"FORMULATION DEVELOPMENT & EVALUATION OF EXTENDED RELEASE DOSAGE FORM OF ANTI DIABETIC DRUG"

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CERTIFICATE

This is to certify that ***Ms. Patel Jahanvi H.*** *has prepared her thesis entitled "****Formulation Development & Evaluation of Extended Release Dosage Form of Anti diabetic drug****", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. She has carried out the work at the Department of Formulation & Development, Torrent Research Centre, Bhat, Gandhinagar.*

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DECLARATION

I declare that the thesis "Formulation Development and Evaluation of Extended Release Dosage Form of Anti diabetic Drug ", has been prepared by me under the guidance of Mr.Sujay Rajhans, Assistant General Manager, Torrent Research centre and Dr. Tejal A. Mehta ,Head Of Department of Pharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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CONTENT

ABSTRACT

FORMULATION DEVELOPMENT & EVALUATION OF EXTENDED RELEASE DOSAGE FORM OF ANTIDIABETIC DRUG

The drug chosen for the present investigation was DCPT 070, is an orally active anti diabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) Type II. Unlike sulfonylurea, DCPT070 usually does not produce hypoglycaemia in diabetic and nondiabetic individuals. So, it is more appropriately referred to as antihyperglycemic agent and found to be well-tolerated and safe on chronic use. DCPT 070 is highly soluble drug as well as having short half life i.e. 2-4 hrs. Its bioavailability is 50-60% only. So main aim is to formulate the drug into extended release formulation which can sustained the drug release for 12 hrs in cost effective manner. The dissolution profile of formulated tablets was match with the innovator product. Extended release formulations were formulated by using different polymers like HPMC K100MCR, HPMC K15MCR, Carbopol 71G and combination of polymers taking polymers intragranularly, extra granularly, intragranularly as well as extra granularly and optimized the all three polymer concentration. Tablets were also prepared to check effect of binder on drug release. The best batch was selected from optimized batches. The tablets were evaluated for various parameters like Hardness, Thickness, Friability, Diameter, Cumulative % drug release. Dose dumping studies also were carried out for optimized batch. Calculation of similarity and dissimilarity factor were calculated taking innovator as reference. Finally batch containing HPMC K100MCR 10% intragranularly and 12% extra granularly was selected as best batch as it have optimized tableting parameters and cumulative % drug release. A result shows that there was no effect of binder on drug release. Similarity factor of best batch was greater than 50.Dose dumping studies reveal that there was no dose dumping in optimized batch.

3. AIM OF PRESENT INVESTIGATION

The drug chosen for the present investigation was DCPT 070, is an orally active anti diabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) Type II. Unlike sulfonylurea, DCPT070 usually does not produce hypoglycemia in diabetic and nondiabetic individuals. So, it is more appropriately referred to as antihyperglycemic agent and found to be well-tolerated and safe on chronic use.

DCPT 070 has some problems in formulation Development which includes:

1. Short Half Life i.e. 2-4hrs
2. Absolute bioavailability 60 %
3. Dosing frequency of DCPT070 Immediate release formulation is 2-3 times a day.
4. Relatively High dose(500mg, 1000mg)
5. Immediate release dosage form having various adverse effects like anorexia, nausea, vomiting, and occasionally diarrhea. These adverse events may be partially avoided using sustained release dosage form.

The main aim of present investigation is

- To formulate extended release formulation of DCPT070 in cost effective manner which can sustain the release for 10 hrs and thereby, decrease adverse effect of DCPT070 as occur in immediate release formulation by maintaining the plasma drug concentration within therapeutic concentration and thereby decreases dosing frequency and increase patient compliance.

- Extended release formulation potentially avoiding undesirable peaks and troughs associated with multiple immediate release preparations. Various methods are used to extend the drug release, among which matrix based system(tablets) was selected

- Then matching of dissolution profile of formulated extended release tablets with the innovator tablets.

PLAN OF WORK:

Preformulation Studies

⬇

Identification of DCPT070

⬇

Selection and optimization of polymer concentration

⬇

Evaluation of formulated tablets for following parameters
Hardness,Friability ,Weight Variation Cumulative % drug release , Thickness

⬇

Comparison of dissolution Profile with innovator product

⬇

Evaluate the effect of Binder on release of drug

⬇

Selection of best batch from optimized batch

⬇

Dose dumping studies of optimized batch

⬇

Stability studies of best batch

1. INTRODUCTION

1.1 INTRODUCTION TO SOLID DOSAGE FORM

PHARMACEUTICAL SOLID ORAL DOSAGE FORM:

Drug treatment requires getting a drug to its target site or sites, specific sites in tissues where the drug performs its action. Typically, the drug is introduced (the process of administration) into the body far from this site. The drug must move into the bloodstream (the process of absorption) and be transported to the target sites where the drug is needed (the process of distribution). Some drugs are chemically altered (the process of metabolism) by the body before they perform their action; others are metabolized afterward; and still others are not metabolized at all. The final step is the removal of the drug and its metabolites from the body (the process of elimination). Drugs are introduced into the body by several routes. They may be taken by mouth (orally); placed under the tongue (sublingually); sprayed into the nose and absorbed through the nasal membranes (nasally); breathed into the lungs, usually through the mouth (by inhalation); given by injection into a vein (intravenously), into a muscle (intramuscularly), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously); inserted in the rectum (rectally) or vagina (vaginally); installed in the eye (by the ocular route); applied to the skin (cutaneously) for a local (topical) or body wide (systemic) effect; or delivered through the skin by a patch (transdermally) for a systemic effect. Each route has specific purposes, advantages, and disadvantages. [1-3]

Oral administration is the most popular route for the systemic delivery of drugs due to ease of ingestion, self medication, pain avoidance, versatility (to accommodate various types of drug candidates), and, most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. [4]

Current research in the fields of drug delivery and drug targeting is blooming in a quantitative sense. This is exemplified by the success of Controlled Release Society meetings and the overwhelming increase in research publications on these

topics in the international pharmaceutical and biomedical literature over the last few years. [5]

Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach, but usually, most of the drug is absorbed from the small intestine. The drug passes through the intestinal wall and then the liver before it is transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount reaching the bloodstream. Consequently, to obtain the same effect, such drugs are often given in smaller doses when they are injected directly into the bloodstream (intravenously).

For oral administration, if a tablet releases the drug too quickly, the blood level of the drug may become too high, causing an excessive response. If the tablet does not release the drug quickly enough, much of the drug may be eliminated in the feces without being absorbed. This requires that drug manufacturers have to formulate their tablets to release the drug at the desired speed.

So before attempt to develop an oral delivery system it is necessary to have a basic understanding and sound knowledge of the following aspects:

i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
ii) The anatomic and physiologic characteristics of the GIT, and
iii) Physicochemical characteristics and the drug delivery mode of the dosage form to be designed. [6]

1.2 INTRODUCTION TO EXTENDED RELEASE FORMULATION

1.2.1 Extended Release Dosage Form:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms.[7]

Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there for the desire time, be excluded from other site and get rapidly removed from the site of planned after its action. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research.[8]

This ideal dosing regimen, which enhances patient compliance and helps guard against overdosing and side effects, is made possible by controlled release delivery systems, which use a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream.[9]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system.[10]

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for extended release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than for the parentral route.[11]

Over the past 30 years, as the expense and complications involved in marketing new drugs entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs however is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.[12]

The enormous problem of patient compliance as well as the therapeutic desirability of controlled tissue drug levels over the time course of therapy is sufficiently compelling reasons to warrant placement of drugs in a sustained form of drug delivery.[13]

In the past, many of the terms used to refer to therapeutic systems of controlled and extended release have been used in an inconsistent and confusing manner.[13] Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[14]

Modified release drug delivery system may be divided conveniently into four categories:

1. Delayed release
2. Extended release
3. Site-specific targeting
4. Receptor targeting

Extended release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered as controlled release drug delivery system.[15]

1.2.2 Classification of controlled release drug delivery systems[16]:

Table No. 1: [Classification of controlled release drug delivery system**]**

TYPE OF SYSTEM	RATE-CONTROL MECHANISM
Diffusion controlled ➢ Reservoir system ➢ Monolithic system	} Diffusion through membrane
Water penetration controlled ➢ Osmotic system ➢ Swelling system	- transport of water through semi permeable membrane - water penetration into glossy polymer
Chemical controlled ➢ Monolithic system ➢ Pendant system ➢ Ion exchange resins	- Surface erosion or bulk erosion - Hydrolysis of pendent group and diffusion from bulk polymer -Exchange of acidic or basic drugs with the ions present on resins.
Regulated system ➢ Magnetic, Ultrasound	- External application of magnetic field or ultrasound to device

Extended release preparations:

These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristics of the conventional intermittent dosage regimen. Extended release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action.[17]

Controlled release preparations:

Although this term has been interchanged widely with extended release preparations in the past, recently it has become customary to restrict the latter term to oral formulations where the mechanism of prolonged action is dependent on one or more of the environmental factors in the gastrointestinal tract such as pH, enzymes, gastric motility etc. On the other hand, the term controlled release dosage form usually applies to preparations that are designed for all routes of administration and where the mechanism of prolonged action is inherent and determined totally by the delivery system itself. Consequently, this category offers the current state-of-the-art products where the drug release profile is controlled accurately and often can be targeted to a special body site or a particular organ.

1.2.3 Advantages and Disadvantages of ER DDS:

Advantages of Extended release drug delivery system:

1) Decreased local and systemic side effects:
    - Reduced gastrointestinal irritation.
2) Better drug utilization:
    - Reduction in total amount of drug used.
    - Minimum drug accumulation on chronic dosing.
3) Improved efficiency in treatment:
    - Optimized therapy.

- Reduction in fluctuation in drug level and hence more uniform pharmacological response.
- Special effects e.g. sustained release aspirin provides sufficient drug so that on awakening the arthritic patient gets symptomatic relief.
- Cure or control of condition more promptly.
- Less reduction in drug activity with chronic use.
- Method by which extended release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for extended release.

4) Improved patient compliance:
   - Less frequent dosing
   - Reduced night-time dosing
   - Reduced patient care time.

5) Economy:

   Although the initial unit cost of extended release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period maybe less. Economy may also result from a decrease in nursing time and hospitalization time.[18]

Disadvantages of Extended release drug delivery system:

ER dosage forms have following disadvantages.

1. Cost is very high.
2. Unpredictable and often poor in vitro: in vivo correlation.
3. Dose dumping.
4. Reduce potential for dosage adjustment and increase potential for pass clearance and poor systemic availability in general.
5. The effective drug release period is influenced and limited by G.I. residence time.

1.3 INTRODUCTION TO MATRIX TABLETS

Matrix Tablets [19]

These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials.

1.3.1 Classification of Matrix Tablets

A. On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

1. Hydrophobic Matrices (Plastic matrices):

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles.

Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acryl ate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices:

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups

I. Cellulose derivatives: methylcellulose 400 and 4000cps; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cPs; and sodium carboxymethylcellulose.

II. Noncellulose natural or semi synthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.

III. Polymers of acrylic acid: Carbopol 934

4. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolized or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

B. On the Basis of Porosity of Matrix

Matrix system can also be classified according to their porosity and consequently, macroporous; microporous and non-porous systems can be identified:

1. Macro porous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the networkmeshes. In this case, only the polymeric phase exists and no pore phase is present.

