-1}. In each case the spectra was compared with the pure pentoxifylline spectrum to detect the interactions between drug and excipient.

The FTIR Graphs of drug and excipients were shown in the **Fig. 12,13.**

6.1.3 Physical properties:

For a drug substance to formulate into a dosage form, it is necessary to study the physiochemical properties of bulk drug.

Determination of bulk density and tapped density:

1) Bulk density:[56]

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies (M).It is expressed in gm/ml. Weighed quantity of powder was transferred into a 50 ml measuring cylinder without tapping, during transfer the volume occupied by granules was measured (V0). Bulk density was measured by using formula.

Bulk density = M/Vo

Where,

M = Mass of the powder

Vo= Volume of the powder

2) Tapped Density:

Weighed quantity of powder was taken into graduated cylinder, volume occupied was noted down (M). Then cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the final reading was denoted by (Vi).The % Volume variation was calculated by using the following formula.

Tapped density = M/Vi

Where,

M = Mass of the powder

Vi = Tapped volume

3) Carr's index:[57]

Compressibility is the ability of powder to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of powder were determined, which is given as Carr's compressibility index.

CI=Vi-V0 / Vi × 100

Where,

CI = Compressibility index

V0 = Bulk density

Vi = Tapped density

Table 5 : Compressibility index

Compressibility index (%)	Flow characters
< 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
> 32	Very poor

4) Hausner's ratio:

It is a measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Hausner Ratio = Vi / Vo

Where,

V0 = Bulk density

Vi = Tapped density

Table 6 : Hausner's ratio

Flow characters	Hausner ratio
Excellent	1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very Very poor	>1.60

5) Angle of repose:[58]

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the flow ability of powder.

Procedure:

A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface .The radius was measured and angle of repose was calculated by using the formula.

θ = tan -1(h/r)

Where,

θ = Angle of repose,

h = height of the heap of pile,

r = radius of base of pile.

Table 7 : Flow Properties and Corresponding Angle of Repose

Flow properties	Angle of repose(θ)
Excellent	25-30
Good	31-35
Fair – aid	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

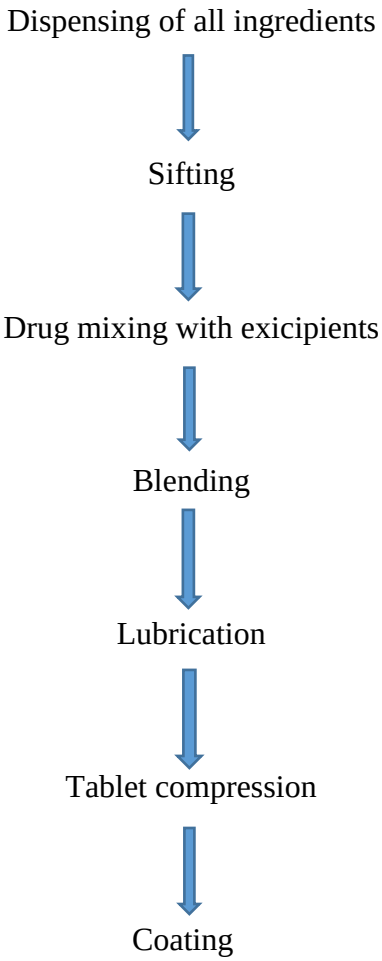
6.2 Formulation development:

The main objective of this formulation development is to design a extended release drug delivery system in the form of a tablet.

❖ Wet granulation method:

Pentoxifylline extended release tablet were prepared by wet granulation method.

Fig : Manufacturing flow chart



Step I: Dispensing of materials

- All the ingredients were weighed accurately as per manufacturing formula (Table). Weighed raw materials are dispensed, packed in an individual clean poly bags and labeled.

Step II: Sifting

- Accurately weighed quantity of pentoxifylline API was sifted through 40 # mesh. Weighed quantity of Lactose, MCC 101, CCS was passed through 40# mesh separately.

Step III: Preparation of binder solution

- Povidone was diluted in sufficient quantity of water.

Step IV: Dry mixing

- All the materials were dry mixed for 10 minutes.

Step V: Granulation

- Binder solution is added to the dry mix slowly. After the addition of the binder, it is mixed for about three minutes to form granules.

Step VI: Drying

- blend was loaded in tray dryer and dried at a temperature of 55°C. Drying is continued until loss on drying reaches NMT 2%.

Step VII: Sizing

- Blend was sifted through 20#mesh.

Step VIII: Pre lubrication

- Colloidal silicon dioxide (Aerosil) was sifted through 40#mesh and kept aside. Load this in octagonal blender along with the blend.

Step IX: Lubrication

- Magnesium stearate was sifted through 40#mesh and added to the above step and mixed for 2 minutes in blender.

Step X: Compression

- Compression was carried out in 8 stationed compression machine with 15/7 inch, standard concave plain on both sides. Blended material was loaded in a hopper and powder was compressed to tablets by operating rotary tablet compression machine. Physical parameters like Weight variation, Hardness, Thickness, are monitored to meet the predefined specifications and noted.

Core tablet specifications:

Description: White coloured, caplet shaped, uncoated tablet.

Average weight (mg): 600 mg ± 5%

Hardness: Not Less Than 4 kg/ cm2

Thickness: 5.10mm to 5.40mm

Friability: Not More Than 1.0 %

Assay of API: 95%-105%

Step XI: Coating

Inner layer coating solution:

- Methylene Chloride was transferred into a stainless steel vessel. To this PEG 6000 and HPMC K4M was added and stirred well.
- Finally Isopropyl alcohol was added with above solution under constant stirring to avoid lumps formation.
- The prepared tablets were coated in a coating pan till the average weight build up.

Outer layer coating solution:

- Isopropyl alcohol was transferred into a stainless steel vessel. To this HEC was added and stirred well.
- Finally Methylene Chloride was added with above solution under constant stirring to avoid lumps formation.
- The prepared tablets were coated in a coating pan till the average weight build up.

Table 8: Coating specifications

Inlet temperature(°C)	40-50
Outlet temperature(°C)	40-45
Spray pump(rpm)	6-8
Air pressure(kg/cm^2)	4-5
Pan (rpm)	4-8

Coated tablet specifications:

Description: White coloured, Caplet shaped, Coated Extended release tablet.

Average Weight (mg) : 648 ± 5%

Thickness : 5.20 - 5.60mm

Assay of API : 95%-105%

Dissolution (as per USP) :

1st hour – NMT 30%

4th hour – Between 30% and 55%

8th hour – NLT 60%

12th hour – MLT 80%

Table 9 : Formulation of Pentoxifylline Extended Release tablet

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Pentoxifylline	400	400	400	400	400	400	400	400	400
Microcrystalline cellulose	60	60	60	60	60	60	60	60	60
Lactose	92.8	92.8	92.8	92.8	92.8	92.8	92.8	92.8	92.8
Povidone k-30	22	22	22	22	22	22	22	22	22
Croscarmellose sodium	18	18	18	18	18	18	18	18	18
Colloidal silicon dioxde	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**
Coating									
Inner layer									
HPMC K4M (mg)	12	18	6	18	24	12	24	36	12
Isopropyl alcohol	15	22.5	7.5	22.5	30	15	30	45	15
Methylene dichloride	15	22.5	7.5	22.5	30	15	30	45	15
Outer layer									
Hydroxyethyl cellulose (mg)	12	6	18	18	12	24	24	12	36
Isopropyl alcohol	15	7.5	22.5	22.5	15	30	30	15	45
Methylene dichloride	15	7.5	22.5	22.4	15	30	30	15	45
Weight gain (%)	4%	4%	4%	6%	6%	6%	8%	8%	8%
Total weight (mg)	**624**	**624**	**624**	**636**	**636**	**636**	**648**	**648**	**648**

6.3 Evaluation of core and coated tablet:

6.3.1 General appearance:

The general appearance of a 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, color, presence or absence of odour, taste etc.

6.3.2 Weight variation:[59]

Twenty tablets were selected randomly from a particular batch and weighed individually using an electronic balance and average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviations shown in table and none deviate by more than twice the percentage.

Table 10 : Weight variation limits (as per USP)

Average weight of tablet(mg)	Maximum% difference allowed
130 mg or less	10
130-324	7.5
324 or more	5

6.3.3 Thickness:

Ten tablets from the representative sample were taken and individual tablet thickness was measured by using digital vernier calipers. Average thickness and standard deviation values were calculated.

6.3.4 Hardness:[60]

Hardness indicates the ability of a tablet to withstand mechanical shockes while handling. Tablet hardness was measured by using Monsanto hardness tester. It is expressed in kg/cm^2. From each batch ten tablets were measured for the hardness and average values was recorded.

6.3.5 Friability Test:

From each batch, 10 tablets were accurately weighed and placed in the friability test apparatus. Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were dedusted and reweighed. The friability was calculated as the percentage weight loss.

% Friability was calculated as follows

% Friability = (W1 – W2) x 100/W1

Where,

W1 = Initial weight of the tablets.

W2 = Final weight of the tablets.

Friability values below 1 % are generally acceptable.

6.3.6 Swelling studies:[61]

Swelling of tablet excipients (polymer) involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of percentage weight gain by the tablet.