Table No 2 [Polymers used in Matrix tablets]

Types of polymers	Examples
Hydrogels	Polyhydroxyethyle methylacrylate (PHEMA) , Cross-linked polyvinyl alcohol (PVA) , Cross-linked polyvinyl pyrrolidone (PVP) , Polyethylene oxide (PEO) , Polyacrylamide (PA)
Soluble polymers	Polyethylene glycol (PEG) ,Polyvinyl alcohol (PVA) ,Polyvinyl pyrrolidone (PVP) , Hydroxypropyl methyl cellulose (HPMC)
Biodegradable polymers	Polylactic acid (PLA) , Polyglycolic acid (PGA) Polycaprolactone (PCL) , Polyanhydrides , Polyorthoesters
Nonbiodegradable polymers	Polyethylene vinyl acetate (PVA) , Polydimethyl siloxane (PDS) , Polyether urethane (PEU) , Polyvinyl chloride (PVC) , Cellulose acetate (CA) , Ethyl cellulose (EC)
Mucoadhesive polymers	Polycarbophil , Sodium carboxymethyl cellulose , Polyacrylic acid , Tragacanth , Methyl cellulose , Pectin
Natural gums	Xanthan gum , Guar gum , Karaya gum

1.3.2 Advantages and Disadvantages of Matrix Tablets: [19]

Advantages of Matrix Tablets

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds

Disadvantages of the Matrix systems:

- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.3.3 Factors affecting ER dosage form design: [19]

- **Biological factors influencing oral extended release dosage form design:**

i) Biological half-life:

Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.

ii) Absorption:

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. 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.

iii) Metabolism:

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.

- **Physicochemical factors influencing oral extended release dosage form design:**

i) Dose Size:

In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for extended release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

ii) Ionization, pKa, and aqueous solubility:

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. 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. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

iii) Partition coefficient:

Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.

iv) Stability:

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that 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 form.

1.3.4 Criteria to be met by drug proposed to be formulated in sustained release dosage forms: [20]

a) Desirable half-life:

The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional

dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

b) High therapeutic index:

Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.

c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.

e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f) First pass clearance:

As discussed earlier in disadvantages of controlled delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

1.4 PATENTED TECHNOLOGIES OF MODIFIED RELEASE DRUG DELIVERY SYSTEM [21]

1. Port technology
2. Flamel technology
3. Elan drug technology
4. Microchip technology for delivery of insulin
5. OROS Push pull technology
6. L – Oros technology
7. En Sotrol technology
8. DUROS Technology

PORT TECHNOLOGY

Port stands for programmable oral release technologies that use a unique coated in capsulated system with opportunity to provide multiple program release of drug. Port technologies offer significant flexibility in obtaining unique and desirable release profile to maximize pharmacological and therapeutic effect. There are mainly two dosage forms for port technology.

Tablet dosage form description

The dosage form consist form of polymer core matrix coated with the semi permeable, rate-controlling polymer. Poorly soluble drugs can coated with port properties solubilization agent to insure uniform control release from the dosage from

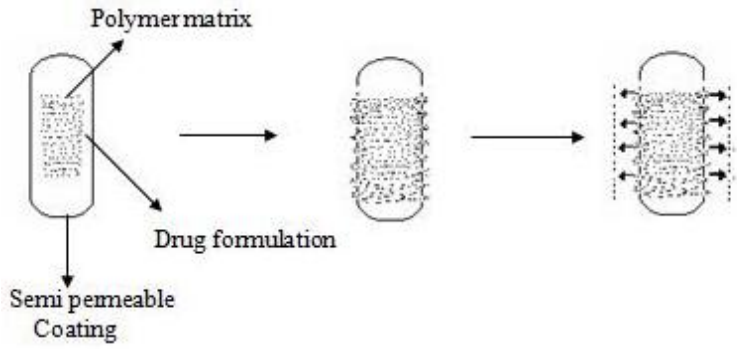


Figure No.: 2 Drug Release Mechanisms from the PORT Tablet

E.g. Port Technology for glipizide,

Port Technology for nifedipine

Capsule dosage form description

The dosage from consist of a hard gelatin capsule coated with the semi permeable, rate controlling polymer. Inside coated capsule is the osmotic energy source, which normally contains the therapeutic agents to be delivers. The capsule is sealed with the water in soluble lipid separators plug and immediate release dosage can be edit above the plug the to complete the dosing option

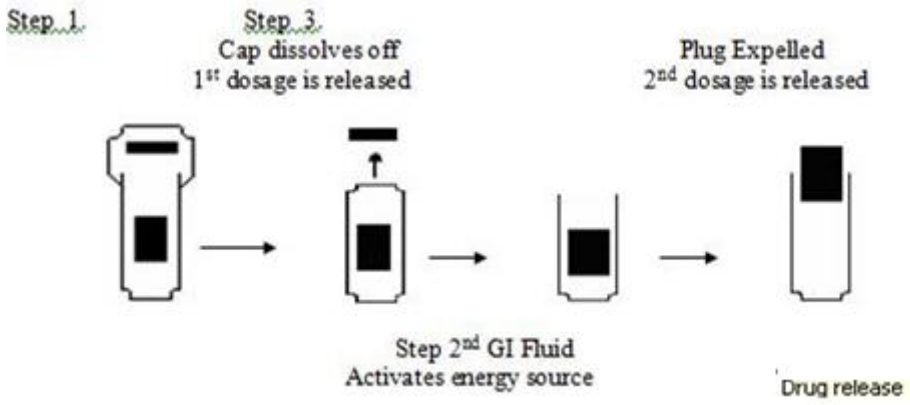


Figure No. : 3 Drug release mechanism from the PORT capsule

Example of port technologies:-

- Delayed release pseudoephedrine
- Multiple program release of phenylpropanolamine

FLAMEL MICRO PUMP TECHNOLOGY

Flamel micro pumps technologies a controlled release system which permits delayed and extended delivery, of small molecule drugs. Technology is suitable in particularly narrow window of absorption from the upper part of the small intestine.

Description

Flamel micro pump technology consists of a multiple per capsule or tablet containing micro particles per capsule or tablet. The 200-500 mm diameter size microform in the stomach and pass into the small intestine, where each micro particle, operation

delivery system release the drug by osmotic pump at a adjustable rate (micro pump 1st or delayed for micro pump 2nd) and over and extended period of transit of time.

Current Flamel products

Lansoprazole

Genvir^{tm}

Surviver Monde

Augmentin SR

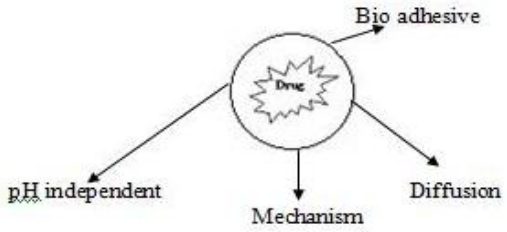


Figure No.: 4 Flamel micro pump technology

The design of micro pump micro particle allows extended transit time, enough plasma mean resident time extended up to 24hours, which is spatially suited drug known to be absorbed only in small intestine. The micro particle design can be adopted to be each drug specifically modifying the coating thickness and composition include the expedients (encapsulation) reduce toxicity and or reduces C_{max} or peak drug concentration in the plasma (an improve patients regimen)

Performance

1. Permit the extended delivery of drugs with a narrow window of absorption.
2. Allow the controlled release of poorly soluble and as well as highly soluble drug
3. Applicable to low dosage (4mg) and high dosage (100mg)

Advantage

1. Easy to swallow (due to the micro particle size)
2. Test masking
3. Good tolerability
4. Avoid dosage dumping
5. Reduce intra and inter variability

6. Allows combination of different drugs who's release can be controlled separate
7. Easy to scale up to industrial high volume production
8. Cost effective process

ELAN DRUG DELIVERY TECHNOLOGY

Elan offers more than 30 years experience in product development, optimization and manufacture and has engaged in successful coloration with more than 30 of the world's leading pharmaceutical companies.

ELAN is focus on providing superior technologies platforms that can offer innovative high value, quality technologies to address the drug delivery challenges of the pharmaceutical industry.

ELAN delivers extensive scientific expenditure to help save difficult drug delivery and life cycle management challenges

ELAN continues to solve problems with poor solubility which can be in corporate in to a Verity of dosage forms as well as customization release profile for oral dosage forms.

Elan products

PRIALT® Ziconotide intrathecal infusion

Azactan® Aztreonam for injection, USP

MAXIpime® Cefepim hydrochloride for injection

MICROCHIP TECHNOLOGIES FOR DELIVERY THE INSULIN

Researchers are working hard to develop an implantable insulin pump that can major blood sugar levels and deliver the exact amount of insulin needed. This would make it possible to mimic the action of natural insulin delivery.

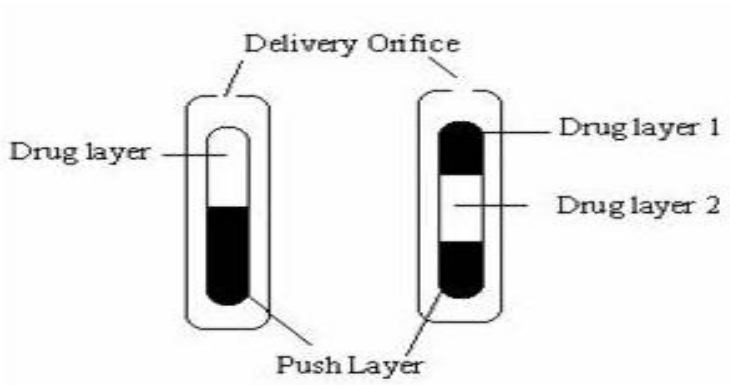
Scientists are making progress with an implantable capsule that continuously produces insulin and release it to the blood stream.

The capsules developers have also over come biocompatibility problems using microchip technologies they has succeeds in creating a capsule that won't be a attacked an destroyers by body's immune system.

OROS® PUSH PULL TECHNOLOGY

Push pulls system compromise bilayer or trilayer tablet core consisting of one push layer and 1 or more drug layer. The drug layer contains the poorly soluble drugs, Osmotic agents and suspending agent. The push layer contains among other things, osmotic agent water swell able polymers. A semi permeable membrane surrounds the tablet core.

Product commercialize using the push pull system include Glucotrol Xl® and



procardia XL both composed of a bilayer tablet core and Concerta® compose of a trilayer .

Figure No.: 5 Bilayer and tri layer OROS Push pull technology

L– OROS^{tm} technology

To overcome the drug solubility issue, Alza developed the L – OROS system where a liquid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semi-

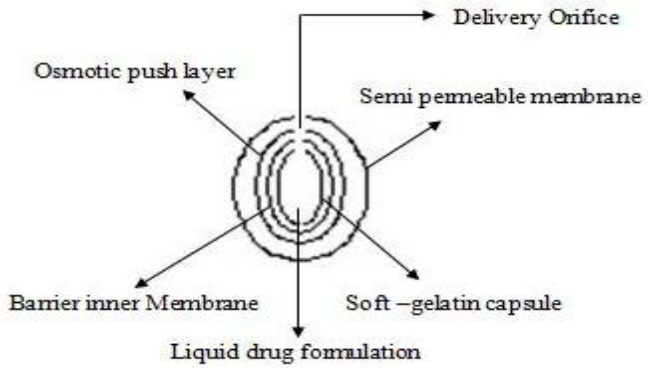


Figure No.: 6 L – OROS^{tm} technology

permeable membrane, drilled with an exit orifice.