Method

One tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 5hrs. The %weight gain by the tablet was calculated by the formula,

Swelling index = (Wt-Wo)×100)/Wo

Where,

Wt = as weight of the tablet at time t.

Wo = as initial weight of tablet.

6.3.7 Disintegration Time:

The disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in

water maintained at a temperature of 37ºC ± 2ºC and the apparatus was switched on. The time taken to disintegrate the tablets completely was noted.

6.3.8 Assay:

Preparation of standard stock solution of Pentoxifylline:

25mg of pentoxifylline was accurately weighed transferred to a 100 ml volumetric flask and made up to 100 ml with distilled water. 1 ml of the solution was diluted to 10 ml with distilled water. The absorbance of the resulting solution was measured at 274 nm.

Preparation of sample solution:

Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. Powder equivalent to 25 mg of pentoxifylline was weighed and transferred to a 100 ml standard flask. The powder was then dissolved in distilled water and sonicated. The volume was made upto 100 ml with distilled water. 1mL of the solution was diluted to 10 ml with distilled water. The absorbance of the resulting solution was measured at 274 nm. The amount of the drugs was determined.

6.3.9 *In-vitro* drug release:[62]

In-vitro release of the drug was determined by estimating the dissolution profile.

Dissolution test for Pentoxifylline:

In-vitro drug release study was carried out using USP apparatus II at 37℃ ± 0.5℃ for 12 hrs, at 100 rpm. Distilled water was used as dissolution medium ,5ml of sample was withdrawn after 1,4,8,12 hours and was replaced with an equal volume of fresh dissolution medium to maintain the equilibrium. Collected samples are analysed by UV spectrophotometer at 274 nm, using water as the blank.

Parameter for dissolution test:

Apparatus : USP apparatus II

Revolution per minute : 100 rpm

Dissolution medium : Distilled water

Temperature : 37 ± 0.50C

Dissolution time : 12hrs

Sample quantity with drawn : 5ml

Sample time interval : 1,4,8,12 hr

6.4 Release Kinetics:[63-65]

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1) Log cumulative percent drug remaining versus time
(first order kinetic model)
2) Cumulative percent drug release versus square root of time
(Higuchi's model)
3) Cumulative percent drug release versus time
(zero order kinetic model)
4) Log cumulative Percent Drug released versus log time
(korsmeyers model)

Drug release kinetics-model fitting of the dissolution Data:

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers-peppas models. Other release parameters, difference factor (f1), similarity factor (f2) can be used to characterize drug dissolution / release profile with the marketed product.

1) Zero-order kinetics:

A zero-order release would be predicted by the following equation.

$Q_t = Q_o + K_{ot}$ **eq (1)**

Where,

Q_t = amount of drug dissolved in time t

Q_o = Initial amount of drug in solution

K_{ot} = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to $k_o t$.

2) First-order kinetics:

A first order release would be predicted by the following equation.

Log C = Log Co - Kt / 2.303 **eq (2)**

Where,

C = Amount of drug remained at time t

Co = Initial concentration of drug

K = First-order rate constant

The data obtained rate plotted as log cumulative percentage of drug remaining versus time which would yield a straight line with a slope of -k/2.303.

3) Higuchi model:

Drug release from the matrix devices by diffusion has been described by following higuchi's classical diffusion equation.

Q = [DE/ τ(2A- ECs) Cst] **eq (3)**

Where,

Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

Cs = solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

Q = Kt ½ **eq (4)**

When the data obtained were plotted as cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

4) Korsmeyers Peppas model:

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

Mt / Mά = Ktn **eq (5)**

Where,

Mt / Mά = fraction of drug released at time‘t’

K = Constant incorporating the structural and geometrical

Characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

Log Mt / Mά = Log K+ n Log t **eq (6)**

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for fickian release, > 0.45 and < 0.89 for non-fickian release, 0.89 for the case 2 type release and > 0.89 super case 2 type release.

6.5 Similarity Factor and Differential Factor Calculation:

The similarity factor (f_2) was defined by CDER, FDA, and EMEA as the “logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and marketed release profiles”. Dissimilarity or difference factor (f_1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and marketed release profiles are identical and increases proportionally with the dissimilarity between the two profiles. There are several methods for dissolution profile comparison. f_2 is the simplest among those methods. Moore & Flanner proposed a

model independent mathematical approach to compare the dissolution profile using two factors f_1& f_2.

$$f_1 = \{ [\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t] \} . 100 \qquad \text{eq (1)}$$

$$f_2 = 50. \text{Log} \{ [1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\} \qquad \text{eq (2)}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time point of the marketed & test product respectively. The factor f_1 is proportional to the average difference between the two profiles, where as factor f_2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f_2 and its significance is shown in the following

Table 11 : Similarity factor f2 and its significance:

Difference Factor	Similarity Factor	Inference
0	100	Dissolutions profile are similar
≤15	≥50	Similarity or equivalence two profiles

6.6 Stability studies:[67]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration for drug registration applications in the European Union, Japan and The United States of America. ICH specifies the length of study and storage conditions.

Table 12 : Stability Storage Conditions

Study	Storage condition	Minimum time period covered by data at submission.
Long term	25ºC ± 2 ºC/ 60% RH ± 5% RH	12 months
Intermediate	30ºC ± 2 ºC/ 65% RH ± 5% RH	6 months
Accelerated	40ºC ± 2 ºC/ 75% RH ± 5% RH	3 months

Stability studies were conducted according to ICH Guidelines; the optimized formulation was packed and stored at three different conditions i.e. Long term, intermediate and accelerated conditions in a stability chamber for a period of 3 months. The samples were evaluated for assay and dissolution studies at regular intervals.

7. Results and Discussion:

7.1 Calibration Curve:

Table 13 : Calibration curve of Pentoxifylline

S.No	Concentration(µg/mL)	Absorbance(nm)
1.	**5**	0.172
2.	**10**	0.352
3.	**15**	0.535
4.	**20**	0.691
5.	**25**	0.86