EN SO TROL TECHNOLOGY

Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies to create optimized dosage form. Solubility enhancement of an order of magnitute or more can be achieved.

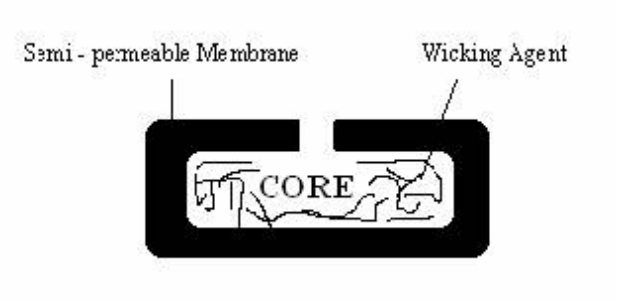


Figure No.: 7 ENSOTROL Technologies

DUROS TECHNOLOGY

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir high impact strength and protects the drug molecules from enzymes, body mostres, cellular components that might deactivate the drug prepare to deliver

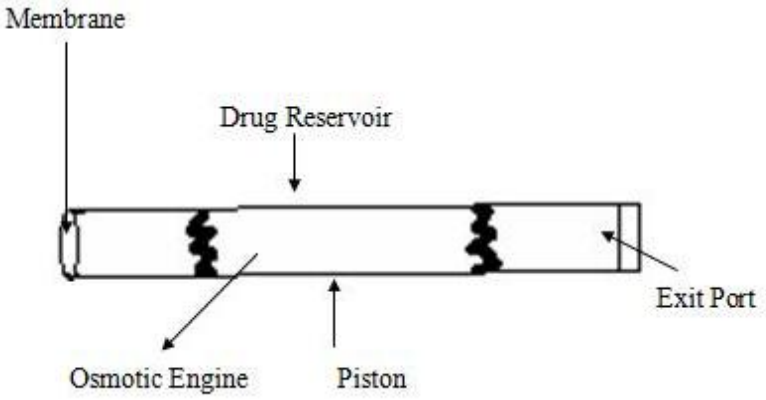


Figure No.: 8 DUROS technology

Advanced application of DUROS technology

- Chronogesic^{tm} (Sufentanil) pain therapy system
- Targeted drug delivery with catheterized osmotic pump
- Site-specific drug delivery using Duros with a precious miniature catheters

Table No. 3 [Example of marketed modified release product] [21]

Name	Marketer	Dosage form	Indication
Carbotrol	Shri Us	Oral capsule	Epilepsy
Glucotrol Xl	Pfizer	Oral Tablet	Hyperglycaemia
Adderall XR	Shri US	Oral Capsule	ADHD
Procardia Xl	Pfizer	Oral Tablet	Angenia / Hypertension
Ortho Evra	Ortho - Mcneil	Trans Dermal Patch	Contraceptiv
Dura gesic	Janssen	Trans Dermal Patch	Chronic pain
Climaa	Berlex	Trans Dermal Patch	Oestrogen replacement
Cata Press TTS	Boehringer Ingheim	Trans Dermal Patch	Hypertension
Liron Dipot	TAP	Intramuscular Injection	Ovearian cancer and Kaposi's sarcoma
Doxil	Ortho biotech	Intravenous infusion	Advance prostate cancer
Viadour	Bayer	Subcupaneous Implant	

1.5 INTRODUCTION TO DISEASE (DIABETES MELLITUS) [22]

Diabetes mellitus is a group of syndromes characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance, and sometimes ketonemia. A wide spread pathological changes are, thickening of capillary basement membrane, increase in vessel wall matrix, and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy, and peripheral vascular insufficiency. Diabetes is not a disease, but a disorder which requires continuous use of drugs for its maintenance.

Two major types of diabetes mellitus are

Type I*:* Insulin dependent diabetes mellitus (IDDM), juvenile onset diabetes.

There is '*β'* cell destruction in pancreatic islets; majority of cases are autoimmune (type I A) antibodies that destroy '*β'* cells are detectable in blood, but some are idiopathic (type II B)- no '*β'* cell antibody is found. In all type I cases, circulating insulin levels are low or very low and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

Type II*:* Non insulin dependent diabetes mellitus (NIDDM), maturity onset diabetes.

This typically involves abnormal '*β'* cell function that result in relative insulin deficiency, insulin resistance is accompanied by decreased glucose transport into muscles and fat cells, and increased hepatic glucose output, all of which contribute to hyperglycemia. Type II diabetes characteristically comprises of pathophysiologic abnormalities like relative insulin deficiency, insulin resistance involving myocytes, and adipocytes, and hepatic insulin resistance (resulting in increased gluconeogenesis and impaired glycogen synthesis).[18]

Following classes of oral hypoglycemic agents are used in the treatment of type II diabetes.

1. Sulfonylureas derivatives
   a. First generation include tolbutamide and chlorpropamide
   b. Second generation includes glibenclamide, glipizide, gliclazide, and glimepiride.
2. Biguanide.
3. Meglitinide analogues are repaglinide and nateglinide.
4. Thiazolidinediones derivatives are rosiglitazone and pioglitazone.
5. Glucosidase inhibitors are acarbose and miglitol.

1.6 INTRODUCTION TO DRUG:

DCPT070

Table No 4: [Drug profile]

BASIC PROFILE	
Pharmacokinetic profile	
Appearance	White to off white crystalline compound
Bioavailability	50 to 60% under fasting conditions
Metabolism	None
Half life	2-4 hr
Excretion	Active renal tubular excretion
Solubility	Freely soluble in water. Practically insoluble in acetone, chloroform, ether
Dissociation Constant	12.4
pH of 1% DCPT070 Aq.solution	6.68

Description: [23, 24]

It is an oral anti-diabetic drug. It is the first-line drug for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function, and evidence suggests it may be the best choice for people with heart failure. It is also used in the treatment of polycystic ovary syndrome.

DCPT070 is the most popular anti-diabetic drug in the United States and it is the BCS class- III category (high solubility &low permeability) drug. One of the most prescribed drugs in the country overall, with more than 40 million prescriptions filled in 2008 for generic alone. When prescribed appropriately, DCPT070 causes few adverse effects—the most common is gastrointestinal upset and unlike many other anti-diabetic drugs, does not cause hypoglycemia if used alone. It also helps reduce LDL cholesterol and triglyceride levels, and may aid weight loss. As of 2009, DCPT070 is one of only two oral anti-diabetics in the World Health Organization Model List of Essential Medicines (the other being glibenclamide).

Clinical use:

The main use for DCPT070 is in the treatment of diabetes mellitus type 2, especially when this accompanies obesity and insulin resistance. DCPT070 is the only anti-diabetic drug that has been proven to protect against the cardiovascular complications of diabetes.

OTHER USES:

Gestational diabetes[26]

Several observational studies and randomized controlled trials have found that DCPT070 is as effective and safe as insulin for the management of gestational diabetes and a small case-control study has suggested that the children of women given DCPT070 instead of insulin may be healthier in the neonatal period.

Contraindications: [27]

DCPT070 is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (creatinine levels over 150 μmol/l, although this is an arbitrary limit), lung disease and liver disease.

Heart failure has long been considered a contraindication for DCPT070 use, although a 2007 systematic review showed DCPT070 to be the only anti-diabetic drug not associated with harm in people with heart failure.

DCPT070 temporarily discontinued before any radiographic study involving iodinated contrast (such as a contrast-enhanced CT scan or angiogram), as contrast dye may temporarily impair kidney function, indirectly leading to lactic acidosis by causing retention of DCPT070 in the body. It is recommended that DCPT070 be resumed after two days, assuming kidney function is normal.

Adverse effects:

1. Lactic acidosis:

The most serious potential side effect of DCPT070 is lactic acidosis; this complication is very rare, and seems limited to those with impaired liver or kidney function.

2. Gastrointestinal:

The most common adverse effect of DCPT070 is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence; DCPT070 is more commonly associated with gastrointestinal side effects than most other anti-diabetic drugs. Gastrointestinal upset can cause severe discomfort for patients; it is most common when DCPT070 is first administered, or when the dose is increased. The

discomfort can often be avoided by beginning at a low dose (1 to 1.7 grams per day) and increasing the dose gradually. Gastrointestinal upset after prolonged, steady use is less common. Long-term use of DCPT070 has been associated with increased homocysteine levels and malabsorption of vitamin B_{12} Higher doses and prolonged use are associated with increased incidence of B_{12} deficiency, and some researchers recommend screening or prevention strategies.

3. Hormonal:

DCPT044 has been reported to reduce the blood levels of thyroid-stimulating hormone in patients with hypothyroidism, and, in men, lutenizing hormone and testosterone. The clinical significance of these changes is still unknown.

Over dosage:

Intentional overdoses with up to 63 g of DCPT070 have been reported in the medical literature. The major potentially life-threatening complication of DCPT070 overdose is lactic acidosis. Treatment of DCPT070 overdose is generally supportive, but may include sodium bicarbonate to address acidosis and standard hemodialysis or continuous veno-venous hem filtration to rapidly remove DCPT070 and correct acidosis.

Mechanism of action of DCPT070: [16]

Despite decades of clinical use, the molecular mechanisms by which DCPT070 acts still have not been definitively determined and many more mechanisms will be elucidated. Unlike secretagogues, DCPT070 has no effect on plasma insulin concentration increase, and due to reduction in glucotoxicity it has an indirect effect on beta cell secretory function (marginal, secondary effect).

When administered to non-diabetic subjects, DCPT070 does not induce hypoglycemia, even in considerable doses. In contrast to phenformin, DCPT070 also appears to have little or no effect on gastrointestinal glucose absorption.

DCPT070 is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral

antihyperglycemic agents. DCPT070 decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, DCPT070 does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With DCPT070 therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

DCPT070 improves hyperglycemia primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis).The "average" person with type 2 diabetes has three times the normal rate of gluconeogenesis; DCPT070 treatment reduces this by over one third. DCPT070 activates AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats; activation of AMPK is required for DCPT070 inhibitory effect on the production of glucose by liver cells.

In addition to suppressing hepatic glucose production, DCPT070 increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation. and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors.

Pharmacokinetics: [25-27]

Absorption and Bioavailability:

DCPT070 has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. Peak plasma concentrations (C_{max}) are reached within one to three hours of taking immediate-release DCPT070 and four to eight hours with extended-release formulations. The plasma protein binding of DCPT070 is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Steady state is usually reached in one or two days.

Distribution

DCPT070 is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. DCPT070 partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of marketed

product, steady state plasma concentrations of DCPT070 are reached within 24 to 48 hours and are generally <1 μg/mL.

Metabolism and Elimination:

Intravenous single-dose studies in normal subjects demonstrate that DCPT070 is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion DCPT070 is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine; DCPT070 is undetectable in blood plasma within 24 hours of a single oral dose. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of DCPT070 elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Drug Interactions: [29]

The H_2-receptor antagonist cimetidine causes an increase in the plasma concentration of DCPT070, by reducing clearance of DCPT070 by the kidneys. both DCPT070 and cimetidine are cleared from the body by tubular secretion, and both, particularly the cationic (positively charged) form of cimetidine, may compete for the same transport mechanism.

A small double-blind, randomized study found the antibiotic cefalexin to also increase DCPT070 concentrations by a similar mechanism. Theoretically, other cationic medications may produce the same effect.

Formulations:

DCPT070 500 mg tablets

DCPT070 IR (immediate release) is available in 500 mg, 850 mg, and 1000 mg tablets, all now generic in the US.

Combinations with other drugs: DCPT070 is sometimes prescribed to type 2 diabetes patients in combination with rosiglitazone. This drug actively reduces insulin resistance, complementing the action of the DCPT070.

1.7 INTRODUCTION TO EXCIPIENTS

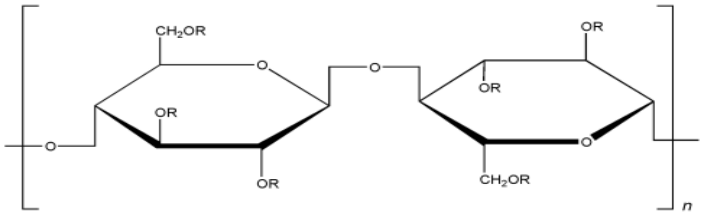
1. HYDROXYPROPYL METHYLCELLULOSE[30]

1. Nonproprietary Names

- BP: Hypromellose
- JP: Hydroxypropylmethylcellulose
- PhEur: Hypromellosum
- USP: Hypromellose

2. Synonyms

Benecel MHPC, E464, hydroxypropyl methylcellulose, HPMC, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Tylopur



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Figure No. : 9 Structure of Hydroxypropyl methylcellulose

3. Functional Category

Coating agent, film-former, rate-controlling polymer, stabilizing agent, suspending agent, tablet binder and viscosity-increasing agent.

4. Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, Hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulation.

5. Uses of Hypromellose

Table No: 5 [Uses of Hypromellose]

Use	Concentration of dry polymers (% w/w)
Binder	2 – 5
Rate-controlling polymer	10 – 80
Film-coating	2 -20
Thickening agent	0.45 -1.0

6. Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

7. Solubility

Soluble in cold water forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform but soluble in mixtures of methyl alcohol and methylene chloride.

2. CELLULOSE MICROCRYSTALLINE[30]

1. Nonproprietary Names

- BP: Microcrystalline cellulose
- JP: Microcrystalline cellulose
- PhEur: Cellulosum microcristallinum
- USPNF: Microcrystalline cellulose

2. Synonyms

Avicel PH, Celex, cellulose gel, Celphere, Ceolus KG, crystalline cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

3. Chemical Name: Cellulose

4. Empirical Formula: $(C_6H_{10}O_5)_n$ where n = 220 **Molecular Weight** 36000

5. Structural Formula

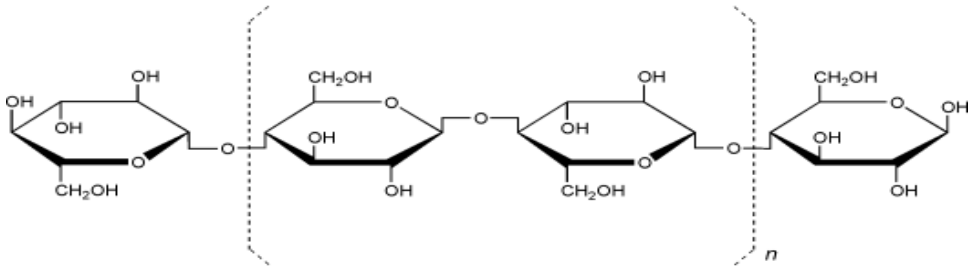


Figure No.: 10 Structure of Microcrystalline cellulose

6. Functional Category

Adsorbent, suspending agent, tablet and capsule diluents, tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, 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 use as a binder/diluent, Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Table No. : 6 [Uses of Microcrystalline Cellulose]

Use	Concentration (% w/w)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

8. Description

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9. Solubility

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

10. Typical Properties

Angle of repose:

498 for Ceolus KG;

34.48 for Emcocel 90M.(9)

Density (bulk):

0.337 g/cm3;

0.32 g/cm3 for Avicel PH-101;(10)

0.29 g/cm3 for Emcocel 90M;(9)

0.29 g/cm3 for VivaPur 101.

Density (tapped):

0.478 g/cm3;

0.45 g/cm3 for Avicel PH-101;

0.35 g/cm3 for Emcocel 90M.(9)

Density (true): 1.512–1.668 g/cm3

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

Melting point: chars at 260–2708C.

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

11. 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.

12. Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13. Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of a-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spraydried to form dry, porous particles of a broad size distribution.

14. Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

3. POVIDONE[30]

1. Nonproprietary Names

- BP: Povidone
- JP: Povidone
- PhEur: Povidonum
- USP: Povidone

2. Synonyms

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

3. Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer.

4. Empirical Formula: $(C_6H_9NO)_n$

Molecular Weight: 2500-3000000

PVP K-30: 50000

5. Structural Formula

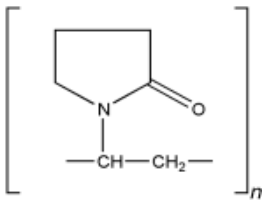


Figure No.: 11 Structure of Povidone

6. Functional Category

Disintegrant, dissolution aid, suspending agent, tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Although Povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, Povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydro alcoholic solutions. Povidone is used as a solubilizer in oral and parentral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Table No: 7 [Uses of Povidone]

Use	Concentration (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

8. Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

9. Solubility

Freely soluble in acids, chloroform, ethanol , ketones, methanol, and water; practically insoluble in ether, hydrocarbons and mineral oil.

4. CARBOMERS[30]

1. Nonproprietary Names

- BP: Carbomers
- PhEur: Carbomera
- USPNF: Carbomer

2. Synonyms

Carbopol, Acitamer, Polyacrylic acid.

3. Chemical name: Carbomer

4. Structural formula

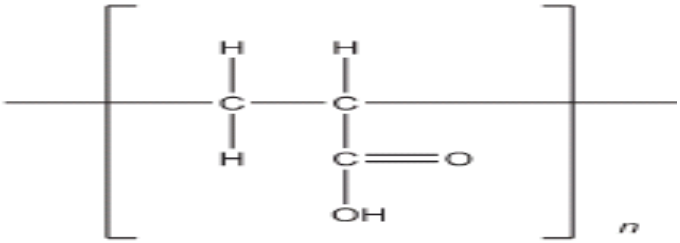


Figure No. : 12 Structure of Carbomer

5. Functional category

Bioadhesive; emulsifying agent; release modifying agent; tablet binder and viscosity increasing agent.

6. Applications in pharmaceutical formulation and technology

In tablet formulations, Carbomers are used as dry or wet binders and as rate controlling excipient.

Table No.: 8 [Uses of Carbopols]

Use	Concentration (%)
Emulsifying agent	0.1-0.5
Gelling agent	0.5-2.0
Suspending agent	0.5-1.0
Tablet binder	5.0-10.0

7. Description

Carbomers are white colored, fluffy, acidic, hygroscopic powders with a slight characteristic odor.

8. Solubility:

Soluble in water and after neutralization, in ethanol (95%) and glycerin. Carbomers do not dissolve but swell to a remarkable extent.

5. MAGNESIUM STEARATE

1. Nonproprietary Names:

- BP: Magnesium stearate
- PhEur: Magnesii stearate
- USP: Magnesium stearate
- JP: Magnesium stearate

2. Synonyms

Magnesium octadecanoate, octadenoic acid, magnesium salts; stearic acid

3. Chemical name: Octadecanoic acid magnesium salt

4. Empirical Formula: **Molecular weight:**

591.34 $C_{36}H_{70}MgO_4$

5. Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional category

Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

8. Description

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

9. Solubility

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

10. Typical Properties

Crystalline forms: high-purity magnesium stearate has been
Isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm3

Density (tapped): 0.286 g/cm3

Density (true): 1.092 g/cm3

Flash point: 2508C

Flow ability: poorly flowing, cohesive powder.

Melting range: 117–1508C (commercial samples); 126–1308C (high purity magnesium stearate).

11. Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst-case daily intake and heavy metal composition.(1) Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled.(2,3) Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.(4) LD50 (rat, inhalation): >2 mg/L(2) LD50 (rat, oral): >10 g/kg.

LITERATURE REVIEW

2.1 LITERATURE REVIEW OF EXTENDED RELEASE FORMULATIONS

1. Raghvendra Rao et al [31] has developed sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG).After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. Different ratios of HPMC/CG/KG like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug upto 12 hrs. Among all the formulations, formulation which contains 20% HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile was comparable with the marketed product.

2. Atul Kuksal et al[32] has developed and characterize extended-release matrix tablets of zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. The in-vitro drug release study revealed that either Eudragit preparation was able to sustain the drug release only for 6 hours (94.3%±4.5% release). Combining Eudragit with ethyl cellulose sustained the drug release for 12 hours (88.1%±4.1% release). Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. In conclusion, the results suggest that the developed sustained-release tablets of zidovudine could perform therapeutically better than conventional dosage forms, leading to improve efficacy and better patient compliance.

3. K.Mahalingan et al[33] developed Clarithromycin delayed release tablet. Clarithromycin tablet was designed for the delaying the release to prolong the duration of drug action with the help of various polymers like Microcrystalline Cellulose, HPMC K4M, HPMC K5M, HPMC 6CPS, PEG 6000 with different additives are used for the trial and error method. The preliminary results from this

study suggest that tablets prepared from MCC, HPMC 6CPS and PEG 6000 can be used to incorporate antibiotics like Clarithromycin and may be effective when administered orally in the stomach against H. pylori.

4. J. Sahoo et al[34] developed propranolol hydrochloride matrix tablets with hydroxy propyl methyl cellulose (HPMC K15M) or Kollidon®SR at different concentrations was investigated with a view to developing twice daily sustained release dosage form. A hydrophilic matrix-based tablet using different concentrations of HPMC K15M or Kollidon®SR was developed using direct compression technique to contain 80 mg of propranolol hydrochloride. The resulting matrix tablets prepared with HPMC K15M or Kollidon®SR fulfilled all the official requirements of tablet dosage forms. The in vitro drug release study revealed that HPMC K15 at a concentration of 40% of the dosage form weight was able to control the release of propranolol hydrochloride for 12 h, exhibit non-Fickian diffusion with first-order release kinetics where as at 40% Kollidon®SR same dosage forms show zero-order release kinetics.