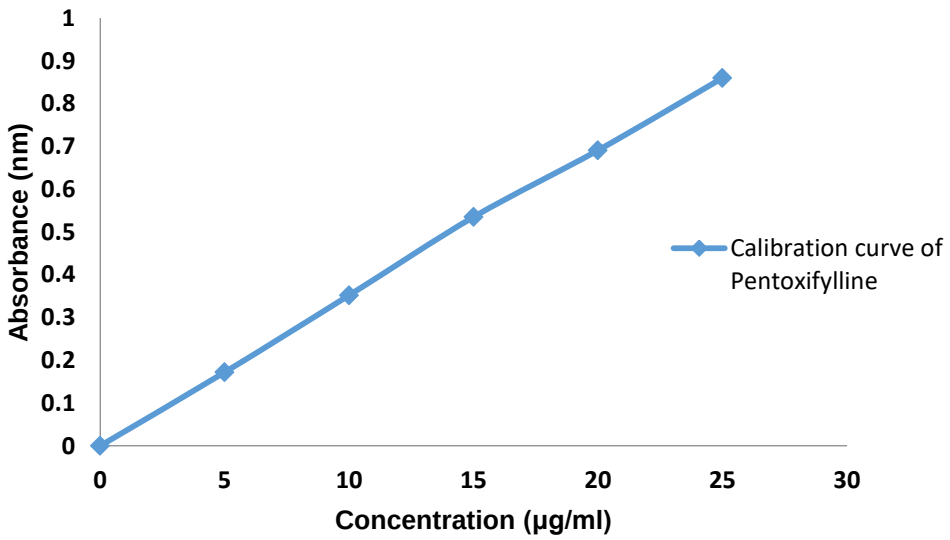


Figure 11 : Calibration curve of pentoxifylline

7.2 FT-IR Studies:

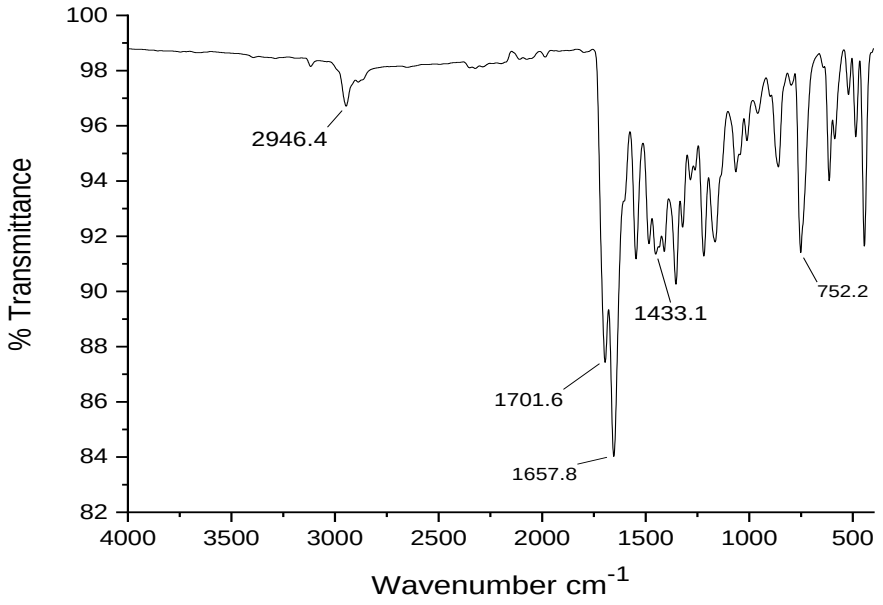


Fig. 12 : FT-IR Spectrum of Pentoxifylline

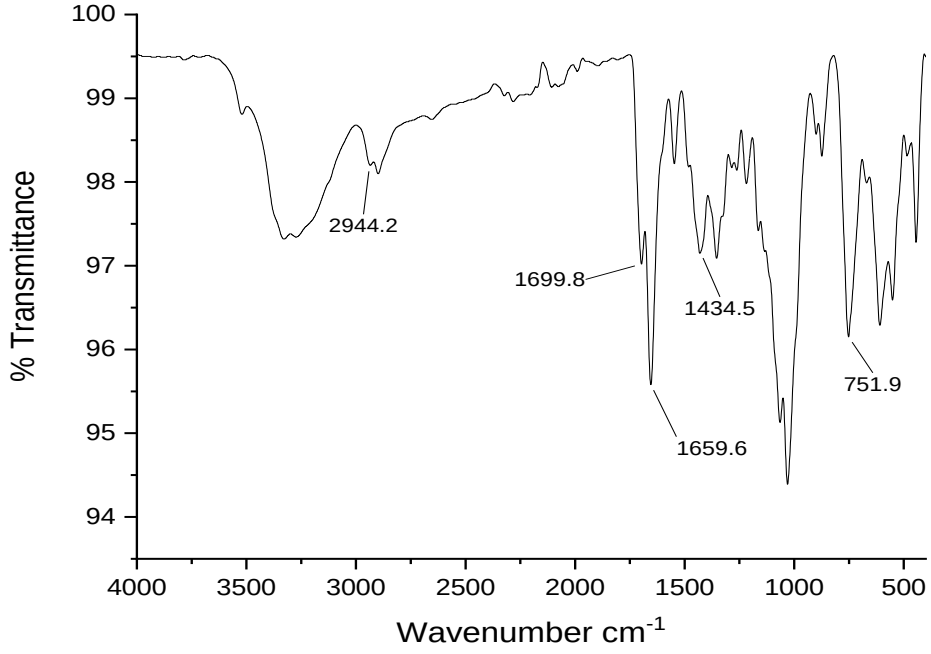


Fig 13: FT-IR Spectrum of Pentoxifylline with Excipients

7.3 Evaluation of granules:

Table 14 : Evaluation of granules

Formulation	Bulk density (g/ml) ± SD	Tapped density (g/ml) ± SD	Carr's index	Hausner's Ratio	Angle of repose(θ)
F1	0.420±0.13	0.478±0.12	12.32±0.49	1.10±0.01	24.39±0.18
F2	0.418±0.11	0.478±0.24	13.14±0.47	1.10±0.14	24.89±0.36
F3	0.425±0.14	0.487±0.11	13.56±0.13	1.26±0.02	25.60±0.28
F4	0.422±0.12	0.480±0.22	13.24±0.20	1.08±0.03	26.10±0.22
F5	0.426±0.11	0.488±0.18	13.46±0.10	1.14±0.04	27.40±0.16
F6	0.422±0.22	0.488±0.15	12.46±0.22	1.18±0.03	24.87±0.44
F7	0.427±0.22	0.482±0.26	12.80±0.30	1.16±0.05	26.90±0.59
F8	0.428±0.17	0.474±0.14	13.44±0.30	1.21±0.05	28.28±0.46
F9	0.424±0.23	0.478±0.17	12.98±0.56	1.18±0.06	24.98±0.41

Mean ± SD(n=3)

The results show that all the formulation blends showed good flow properties and can form uniform tablets.

7.4 Evaluation of Core tablet:

Table 15 : Evaluation of Core tablet

Formulations	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F1	602±0.32	5.3±0.05	7.2±0.06	0.12	99.31±0.17
F2	599±0.28	5.2±0.03	6.8±0.04	0.17	98.64±0.15
F3	600±0.32	5.2±0.02	7.0±0.07	0.17	98.86±0.13
F4	597±0.14	5.1±0.02	7.2±0.04	0.12	99.78±0.16
F5	605±0.26	5.4±0.05	6.8±0.07	0.21	98.80±0.06
F6	603±0.22	5.3±0.02	7.2±0.04	0.12	99.79±0.04
F7	600±0.16	5.2±0.03	7.0±0.03	0.10	98.83±0.13
F8	600±0.14	5.2±0.03	7.2±0.01	0.13	99.45±0.08
F9	598±0.21	5.1±0.02	7.0±0.05	0.12	99.87±0.12

Mean±SD(n=3)

From the above post compression parameters the tablets were found to comply with the official standards.

7.5 Swelling Index:

Table 16 : Swelling Index

Time(hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
1	15.5	14.30	17.5	21.50	20.35	24.27	28.50	31.21	34.2
2	20.34	18.34	20.23	27.39	25.23	27.23	33.21	39.40	38.34
3	24.14	22.38	23.80	29.59	29.20	33.27	38.56	43.80	42.31
4	29.98	27.40	26.45	33.26	32.46	36.23	45.59	49.50	46.04
5	28.30	30.23	28.46	35.62	38.42	39.21	48.20	53.30	49.60
6	31.98	33.80	32.91	41.87	41.10	42.45	52.16	57.43	54.57

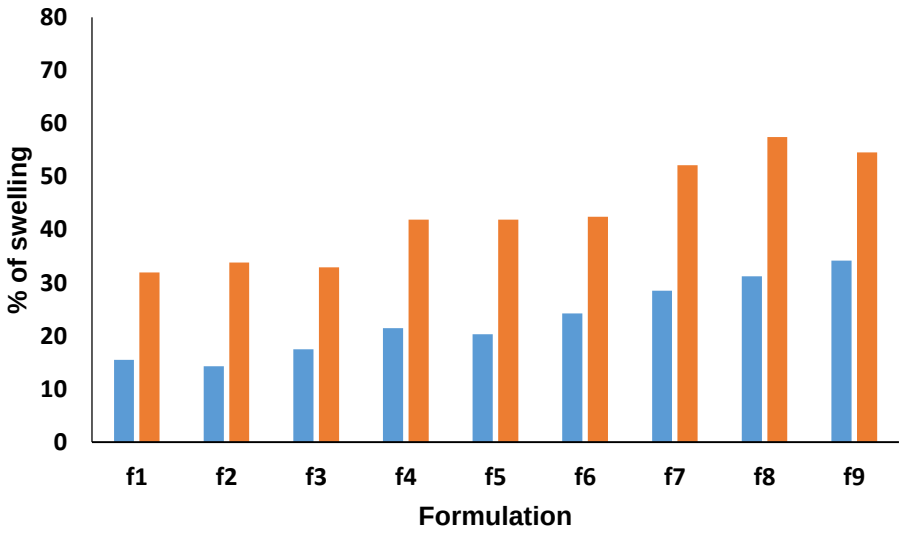


Fig 14 : Swelling Index

7.6 *In-vitro* dissolution study:

Table 17 : *In-vitro* dissolution Profile for formulation F1

S. No	Time(hrs)	Percentage drug release(%)
1.	1	33.32
2.	4	77.85
3.	8	99.76
4.	12	-

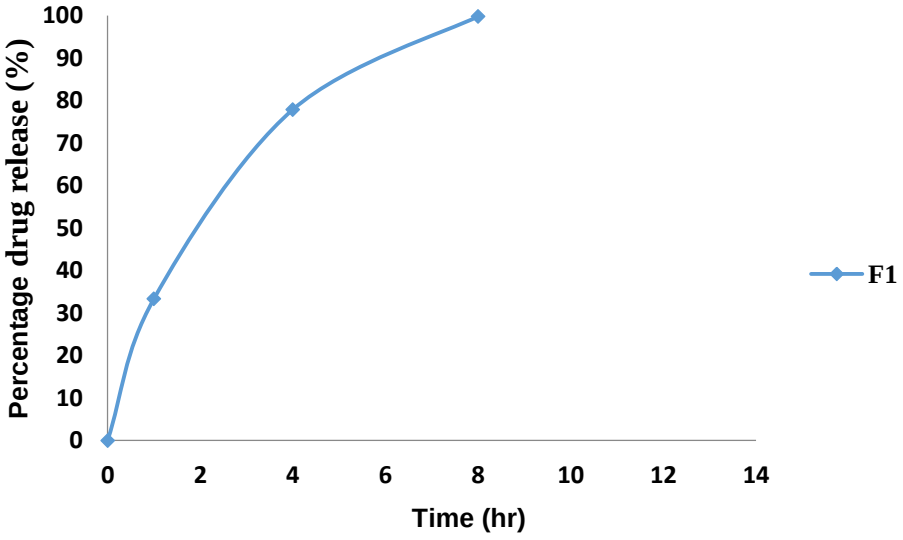


Fig 15 : *In-vitro* dissolution profile for formulation F1

Table 18 : *In-vitro* dissolution Profile for formulation F2

S. No	Time(hrs)	Percentage drug release(%)
1.	1	32.46
2.	4	75.68
3.	8	99.56
4.	12	-

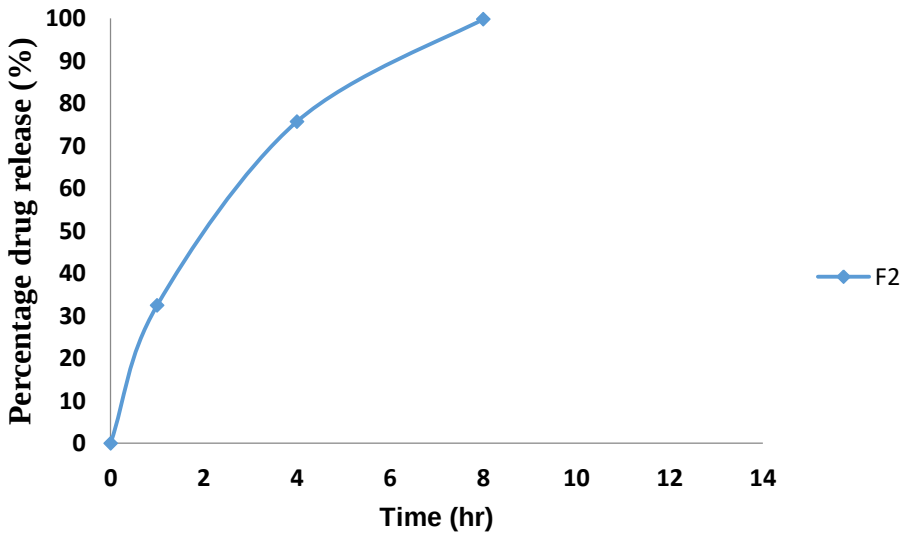


Fig 16 : *In-vitro* dissolution profile for formulation F2

Table 19 : *In-vitro* dissolution Profile for formulation F3

S. No	Time(hrs)	Percentage drug release(%)
1.	1	38.6
2.	4	79.24
3.	8	99.97
4.	12	-

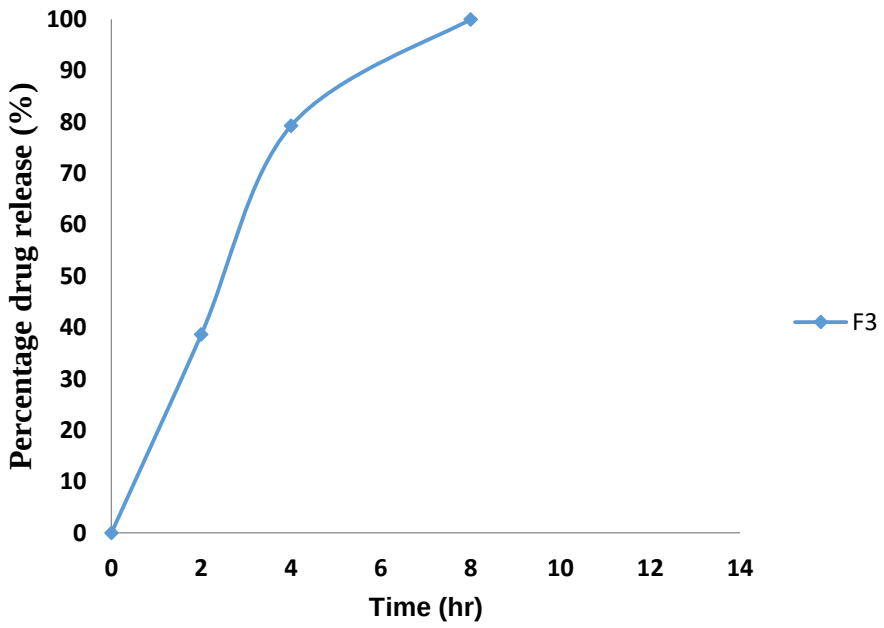


Fig 17 : *In-vitro* dissolution profile for formulation F3

Table 20 : *In-vitro* dissolution Profile for formulation F4

S. No	Time (hrs)	Percentage drug release (%)
1.	1	26.42
2.	4	56.65
3.	8	85.48
4.	12	-

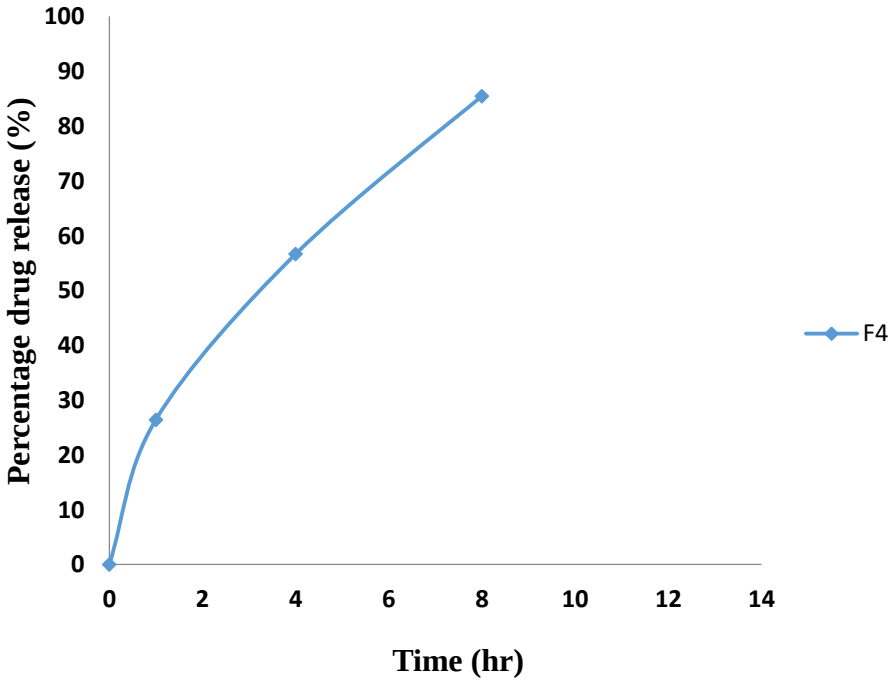


Fig 18 : *In-vitro* dissolution Profile for formulation F4

Table 21 : *In-vitro* dissolution Profile for formulation F5

S. No	Time(hrs)	Percentage drug release(%)
1.	1	25.92
2.	4	55.12
3.	8	84.85
4.	12	-

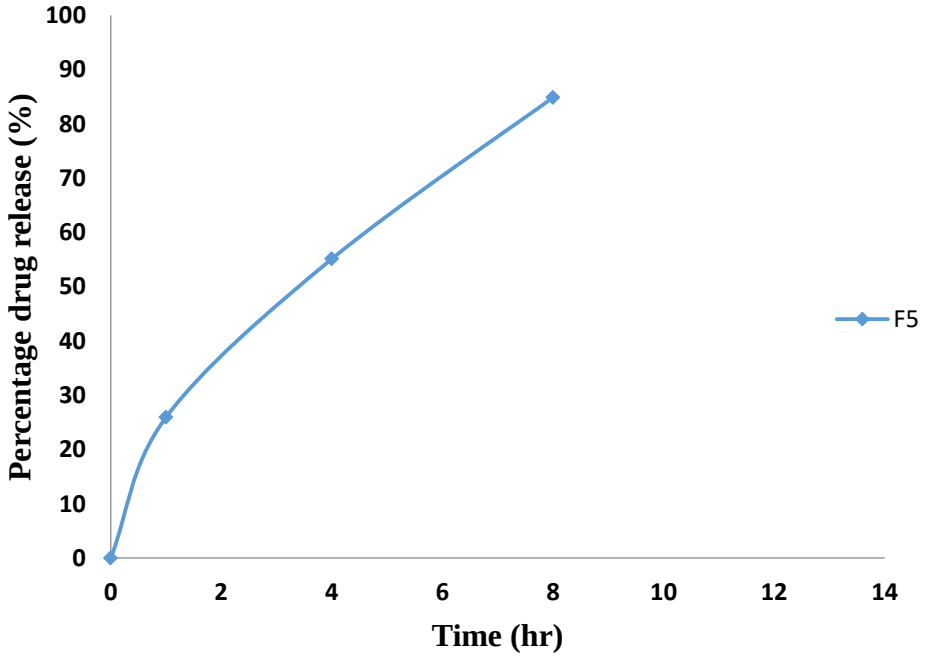


Fig 19 : *In-vitro* dissolution Profile for formulation F5

Table 22 : *In-vitro* dissolution Profile for formulation F6