5. Santanu Ghosh et al[35] developed matrix tablets for oral controlled release of aceclofenac. Matrix tablets of aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose and Guar gum were prepared by wet granulation method and subjected to in vitro drug release studies. Based on the results of the in vitro studies, it was concluded that the HPMC matrix tablets provided oral controlled release of aceclofenac

6. P.Dwarakanadha Reddy et al [36] developed extended-release tablets of Etodolac. Tablets were prepared by wet granulation method. Granules of Etodolac were prepared by using hydroxypropyl Methylcellulose (HPMC) K4 MCR, hydroxypropylmethylcellulose (HPMC) K100 LVCR, anhydrous lactose, and Sodium dihydrogen phosphate dihydrate, povodine, talc and magnesium stearate. The tablets were analysed to determine their hardness, friability, % composition and an in vitro release study was carried out. The release of formulations showed zero-order release kinetics.

7. Dhirendra Kumar et al[37] formulated once daily sustained release matrix tablets of Stavudine to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release tablets were prepared by direct compression and formulated using different drug: polymer ratios, formulations such as F1to F15. Hydrophilic polymers like Hydroxy propyl methyl cellulose (HPMC), Carboxymethyl cellulose (CMC) and Starch 1500 were used. Formulation containing Stavudine: HPMCK15: Na-CMC (1:2:0.5) with hardness 10-11kg/cm2 showed the desired release profile which matched the theoretical release profile. The study proves that the developed sustained release tablet is capable of releasing the drug in a sustained manner for 24 hr.

8. Rakesh K Deore et al [38] prepared oral sustained release matrix tablets of a highly water soluble drug, tramadol hydrochloride, and to evaluate the effect of concentration of the hydrophobic polymer content and method of preparation on drug release**.** The tablets were a mixture of both tramadol hydrochloride and glyceryl palmitostearate (GP) prepared by melt granulation (MG1, MG2, MG3 and MG4 in ratios 1:1, 1:2, 1:3 and 1:4, respectively) or by direct compression (DC, 1:2 ratio)..Of the formulations (MG1 to MG4) prepared by melt granulation, MG4 showed the most suitable sustained release, 58.4 ± 1.1 % in 12 h ($p < 0.05$). Drug release (98.2 ± 0.2 % in 8 h) was highest for DC which was prepared by direct compression. Also, drug release mechanism for the formulations was by Fickian diffusion. Glyceryl palmitostearate is a suitable matrix-forming agent to sustain the release of a water-soluble drug such as tramadol hydrochloride. Melt granulation was a better technique for formulating the product than direct compression.

2.2 LITERATURE REVIEW ON HYDROPHILIC MATRIX POLYMERS

1. R.K.Kar et al [39] has developed oral controlled release matrix tablets of Zidovudine (AZT) in order to improve efficacy and better patient compliance. Tablets were prepared by direct compression method using various proportion of hydrophilic polymer viz; Eudragit RS100 and RL100 along or in combination with hydrophobic polymer ethyl cellulose. Dissolution study revealed that either Eudragit RS100 or RL100 10%,20% w/w of tablet preparations were able to sustain the drug release up to 9 hours, but 30%, 40% as well as ethyl cellulose combination with 20% and 25% w/w of Eudragit RS100 and RL100 were able to sustaining the drug release for 12 hour. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-Fickian diffusion mechanism.

2. B.Mishra et al., [40] aimed to formulate and evaluate hydrophilic matrix tablets of diltiazem hydrochloride to achieve a controlled and sustained drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. Matrix tablets of diltiazem hydrochloride were prepared using polymers like hyroxypropylmethylcellulose (HPMC K15, HPMC K4), sodium carboxymethylcellulose (SCMC) and Guar gum, and different diluents like lactose, starch, microcrystalline cellulose. SCMC matrix tablets showed more hydration and erosion than other matrix tablets. Tablets having HPMC K15 gave more sustained release than other hydrophilic polymers studied and it was comparable with marketed SR tablets. Amount of HPMC K15 and presence of different diluents significantly affected the drug release. It was observed that all the fabricated tablets delivered the drug following Higuchi diffusion mechanism.

3 S. Conti et al., [41] investigated the swelling behavior of matrix systems containing a mixture of hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) with a model soluble drug to find the correlation between the morphological behavior and the drug release performance. The swelling study was conducted on tablets containing only the drug and the two polymers mixture (MB) and on reference tablets containing each polymer and the same drug, at

three different pHs. MB matrices show a similar swelling trend at pH 4.5 and 6.8, while they have different behaviour in acidic fluid. At pH 4.5 and 6.8, all the systems show the typical morphological behaviour of a swellable matrix in which the macromolecular chains in the gel network are held together by weak bonding (physical gel).

4. S. Missaghi, et al., [42] discussed about Dynamics of swelling, erosion, and front movements in matrices having round or oval shape demonstrated disproportional changes in shape, erosion, and swelling in each case. Regardless of original shape, the overall change in aspect ratios during swelling were in the order of HPMC>PEO>HPC, while the extent of drug release from matrices was in the order of PEO>HPMC>HPC. The significance of these effects in relation to change in overall textural properties of each matrix and their erosion characteristics is discussed.

5. Bashar M. Al-Taani et al., [43] designed pH-dependent swellable and erodable buffered matrices and to study the effect of the microenvironment pH on the release pattern of diclofenac sodium. Buffered matrix tablets containing diclofenac sodium, physically mixed with hydrophilic polymer (hydroxypropyl methylcellulose [HPMC]) and pH-dependent solubility polymer (Eudragit L100-55) were prepared with different microenvironment pHs. The release of diclofenac sodium from the buffer matrices was studied in phosphate buffer solutions of pH 5.9 and 7.4. The swelling and erosion matrices containing only HPMC and Eudragit L100-55 were studied in phosphate buffer solution of pH similar to the microenvironment pHs of the matrices. The rate of drug release increased with the increase of the microenvironment pH of the matrices as determined from the slope. The pattern of drug release did not change with the change of microenvironment pH. The swelling and erosion occurred simultaneously from matrices made up of HPMC and Eudragit L100-55. It was concluded from this study that changing the pH within the matrix influenced the rate of release of the drug without affecting the release pattern.

6. **Hamdy Abdelkader et al** [44] investigated different types and levels of hydrophilic matrixing agents, including methylcellulose (MC), sodium alginate (Alg), and sodium carboxymethylcellulose (CMC), in an attempt to formulate controlled-release matrix tablets containing 25 mg baclofen. The tablets were prepared by wet granulation.

Prior to compression, the prepared granules were evaluated for flow and compression characteristics. In vitro, newly formulated controlled-release tablets were compared with standard commercial tablets (Lioresal and baclofen). The excipients used in this study did not alter physicochemical properties of the drug, as tested by the thermal analysis using differential scanning calorimetry. The flow and compression characteristics of the prepared granules significantly improved by virtue of granulation process. Also, the prepared matrix tablets showed good mechanical properties (Hardness and friability). MC- and Alg-based tablet formulations showed high release-retarding efficiency, and good reproducibility and stability of the drug release profiles when stored for 6 months in ambient room conditions, suggesting that MC and Alg are good candidates for preparing modified release baclofen tablet formulations.

7. S. Jamzad et al., [45] worked on a robust matrix CR formulation for glipizide with linear release profile similar to Glucotrol XL. It was shown that release profile could be maintained within an acceptable range by controlling the degree of swelling/hydration of the matrix. Regardless of the composition of the formulation, linearity of release was fully dependent on synchronization of three parameters namely swelling, erosion and textural properties of the matrix. Changes in the formulation within ±20% w/w of release modifying agents did not change either the drug release kinetics or the synchronization characteristics. The robustness observed can lead to ease of scale-up, successful in-vivo performance, and improved compliance with SUPAC guidelines.

8. Manthena V.S. Varma et al., [46] investigated to understand the influence of gastrointestinal (GI) pH on the gel layer formation and its dynamics for various hydrophilic/swellable matrices, in the process of developing a pH-independent controlled release system for a basic drug, oxybutynin hydrochloride (OXB). Cylindrical matrices (8-mm diameter) without and with fumaric acid, were readily prepared by direct compression. Formulations were evaluated for in vitro drug release, and gel layer dynamics was studied by viscosity measurements and texture profiling analysis. In the in vitro drug release study, OXB, which shows pH-dependent solubility, showed faster release from all the matrices in pH 1.2 medium.

Release rates enhanced to a lesser extent with change of medium from pH 6.8 to pH 1.2, for HPMC polymer matrices. In conclusion, understanding the influence of GI physiological pH on the gel layer dynamics and manipulating the micro-environmental pH provides efficient and predictable in vivo performance from these swellable cylindrical matrices.

9. Søren Kiil et al., [47] worked related to the on-going development of mathematical models describing transient drug delivery from hydroxypropylmethylcellulose (HPMC) matrices. Using data for verification of simulations, a detailed mathematical model, taking into account water-induced swelling, drug dissolution, and external and internal mass transport resistances of dissolved drug, has been developed. In contrast to earlier models, explicit equations for the rate of movement of the swelling, diffusion and erosion fronts, with the relevant physical properties of drug and HPMC matrix contained in the equations, were derived. Simulations have been compared to transient experimental data for three drugs of very different water solubility and a good agreement was found, taking into account the uncertainty of key input parameters. Furthermore, the model predicts the presence of the drug particle translocation phenomenon observed experimentally.

10. Ping Gao et al., [48] characterized the effect of hydroxypropyl methylcellulose (HPMC)/lactose ratio and HPMC viscosity grade (molecular weight) on solute release and swelling of matrix tablets. We used a semi quantitative optical imaging method to monitor the swelling of matrices with HPMC content from 20% to 80% (w/w) and four viscosity grades. Several aspects of the swelling process common to all formulations were revealed: (i) swelling is anisotropic with a preferential expansion in the axial direction, (ii) swelling is isotropic with respect to the gel layer thickness and composition in both axial and radial directions, (iii) the gel layer develops in three stages, and (iv) water penetration is Fickian in nature and essentially constant for all formulations. The strong dependence of HPMC release on viscosity grade is explained on the basis of the concept of polymer disentanglement concentration. We analyzed drug release rates using a model for a reservoir-type release system that

incorporates swelling kinetics. HPMC/lactose ratio modulates drug release rate by altering drug diffusivity, a function of gel composition. For fast dissolving matrices (≤100 cps) swelling in homogeneity is proposed as being responsible for a higher apparent drug diffusivity and release rate.

11. Ranga Rao et al. [49] looked at six drugs of 1/0.9 to 1/10,000 solubility.20 From a matrix containing METHOCEL K4M Premium, there was very little difference in the release of pindolol (1/10,000), allopurinol (1/2000), and salicylic acid (1/460), while Na salicylate (1/0.9) was much different. However, when the polymer erosion was measured for drug-polymer compacts and for HPMC itself, all drugs in the study caused an equivalent increase in the extent of erosion.

12. Nilesh S.Patil et al [50] formulated and characterize extended release matrix tablets of metoprolol succinate using hydrophilic polymers like Hydroxy Propyl Methyl Cellulose (Methocel K100M), hydrophobic polymer Ethyl Cellulose (Ethocel FP10), Lactose Monohydrate and Magnesium Stearate, and these selected matrices were directly compressed into tablet. Undesirable side effects of ß blocker mainly because of blockade of ß2 receptors. The main advantages of extended release or controlled release formulation are its ability to maintain ß1 selectivity over 24hours, but with relative lack of peak plasma concentration, thus avoiding decreased clinical ß1 selectivity as seen at high plasma concentration. Release kinetics evaluated by using USP II (Paddle) dissolution apparatus. In-vitro release study showed that for 100 mg label claimed were well suited to extend release for 20 hours. In-vitro swelling studies revealed that, the drug release governed by swelling of polymer and it is non-fickian or transport anomalous diffusion.

14. Avachat A. et al.[51] developed and characterize an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and

erosion degree of tablet were also investigated. The in vitro drug release study revealed that HPMC K100CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (f_2) above 50. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release.

15. Shahla Jamzad et al. [52] developed a new monolithic matrix system to completely deliver glipizide, a Biopharmaceutics Classification System (BCS) Class II drug in a zero order manner over an extended time period. Two approaches were examined using drug in formulations that contain swellable hydroxypropylmethylcellulose (HPMC) or erodible polyethylene oxide (PEO). The matrices were prepared by dry blending selected ratios of polymers and ingredients using direct compression technique. Glucotrol XL push-pull osmotic pump (PPOP) was used as the reference. The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. Linear and reproducible release similar to that of Glucotrol XL was achieved for optimized matrices ($f_2 > 50$) independent of hydrodynamic conditions. The kinetics of drug delivery was directly related to the synchronization of swelling, erosion and fractional release. HPMC matrices showed a significantly greater degree of hydration and swelling and stronger texture property relative to PEO matrices. Results indicate that in the case of low dose/low soluble drug, total drug release in a zero order manner heavily depends on the synchronization of erosion and swelling fronts during the entire dissolution study.

17. Brunella Cappello et al. [53] developed a tablet for the buccal delivery of the poorly soluble drug carvedilol (CAR), based on poly(ethyleneoxide) (PEO) as bioadhesive sustained-release platform and hydroxypropyl-β-cyclodextrin (HPβCD) as modulator of drug release. As first, PEO tablets loaded with CAR/HPβCD binary systems with different dissolution properties were tested for CAR and HPβCD release features and compared to PEO tablets containing only CAR. When the drug was incorporated as CAR/HPβCD freeze-dried product, all CAR content was released from the tablet in about 10 h, displaying a constant release regimen after a transient.

The effect of HPβCD incorporation on the release mechanism, was rationalized on the basis of the interplay of different physical phenomena: erosion and swelling of the tablet, drug dissolution, drug counter-diffusion and complex formation. In the second part of the study, the potential of HPβCD-containing PEO tablets as buccal delivery system for CAR was tested. It was found that the incorporation of HPβCD in the tablet did not alter significantly its good adhesion properties. The feasibility of buccal administration of CAR was assessed by permeation experiments on pig excised mucosa. The amount of CAR permeated from PEO tablet was higher in the case of HPβCD-containing tablets, the maximum value being obtained for CAR/HPβCD freeze-dried system. Our results demonstrate that, when the tablet is employed as transmucosal system, the role of drug dissolution enhancement in the hydrated tablet is much more relevant than in solution for increasing the delivery rate.

4. PREFORMULATION STUDIES

Pre-formulation study is the first step in the rational development of dosage form of a drug substance. The objective of Preformulation study is to develop a portfolio of information about the drug substance, so that this information proves useful to develop a formulation. Pre-formulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with other excipients.

Pre formulation Studies includes:

- Organoleptic characteristics
- Sieve analysis
- Bulk density
- Tapped density
- Compressibility index
- Hausner ratio
- Particle Size distribution
- Compatibility study

- **Organoleptic Characteristics:**

A sample of API was tested for appearance, taste and odor.

PROPERTY	RESULT
Description	White hygroscopic Crystalline powder
Taste	Bitter
Odour	Odorless powder
Color	White powder

- **Flow properties:**

Angle Of Repose:

Procedure:

A funnel was kept vertically in a stand at a specified height above a paper placed on horizontal surface. The bottom was closed and 10gm of sample powder was filled in funnel. The funnel was opened to release the powder on paper to form a smooth conical heap. The height of heap was measured using the scale. A border of heap was

marked circularly and its diameter was measured at four points. The average diameter was calculated and radius was found out from it.

The angle of repose was calculated using following formula:

$\tan \theta = h / r$

$\theta = \tan^{-1} h / r$

Where; h = height of the heap

r = radius of the heap

Table No: 9 [Flow property of powders according to angle of repose]

Flow property	**Angle of repose (degrees)**
Excellent	25 – 30
Good	31 – 35
Fair – aid not needed	36 – 40
Passable – may hang up	41 – 45
Poor – must agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	> 66

Density and compressibility measurement:

Bulk density:

The powder to be tested was sized appropriately to break lumps during storage. This powder was then poured in to the measuring cylinder up to $3/4^{th}$ capacity. The powder was leveled without tapping. The weight and height of powder was used to calculated bulk density by following equation:

Bulk density = mass (gm) / bulk volume (ml)

Tapped density:

Now this cylinder was put in the holder of tapped density apparatus where it was tapped at an average rate of 300 drops / minute, for 500 taps. After 500 tapes volume of powder (v_0) was noted and again tapped for another 750 taps. This gave a new

volume (v_f). If the difference between v_0 and v_f was more than 2%, another 1250 taps are given repeatedly until the difference reduces to less than 2%.

Tapped density determined from following equation:

Tapped density = mass (gm) / tapped volume (ml)

Compressibility of powder can be calculated using following formulas:

$$\text{Compressibility Index} = 100 \times \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Correlation between compressibility of powder, compressibility index and Hausner's ratio has been depicted in table 10.

Table No: 10 [Compressibility of powder based on Compressibility Index and Hausner's Ratio]

Compressibility Index (%)	**Compressibility**	**Hausner's ratio**
≤10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
≥ 38	Very, very poor	> 1.60

Particle size Distribution:

Procedure:

The sieves of different sizes were fitted in the platform of sieve shaker in such a way that coarse sieve was placed on top corresponding to finer sieves. 50gm of DCPT 070 was placed on top sieve and shaker was started. After 3 minutes the machine was stopped and weight of powder retained on each sieve was determined. Percentage retention on each sieve was calculated by following equation:

$$\% \text{ powder retained} = \frac{\text{Amount of powder retained (gm)}}{\text{Total amount of powder (gm)}} \times 100$$

Physical compatibility study:

In tablet dosage form drug is in intimate contact with the excipients. The later could affect the stability of the drug. Knowledge of drug excipients interaction is therefore very useful to the formulator in selecting appropriate excipients.

Procedure:

DCPT 070 was mixed with the excipients in different ratios and kept in cleaned vials in stability chamber at 40°C ±2°C/75% ± 5% RH. Visual observation was carried out at interval of 7 days for 1 month.

Solubility of Drug:

DCPT070 is soluble to the degree of 1 part in 2 part of water and 1 part in 100 parts of ethanol. It is practically insoluble in chloroform, acetone, methylenedichloride and ether.

Table No: 11 [Particle size distribution OF DCPT070]

Sieve #	**Retained powder (gm)**	**Cumulative retention (gm)**	**% Cumulative retention**
30	5.64	5.64	11.11
40	2.23	7.87	15.5
60	3.79	11.66	22.97
80	2.43	14.09	27.75
Passed through 80#	36.67	50.70	100

RESULTS:

Parameters	**Value**
Bulk Density (gm/ml)	0.3839 gm/ml
Tap. Density(gm/ml)	0.8013 gm/ml
Hausner Ratio	2.086
Carr's Index (%)	50
LOD (%)	0.27

Drug Excipients compatibility studies:

Table No.: 12 [Drug Excipients compatibility Studies]

Sr. No.	**Combination of Materials**	**Ratio of API to Excipients**
1	API alone	1
2	API + xanthan gum	1 : 1
3	API + Microcrystalline cellulose 102	1 : 0.5
4	API + Sodium CMC	1: 1
5	API + PVP K 30	1 : 1
6	API + Carbopol 71G	1 : 1
7	API + HPMC K4M	1 : 1
8	API + HPMC K100MCR	1 : 1
9	API + HPMC K15MCR	1 : 1
10	API + Magnesium stearate	1 : 0.5

(A) Package details: Transparent glass vials with rubber stopper and aluminum seal

(B) Test to be performed:

Physical Observation

Related Impurities

Physical observation:

Physical observation of sample was done at every week for any color change, lumps formation or any other visual changes.

Result:

At the time of physical observation after the completion of study, there were no any type of color changes, lump formation or any significant visual changes observed.

Results are summaries as under in table No. 13

Table No. 13 Results of Drug Excipients compatibility studies

Samples	Ratio of API to Excipients	Physical observation	Impurity A	Impurity B	Impurity C	Total impurity
API alone	1	White blend	0.01	ND	0.01	0.02
API + xanthan gum	1 : 1	White blend	ND	ND	0.02	0.02
API + Microcrystalline cellulose 102	1 : 0.5	White blend	ND	ND	0.02	0.02
API + Sodium CMC	1: 1	White blend	ND	ND	0.01	0.01
API + PVP K 30	1 : 1	White blend	0.01	ND	0.01	0.02
API + Carbopol 71G	1 : 1	White blend	ND	ND	0.01	0.01
API + HPMC K4M	1 : 1	White blend	ND	ND	0.01	0.02
API + HPMC K100MCR	1 : 1	White blend	ND	ND	0.01	0.01
API + Placebo	1:1	White blend	ND	ND	0.01	0.01

5. EXPERIMENTAL WORK

List of instruments/equipments used in the process:

Sr. No.	Equipment Name	Make	Function
I.	Electronic weighing balance(s)	CIP Machinery	Weighing
II.	Comminuting mill with 0.3mm screen	cad mach/Comminuting mill	Milling
III.	Rapid mixer granulator	Diosna	Granulation
IV.	Fluid Bed Drier	Retsch	Drying
V.	Halogen Moisture Balance	Mettler Toledo	LOD determination
VI.	Quanta Blender	Saral /Quanta blender	Blending
VII.	Rotary tablet compression machine fitted with 19 X 9mm biconvex shaped	Korsch , Germany	Compression
VIII.	Hardness Tester	Erweka Hardness Tester, Germany	Hardness testing
IX.	Venire calipers	Erweka Hardness Tester	Thickness measurement
X.	Friability Tester	Electro lab	Friability testing
XI.	Tapped density tester	Electro lab	BD/TD/CI/HR

5.1 IDENTIFICATION OF DCPT 070:

Photometric scanning to determine λ_{max} of DCPT070:

The result of photometric scanning has been shown in figure. It can be seen that DCPT070 absorbance is maximum at 233nm. Therefore, the λ_{max} for API is 233nm.