S. No	Time(hrs)	Percentage drug release(%)
1.	1	28.09
2.	4	57.48
3.	8	88.66
4.	12	-

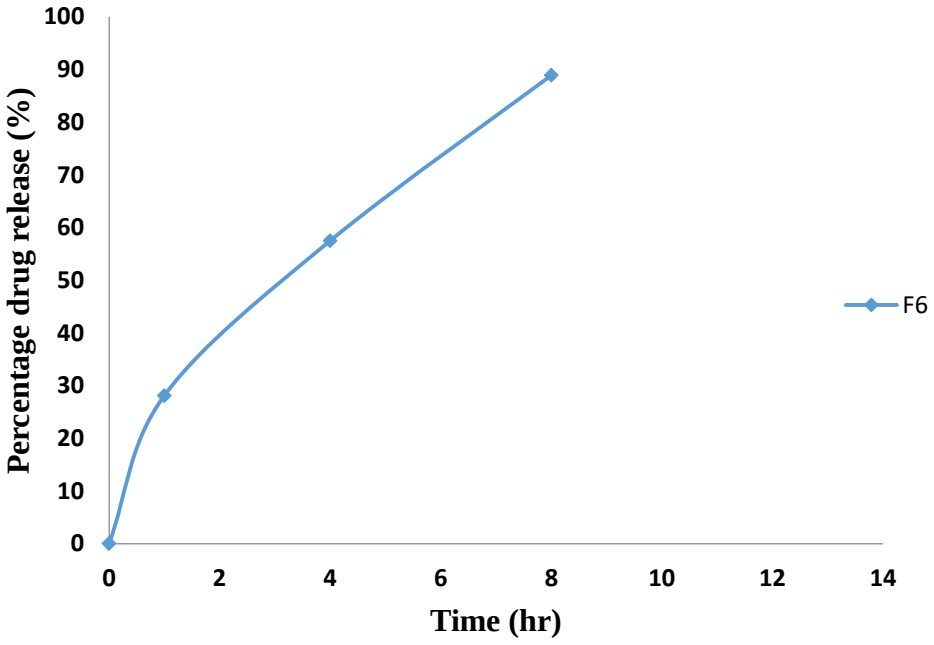


Fig 20 : *In-vitro* dissolution Profile for formulation F6

Table 23 : *In-vitro* dissolution Profile for formulation F7

S. No	Time(hrs)	Percentage drug release(%)
1.	1	19.42
2.	4	36.93
3.	8	76.29
4.	12	96.56

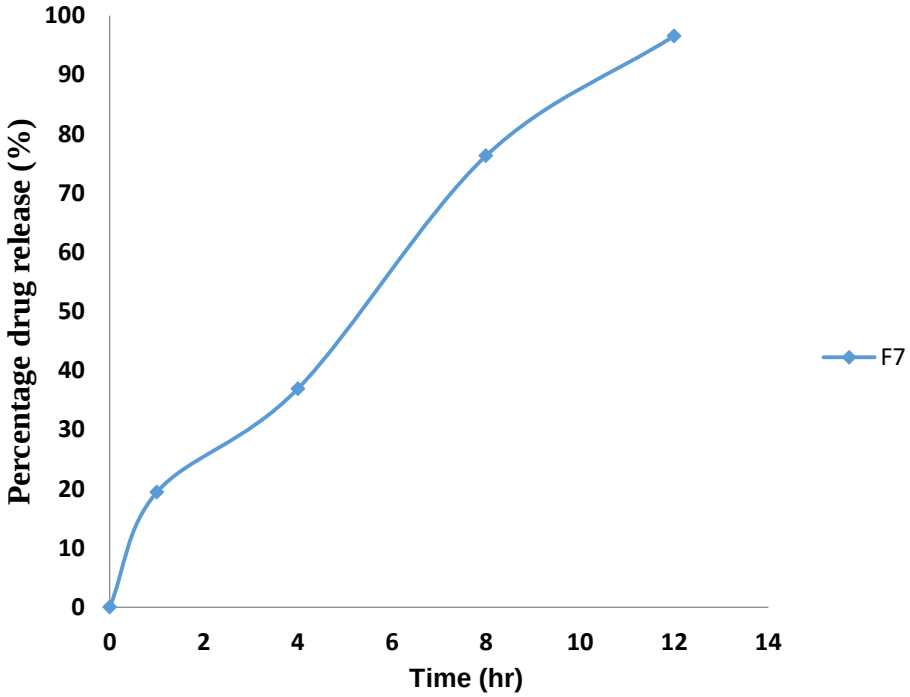


Fig 21 : *In-vitro* dissolution Profile for formulation F7

Table 24 : *In-vitro* dissolution Profile for formulation F8

S. No	Time(hrs)	Percentage drug release(%)
1.	1	16.86
2.	4	35.62
3.	8	73.82
4.	12	94.75

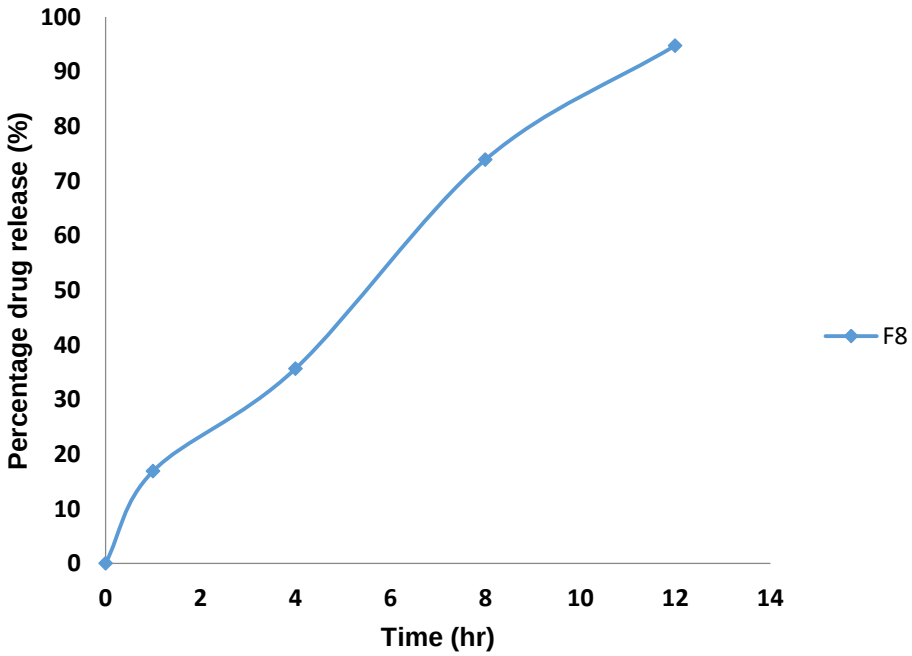


Fig 22: *In-vitro* dissolution Profile for formulation F8

Table 25 : *In-vitro* dissolution Profile for formulation F9

S. No	Time(hrs)	Percentage drug release(%)
1.	1	20.16
2.	4	37.46
3.	8	77.37
4.	12	97.69

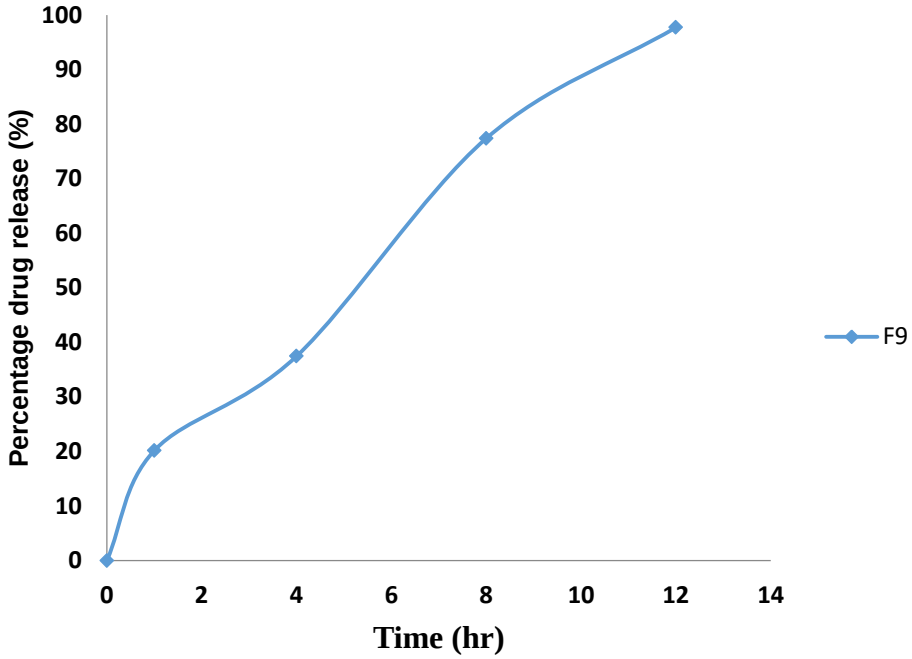


Fig 23 : *In-vitro* dissolution Profile for formulation F9

Table 26 : *In-vitro* dissolution Profile for marketed product

S. No	Time(hrs)	Percentage drug release(%)
1.	1	17.44
2.	4	36.41
3.	8	74.37
4.	12	95.46

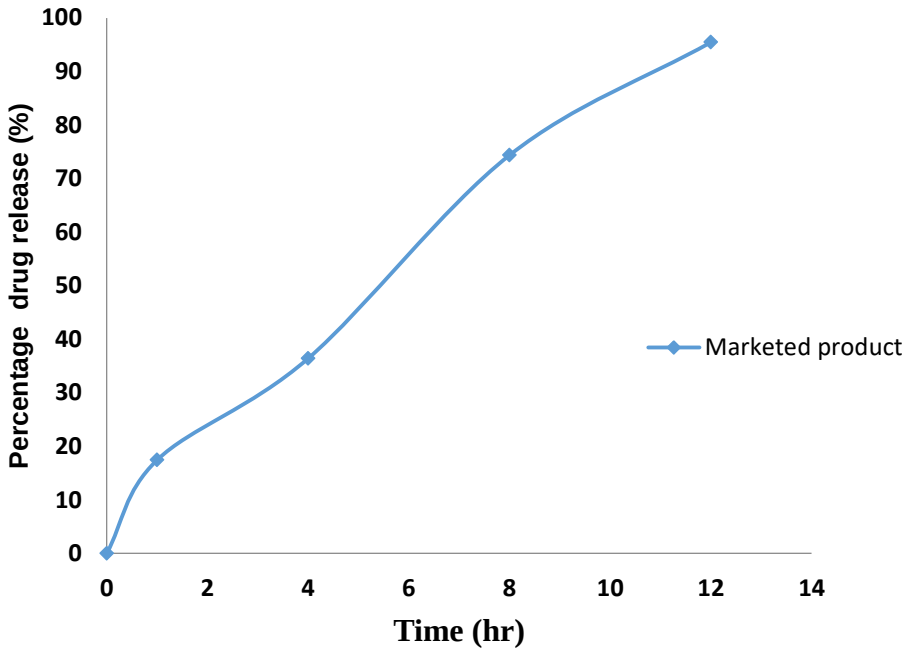


Fig 24 : *In-vitro* dissolution Profile for marketed product

Table 27 : *In-vitro* dissolution Profile for formulation (F1-F9) & Marketed product