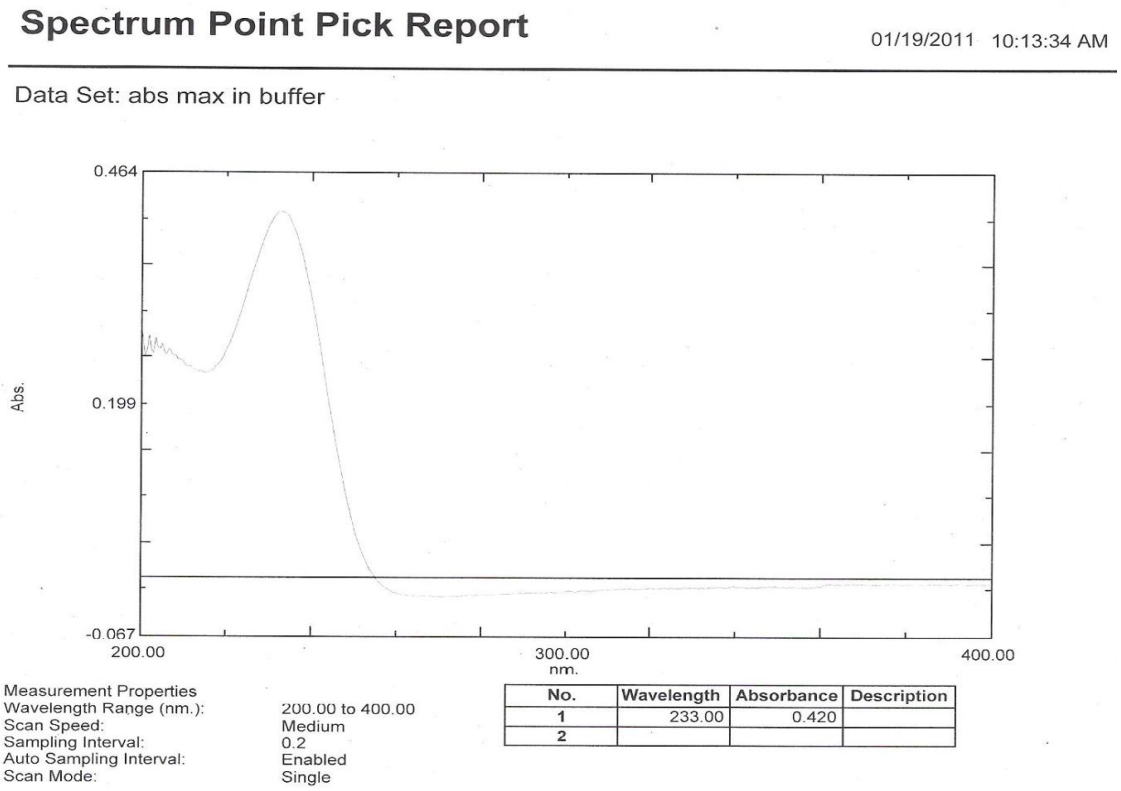


Figure No. :13 - Photometric scanning of DCPT070

5.2 GENERATION OF CALIBRATION CURVE

Standard curve of DCPT070 in phosphate buffer- pH 6.8 at 233nm

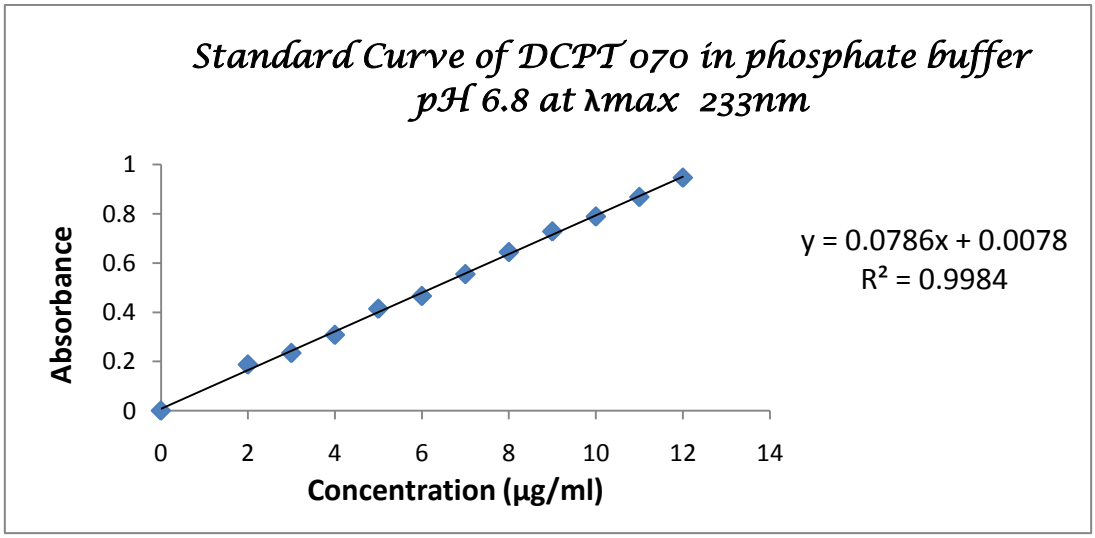


Figure No.: 14 - Standard curve of DCPT070 in phosphate buffer pH 6.8 at 233nm

Table No.: 14 Absorbance readings for Standard curve of DCPT070 in phosphate buffer pH 6.8 at 233nm

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Avg. absorbance	%RSD*
0	0	0	0	0	0
2	0.187	0.188	0.187	0.19	0.31
3	0.234	0.234	0.235	0.23	0.25
4	0.308	0.308	0.308	0.31	0.00
5	0.414	0.414	0.415	0.41	0.14
6	0.466	0.466	0.466	0.47	0.00
7	0.555	0.555	0.555	0.56	0.00
8	0.645	0.644	0.645	0.64	0.09
9	0.729	0.728	0.729	0.73	0.08
10	0.791	0.788	0.789	0.79	0.19
11	0.869	0.869	0.868	0.87	0.07
12	0.948	0.948	0.946	0.95	0.12

*RSD- Relative Standard Deviation; n=3

Standard Curve of DCPT070 in water at 233nm

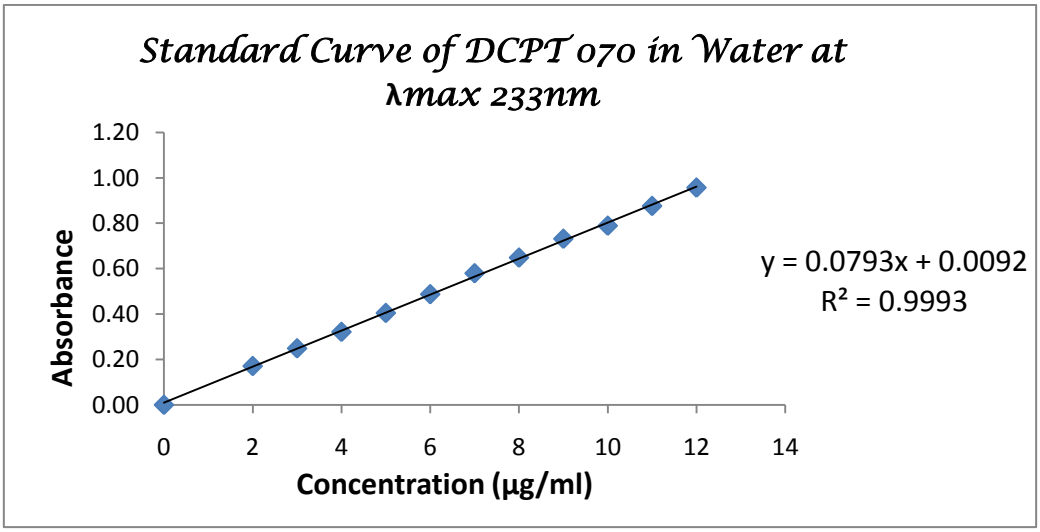


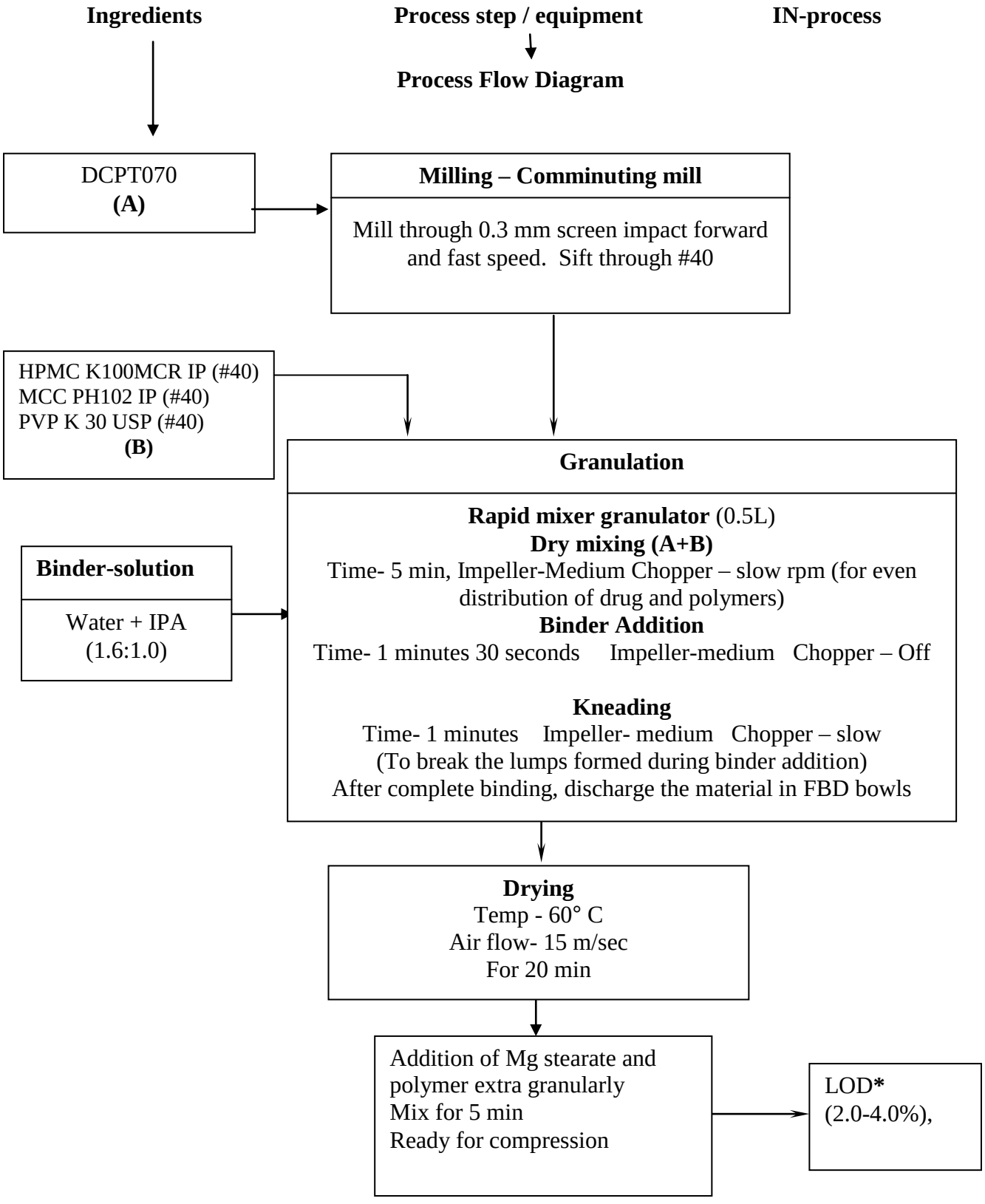
Figure No. : 15 - Standard curve of DCPT070 in water at 233nm