Time interval (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed product
1	33.32	32.46	38.6	26.42	25.92	28.09	19.42	16.86	20.16	17.44
4	77.85	75.68	79.24	56.65	55.12	57.48	36.93	35.62	37.46	36.41
8	99.76	99.56	99.97	85.48	84.85	88.66	76.29	73.82	77.37	74.37
12	-	-	-	-	-	-	96.56	94.75	97.69	95.46

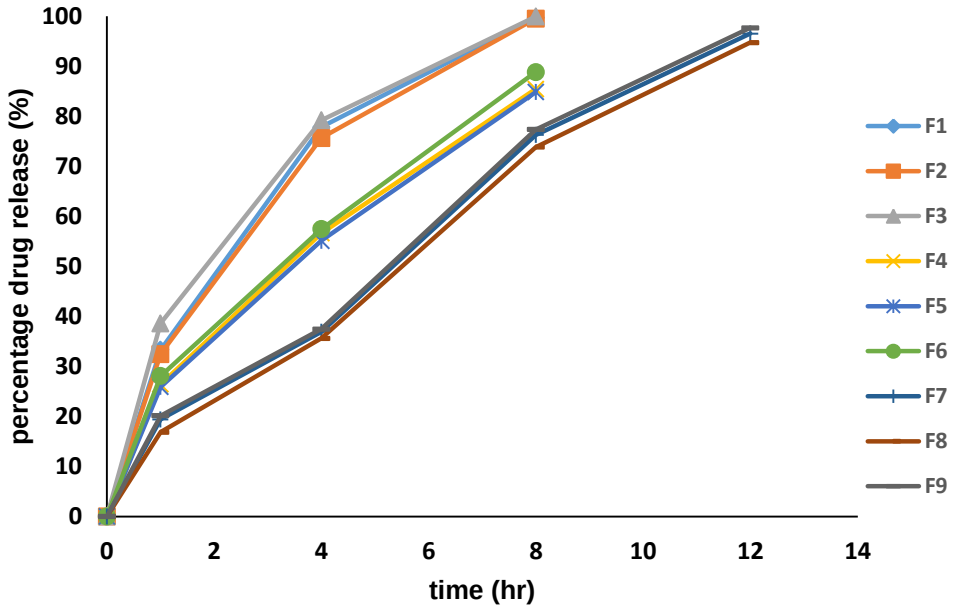


Fig 25: *In-vitro* dissolution profile for formulation (F1-F9)

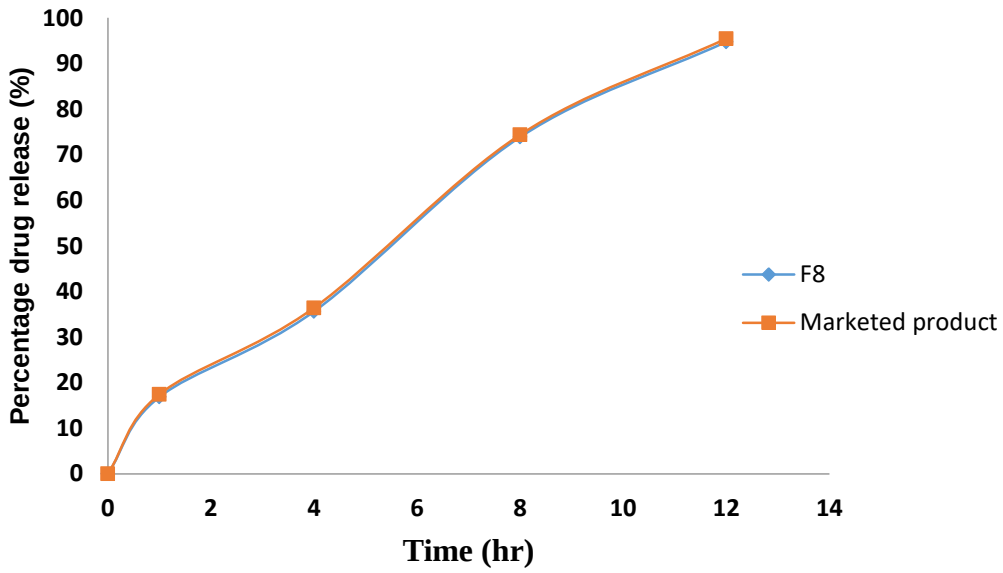


Fig 26 : Comparison of optimized formulation (F8) with Marketed product

7.7 Release kinetics:

Table 28 : Kinetic studies of matrix Tablets

% drug release	Time t	Square root of time	Log% release	Log t	Log% remain
16.86	1	1.0000	1.2269	0.0000	83.1400
35.62	4	2.0000	1.5517	0.6021	64.3800
73.82	8	2.8284	1.8684	0.9031	26.1400
94.75	12	3.4641	1.9766	1.0792	5.2500

OPTIMIZED FORMULATION	Zero-order kinetics		First-order kinetics		Higuchi		Korsmeyer-Peppas	
	K	r^2	K	r^2	K	r^2	N	r^2
	7.81	0.9942	-0.1019	0.936	27.72	0.9571	0.7062	0.9788

1) **Zero Order Kinetics:**

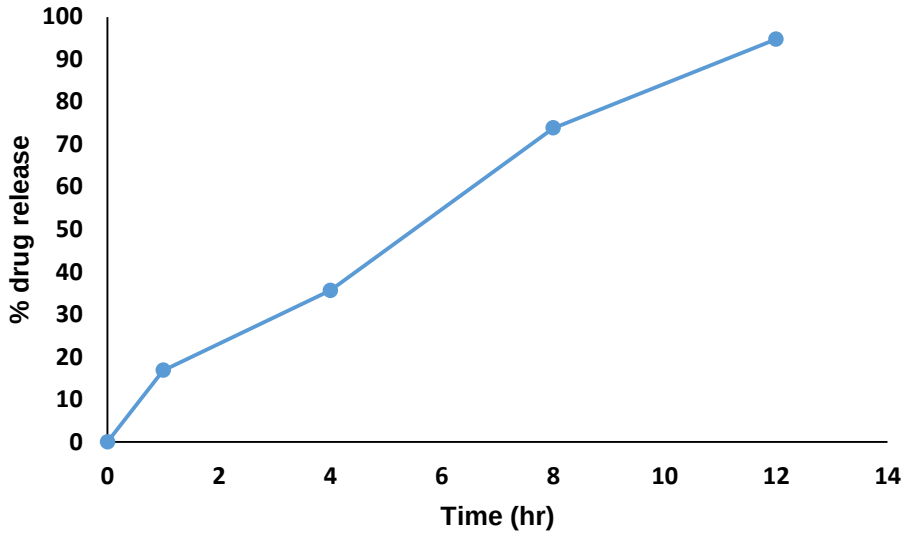


Fig 27 : Graph for the formulation F8-Zero Order Kinetics

2) **First order kinetics:**

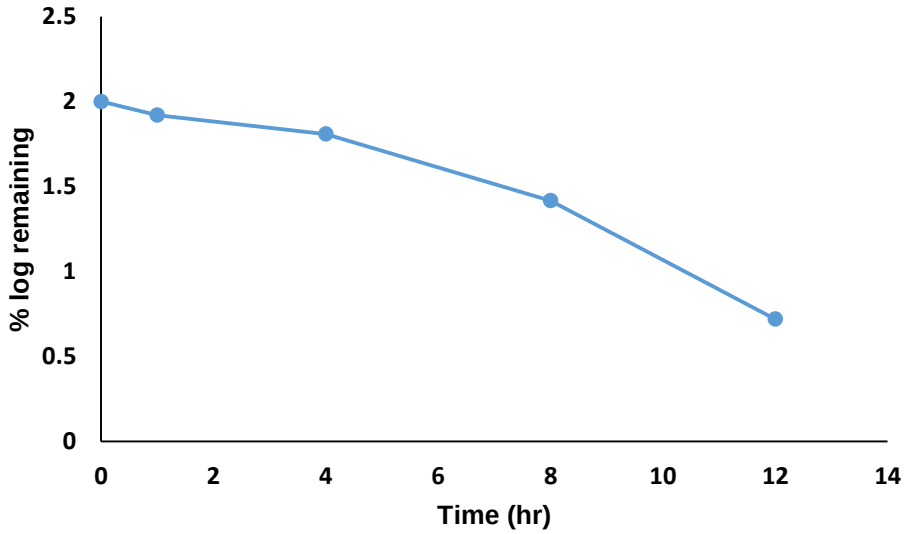


Fig 28 : Graph for the formulation F8-First Order Kinetics

3) Higuchi Kinetics:

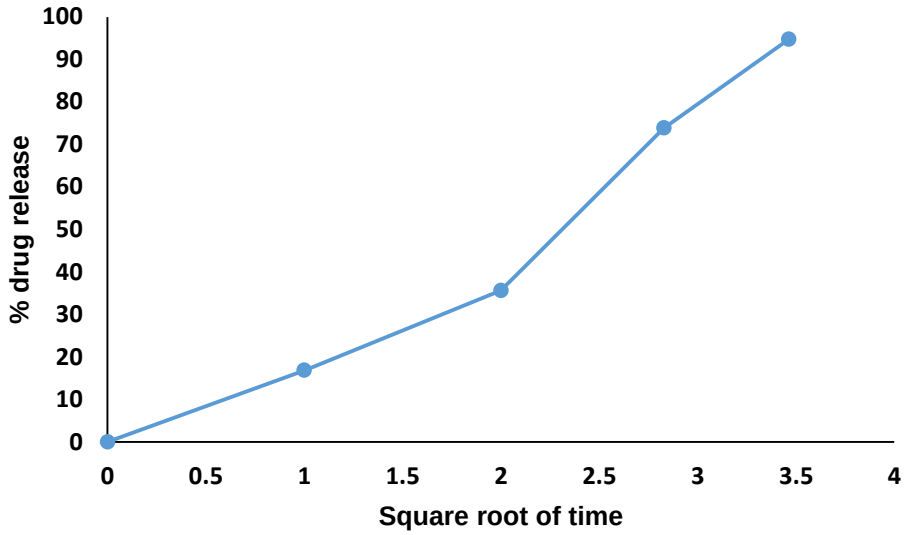


Fig 29 : Graph for the formulation F8-Higuchi model

4) Korsmeyers Peppas Model:

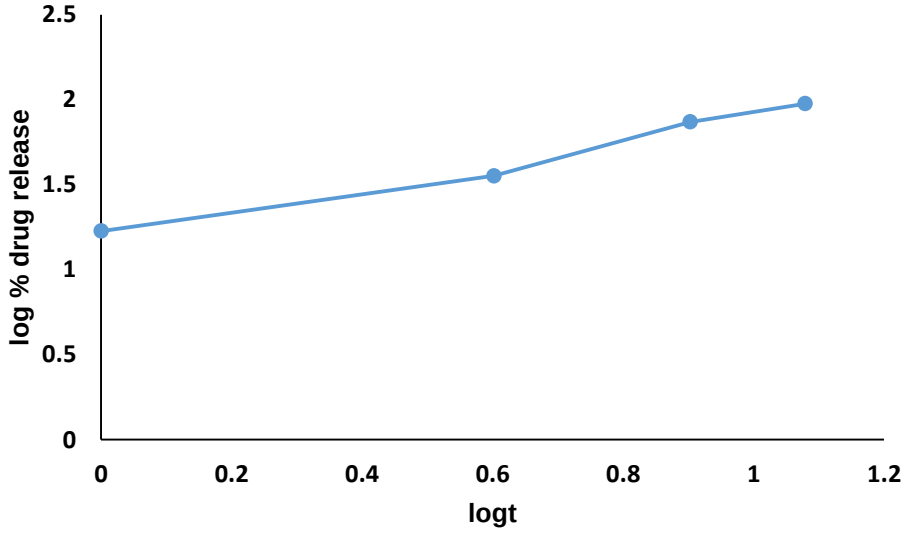


Fig 30 : Graph for the formulation F8- Korsmeyers Peppas model

7.8 Similarity Factor and Differential Factor:

Table 29 : Comparision between Test and Reference Product

S.No	Time(hrs)	Percentage drug release(%) (test)	Percentage drug release(%) (reference)
1	1	16.86	17.44
2	4	35.62	36.41
3	8	73.82	74.37
4	12	94.75	95.46

Table 30 : Similarity Factor and Differential Factor Calculation

Differential Factor - F1 [Acceptance Criteria : 0 -15]	2
Similarity Factor - F2 [Acceptance Criteria : 50-100]	92

7.9 Stability Studies:

Table 31 : Accelerated Stability Study

Storage conditions at 40ºC ± 2˚C /75 % ± 5%RH

Parameters	Initial	1st Month	2nd Month	3rd Month
Description	White colour, Caplet shape, Polymer coated tablet.	Complies	Complies	Complies
Average weight (mg)	648	648	647.5	647.3
Thickness (mm)	5.65	5.65	5.64	5.64
Hardness (kg/cm2)	7.2	7.2	7.1	7.1
Assay (%)	99.45	99.45	99.27	99.14
Dissolution	94.75	94.67	94.52	94.43

Discussion

Preformulation:

The experimental work started with the raw material analysis of pentoxifylline as per USP, the physical properties such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose values were depicted.

7.1 Calibration curve:

The calibration curve of pentoxifylline was prepared in distilled water at determined wavelength at 274 nm. The r^2 and slope were found to be 0.9995 and 0.03451. The results were shown in **Table 13 and Fig:14.**

7.2 FT-IR Studies:

The IR spectra of pure drug showed sharp peaks at 2945 cm^{-1} for –CH,1701cm^{-1} for –CO, 1658cm^{-1} for amide −CO stretching, 1433cm^{-1} for $–CH_3$, 752cm^{-1} for $–(CH_2)n−$ skeletal vibration. These peaks were found to be prominent in the spectra of physical mixtures containing the drug and excipients. This indicates there was no interaction between drug and excipients shown in the **Fig: 12-13.**

7.3 Evaluation of Physical Mixture:

Bulk density, Tapped density, Carr's index and Hausner's ratio, Angle of repose were evaluated for the prepared blend.

The formulations F1 to F9, it shows good flow property. The angle of repose was found to be in the range 24.39° to 28. 28°.Compressibility index was carried out, it found between12.32 to 13.56, indicating the powder blend has the required flow property for compression. Hausner's ratio was calculated for the blend, it was found to be 1.10-1.26. The results showed in the **Table: 14.**

7.4 Evaluation of Core Tablet:

The results are shown in the **Table:15.** The hardness of tablets of each batch ranged between 6.8 to 7.2 kg/cm^2, this ensures good handling characteristics of all batches. Thickness of all the formulation was found to be in the range 5.10 mm to 5.40 mm. Friability of all the formulations were found to be in the range 0.12% to 0.21%. The percentage of drug content for F1 to F9 was found to be 98.64% to 99.87%, it complies with official specifications.

7.5 Determination of Swelling index for Pentoxifylline:

Formulation F8 shows a higher swelling index due to the fact that the viscosity of the polymer has a significant effect on the swelling process. As can be seen from the above, since the polymer gradually absorbs water and swells due to its hydrophilicity, the swelling of the tablet goes through and swells with time, and the water absorption rate increases as the viscosity of the polymer increases. At the end, the polymer of the higher viscosity shows the maximum absorption. It was shown in above **Table 16 and Fig.14.**

7.6 Effect of HPMC K4M and HEC on drug release:

All the formulations were prepared by wet granulation technique. Different formulations were developed using different weight gain (4%, 6%, 8%) of polymer. Basically, HPMC and HEC is a hydrophilic polymer which controls the release rate of the drug for the extended period of time.

Effect of 4% weight gain by coating on drug release

For the formulation From F1-F3 containing 4% of HPMC K4M and HEC, the formulation F1 containing 2% HPMC K4M and 2% HEC, the release from the formulation was found to be 99.76% at the end of 8th hour which shows the release was not within the USP specification limit. Drug release was shown to be high due to low polymer concentration. The results were shown in the **Table 17 and Fig.15.**

For the formulation, F2 containing 3% of HPMC K4M and 1% of HEC, the release from the formulations were found to be 99.56% at the end of 8th hour which shows the release was not within the USP specification limit. As the polymer concentration was low, the drug release shows high. The results were shown in the **Table 18 and Fig.16.**

For the formulation F3 containing 1% of HPMC K4M and 3% of HEC, the release from the formulations were found to be 99.97% at the end of 8th hour which shows the release was not within the USP specification limit. As the polymer concentration was low, the drug release shows high. The results were shown in the **Table 19 and Fig.17.**

Effect of 6% weight gain by coating on drug release

For the formulation F4-F6, the polymer weight was increased to 6% of HPMC K4M and HEC, the formulation F4 containing 3% HPMC K4M and 3% HEC drug release were found to be 85.48%. The 4th houre not within the specified limits, but the release was improved compared to F3, the concentration of polymer concentration was high, which provides the slow release of drug, it was further reduced. The results were shown in the **Table 20 and Fig.18.**

Formulation F5 HPMC K4M was increased to 4% and HEC was reduced to 2%, the release was found to be 84.85%, because high concentration of HPMC K4M. The 4th hour drug release was not within the USP limits. The results were shown in the **Table 21 and Fig.19.**

Formulations F6, the polymer was reduced to 2% of HPMC K4M and 4% of HEC the release was found to be 88.66%. The 4th hour drug release was not within the USP limits. The results were shown in the **Table 22 and Fig.20.**

Effect of 8% weight gain by coating on drug release

Hence, to meet the required release profile, polymer concentration was further increased 8% for the formulation F7 (4% of HPMC K4M and 4% of HEC), 96.56% of the drug was released at the end of 12 hours. The results showed that the drug release time was prolonged due to its polymer concentration. The results were shown in the **Table 23 and Fig.21.**

Formulation F8 containing 6% of HPMC K4M and 2% of HEC, which shows 94.75% of the drug was released at the end of 12 hours. Furthermore, the polymer concentration was changed to the next trial. The results were shown in the **Table 24 and Fig.22.**

Finally, the release from the formulation F9 containing 2% of HPMC K4M and 6 % of HEC, which shows 97.69% at the end of 12th hour, which was within the USP limits. The results were shown in the **Table 25 and Fig.23.**

When the amount of polymer was increased, the drug release was found to be decreased. The type and amount of polymer influenced the rate and release of the drug. Were the formulation F1-F6 as shown controlled releas but doesn't meet a USP specification. F7-F9 showed better controlled release than all of the above

formulations, which were observed to meet USP specifications for extended-release tablets. Then the formulation F7-F9 was compared with marketed product, F8 shows similarity factor – 92. So, F8 was selected optimized formulation

Interpretation of Dissolution Profile:

The results of the dissolution studies indicated that the release was affected by the weight of the polymer. The polymer, HPMC K4M, HEC had a retarding effect with high concentration(amount). When the polymer weight is high, the drug release was found to be slow. Once there is a sufficient polymer weight is achieved in the core of the tablet or in the matrix system, dissolution give a uniform layer is formed to protect the drug release immediately into the dissolution medium.

Evaluation of coated tablet:

The optimized formulation F8 was observed. The thickness was found to be in the range 5.65mm. The hardness was found to be 7.2 kg/cm2. The percentage of drug content was 99.45%. Optimized formulation F8, the drug release was found to be 16.86%, 35.62%,73.82% and 94.75% at the end of 1st,4th,8th and 12th hour which was within the USP limit. Formulation F9 shows the similar release profile to marketed product.

7.7 Release kinetic study for optimized matrix tablet:

Dissolution data of the optimized formulation was fitted to various kinetic models (zero order, first order, Higuchi and Korsmeyers Peppas) in order to describe the drug release profile. A plot of the cumulative percent drug release as a function of time shows that none of the formulations followed the first order or Higuchi Kinetics (Table:) the line of best fit obtained was zero order release kinetics (R2=0.9942) and Korsmeyers Peppas model, the drug release data further analyzed for curve fitting and the results (n=0.7062) confirmed that the formulation follows non–fickian (anomalous) diffusion kinetics.

7.8 Comparison between Optimized batch and Marketed product:

The optimised formulation F8 was compared with the commercially available product. In optimized formulation, the drug release was found to be 16.86%,35.64%,73.82% and 94.75% at the end of 1st,4th,8th and the 12th hour was seened to be close to the marketed product, the drug release was found to be 17.44%, 36.46%,74.37 and 95.46%.

Similarity factor (f2) and dissimilarity factor (f1) was calculated between F8 and marketed product. Differential factor (f1) and Similarity factor (f2) was found to be 2 and 92, which shows similar release profile to the marketed product. The results were shown in the **Table. 29 – 30.**

7.9 Stability study:

Stability studies were conducted for the formulation F8. The stability study was performed at 40ºC /75 % RH/ 3 months. The tablets were analyzed for appearance, average weight, thickness, hardness, drug content and in vitro drug release. Overall results indicate that the formulation is stable under the above storage conditions in **Table: 31.**

8. Summary

In the present study an attempt was made to prepare Pentoxifylline Extended release tablet for the treatment of Peripheral artery disease.

Chapter 1- begins with a general introduction presenting an overview of about extended release drug delivery systems. In the part of introduction, the advantages, disadvantages, mechanism of extended release systems and matrix tablets were discussed thoroughly.

Chapter2- described the literature related to this work was surveyed and a brief discussion had been given on each literature.

Chapter 3 - detailed the aim and objective of the present study.

Chapter 4- described the plan of the work.

Chapter 5 -gives information on the selection of drugs and excipients; thereby pentoxifylline is suitable candidate for extended release dosage form.

Chapter 6-deals with the materials and methods used in the present study was given. This chapter covers the details of the experimental methods including evaluation of the core and coated tablets, evaluation of physical mixture, determination of swelling index and also about release kinetics.

Chapter 7- Includes the results and detailed discussion of all the formulations, all the qualitative and quantitative parameters were analyzed and tabulated. The drug excipient compatibility study was done and found to have no interactions.

The precompression parameters (bulk density, tap density, Carrs index, and angle of repose) of the prepared tablets were within the ranges given by official standards, indicating that the physical mixture was found to be free-flowing. In vitro dissolution studies were done for Felodipine Extended release tablet prepared with different concentration of polymer HPMC K4M low viscosity grade and HEC high viscosity grade. Formulation F8 was found to be 94.75% drug release at the end of 12th hours which was within the USP limits.

The kinetic of drug release for formulation F8 was calculated and plotted. The formulation F8 follows zero order release kinetics and the drug release mechanism was found to be non-fickian (anomalous) diffusion. The optimized formulation was compared with marketed product and showed similar release profile.

The optimized tablets, F8 were selected for stability studies were carried out according to ICH guidelines at 40ºC /75 % RH for a specific time period indicated that the physical parameters and drug release characteristics were not altered significantly showing good stability on storage.

9. Conclusion

Pentoxyfylline multi-layered tablets consist of 400 mg prepared by wet granulation technique that can provide zero-order release where the tablet core coated with a hydrophilic and hydrophobic layer as barrier layer with 4, 6, and 8 % of weight gain. Three batches with different ratio of polymer were prepared for every proposed weight gain so as to make 9 batches (3X3). It is evident that an increase in the cover area of the core tablet results in a decrease of drug release from the system since the cover acts as a barrier hindering the contact of the liquid with the core surface and decreases dissolution rate and provided controlled release. The formulation containing 8% of polymer (6% of HPMC K4M and 2% of HEC) (F8 batch) followed the desired release profile and selected for further studies. The optimized formulation follows zero order release pattern (R^2.9942 with rate of release 7%/hr) and the drug release mechanism was non-fickian (anomalous transfer). Therefore, swelling and diffusion mechanisms were found to be responsible for the prolonged release of pentoxifylline from formulated matrix tablets. The optimized formulation compared with marketed formulation, were found to have a similar *In vitro* release profile, which is confirmed by f_1 *and* f_2 values. In terms of physical properties and drug content, the formulation (F8) was found to be stable for 3 months under accelerated conditions.

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PHARMACY EDUCATION - 2nd WEBINAR SERIES
Wednesday, June 10, 2020 @ 10.00am - 1.00pm
This is to certify that
Prof./Dr./Mrs./Ms./Mr. KARUNANITHY R
has attended a 2nd Webinar Series entitled
"Advancing Scientific knowledge in times of Pandemics in the area of COVID-19"
organized by C.L.Baid Metha College of Pharmacy.
Prof. Dr. GRACE RATHNAM
Principal & Convenor
Dr. U.UBAIDULLA
Co-convenor
Dr. R.KUMARVELRAJAN
Organizing Secretary


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(Ministry of HRD Initiative)
CERTIFICATE
OF APPRECIATION TO
KARUNANITHY R
PARTICIPANT
for Participation in
"INTERNATIONAL WEBINAR: IMPURITY PROFILING OF PHARMACEUTICALS"
held on June 30, 2020 | 6-8 PM IST
Dr. S.P. Dhanabal
Principal
Dr. N. Krishnaveni
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This is to certify that

KARUNANITHY R

from C.L.BAID METHA COLLEGE OF PHARMACY, CHENNAI-97.

has actively participated in webinar on

"BIOACTIVE MOLECULES FROM BACTERIAL STRAINS"

organized by Sree Sastha Pharmacy College , Chennai

on 02nd July 2020

Prof S.Rameswari
Coordinator

4GLQG0-CE000395

Dr.V.Dhanapal
Principal