Table No.: 15 Absorbance readings of Standard curve of DCPT070 in water at 233nm

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Avg. absorbance	%RSD
0	0	0	0	0.00	0.00
2	0.17	0.172	0.171	0.17	0.58
3	0.249	0.248	0.25	0.25	0.40
4	0.322	0.322	0.321	0.32	0.18
5	0.405	0.405	0.405	0.41	0.00
6	0.488	0.487	0.488	0.49	0.12
7	0.581	0.579	0.58	0.58	0.17
8	0.65	0.649	0.648	0.65	0.15
9	0.731	0.732	0.733	0.73	0.14
10	0.789	0.789	0.791	0.79	0.15
11	0.877	0.876	0.877	0.88	0.07
12	0.957	0.958	0.958	0.96	0.06

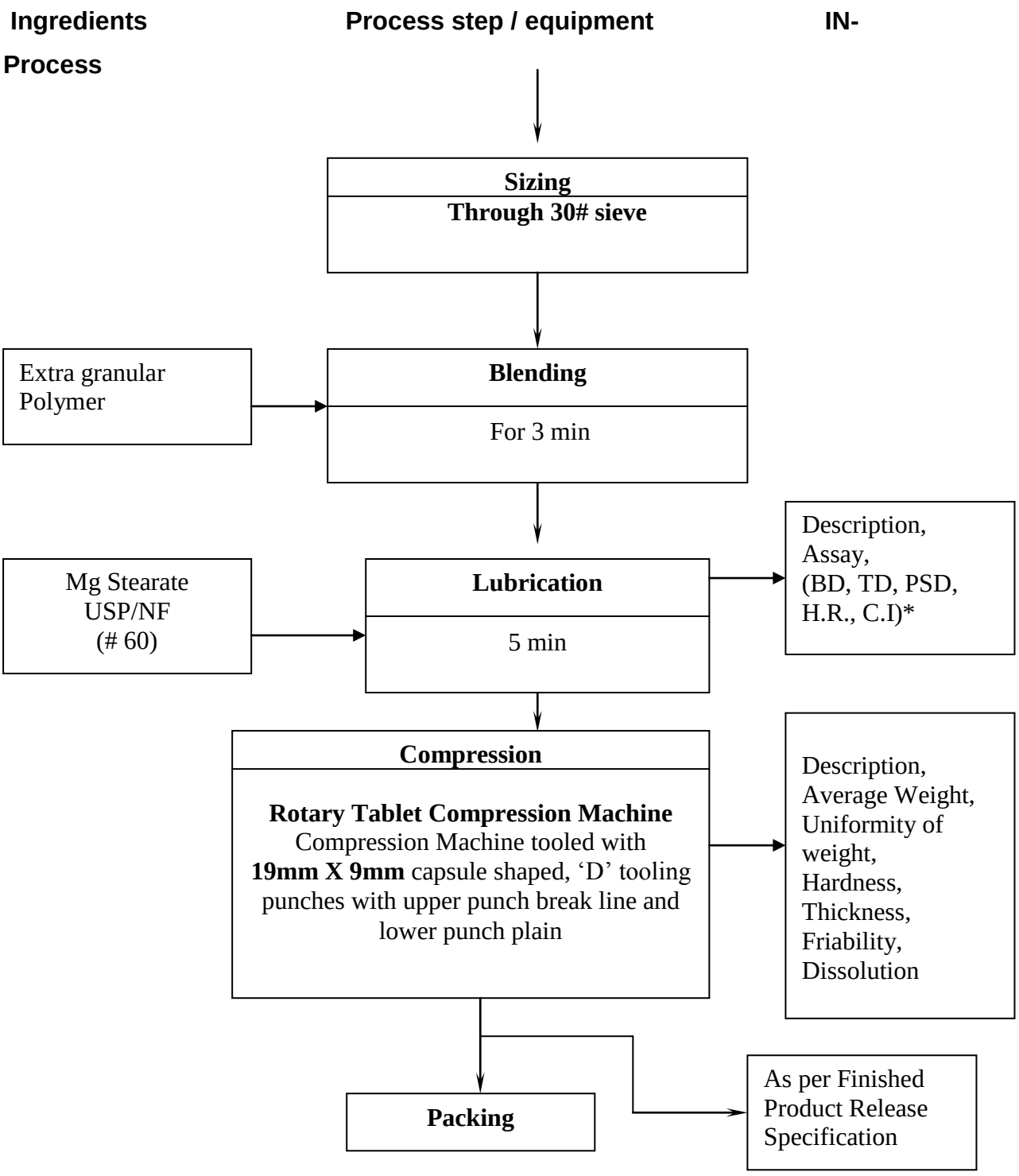
The linearity data and calibration curve have been shown in figure No. (14, 15). It can be seen that relationship between absorbance and concentration is linear.

5.3 PROCESS FLOW DIAGRAM OF DCPT070 BATCH - SCHEMATIC:



***** LOD- Loss on Drying

Process Flow Diagram – Schematic (Continue):



*****BD- Bulk Density, TD- Tapped Density, H.R. – Hausner's Ratio, C.I. – Carr's Index,

PSD- Particle Size Distribution

In Process Evaluation Parameters: [54, 55]

Stage	Test	Acceptance Criteria
Drying	Loss on drying (105°C)	3.0 % (Limit 2.0 – 4.0 %)
	Residual Solvent (Isopropyl Alcohol)	NMT 5000 ppm
Lubrication	Description	White to off-white granular powder.
	Bulk density, Tapped Density, Compressibility Index, Hausner's Ratio, PSD	-
	Description	White, Capsule shaped, biconvex, uncoated tablet with lip break line on both sides.
Compression	Uniformity of weight	Not more than two of the individual weights deviate from the average weight by more than 5.0% and none Deviates by more than 10.0%.
	Hardness (Erweka hardness tester)	150±10N
	Thickness (Erweka hardness tester)	-
	Friability	Not more than 1.0 %
Dissolution	Dissolution apparatus type II(paddle) (In 1000ml of pH6.8 phosphate buffer at 37±0.5° C)	**1 hour:** Not less than 20.0% and not more than 40.0% of the labeled amounts of DCPT070. **3 hour:** Not less than 45.0% and not more than 65.0% of the labeled amounts of DCPT070. **10 hour:** Not less than 85.0% of the labeled amounts of DCPT070.

Assay	Assay (Each uncoated sustained release tablet contains: DCPT070	Not less than 95.0% and not more than 105.0% of the average content of DCPT070.

5.4 EXPERIMENTAL TRIALS

5.4.1 LIST OF TRIALS TAKEN

1. Selection of polymers:

HPMC K15MCR

HPMC K100MCR

} Due to its rapid hydration, good compression and gelling characteristics along with ease of use, availability and very low toxicity

Carbopol 71G – Due to its use in less concentration as well
Improve friability and hardness.
It has good flow property.[56]

Trial No.	Polymer Taken	Way of polymer taken
Optimization of Polymer Concentration:		
1A	HPMC K100MCR	20% Total Intragranularly
2B	HPMC K100MCR	20% Total Extra granularly
1.	HPMC K100MCR	10% intra and 10% Extra
2.	HPMC K100MCR HPMC K15MCR	10% Intra granular 10% Extra granular
3.	HPMC K100MCR Carbopol 71G	10% Intra granular 10% Extra granular
4.	HPMC K100MCR	10% intra granular and 11.25% Extra granular
5.	HPMC K100MCR HPMC K15MCR	10% Intra granular 15% Extra granular
6.	HPMC K100MCR Carbopol 71G	10% Intra granular 11.25% Extra granular
7.	HPMC K100MCR	10% intra and 12% Extra
8.	HPMC K100MCR HPMC K15MCR	10% Intra granular 17.5% Extra granular
9.	HPMC K100MCR Carbopol 71G	10% Intra granular 11% Extra granular
Selection of best batch from optimized batch		

Trials to check the effect of combination of polymer extra granularly:		
10	HPMC K100MCR Carbopol 71G + HPMC K100MCR	10% Intra granular 5.625% + 5.625% Extra granularly
11	HPMC K100MCR Carbopol 71G+ HPMC K100MCR	10% Intra granular 3.375% + 7.875% Extra granularly
12	HPMC K100MCR Carbopol 71G+ HPMC K100MCR	10% Intra granular 7.875% + 3.375% Extra granularly
Trials to check effect of Binder on tablet characteristics:		
13.	HPMC K100MCR PVP K30	10% Intra+ 10% Extra 2.5%
14.	HPMC K100MCR PVP K30	10% Intra+ 10% Extra 5%
15.	HPMC K100MCR PVP K30	10% Intra+ 10% Extra 7.5%
16.	HPMC K100MCR PVP K30	10% Intra+ 12% Extra 2.5%
17	HPMC K100MCR PVP K30	10% Intra+ 12% Extra 5%
18	HPMC K100MCR PVP K30	10% Intra+ 12% Extra 7.5%
Dose dumping study of optimized batch		
Stability Studies of best batch in different packaging material		

5.4.2 TRIALS BY TAKING POLYMER TOTALLY INTRA GRANUALR AND EXTRA GRANULARLLY

First trial started with total Intragranular polymer addition and total extra granular polymer addition to check tableting property and dissolution profile.

Formula:

Sr No	Ingredient	Mg/tab	%w/w	Mg/tab	%w/w
Batch No.		**500/01A**		**500/02A**	
	Intra granularly				
1	DCPT070	500	62.5	500	62.5
2	**HPMC K 100 MCR**	**160**	**20**	**-**	**-**
3	MCC 102	q.s.	-	q.s.	-
4	PVP K 30	40	5	40	5
	Extra granularly				
5	Mg Stearate	21	2.625	21	2.625
7	**HPMC K 100MCR**	**-**		**160**	**20**
	Total weight(mg)	800		800	

Process Parameters:

Granulation Parameters:

Process	Batch No.	Dry mixing	Binder addition	Kneading
Impeller		Medium	Medium	Medium
Load in miliampier	**500/01A**	2.05	2.07	2.25
	500/02A	2.04	2.06	2.21
Chopper		Slow	Off	Slow
Load in miliampier		0.48	-	0.49
Time		5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/01A**	**500/02A**
LOD (%)	1.92	1.75
Bulk density (g/ml)	0.4341	0.4310
Tapped density (%)	0.6252	0.6380
Carr's Index (%)	27.77	29.72
Hausner's ratio	1.44	1.48

Particle size distribution of granules:

Sieve(#)	**Weight(gm)**	**% Retained**
30	0	0.00
40	1.31	8.93
60	2.5	17.04
80	0.83	5.66
100	2.04	13.91
Base	7.99	54.46
Total	14.67	100.00

Compression details:

Parameters	**500/01A**	**500/02A**
Hardness (N)	150±10 (lamination was observed in 2-3 tablets out of 10 tablets)	150±10
Weight Uniformity	Pass as per USP	Pass as per USP
Weight of tablets(mg)	806.21	807.27
Friability (%)	0.3787	0.502
Thickness(mm)	5.19	5.19

Analytical Results:

App II (paddle) vol- 1000ml, 100 RPM Phosphate buffer pH 6.8	Cumulative % Drug Release			
	0 Hr	**1 Hr**	**3 Hr**	**10 Hr**
Acceptance criteria	0%	20-40%	45-65%	>85%
500/01A	0	37.84	59.37	92.71
500/02A	0	45.73	70.84	99.39
Innovator	0	30.46	54.15	91.80

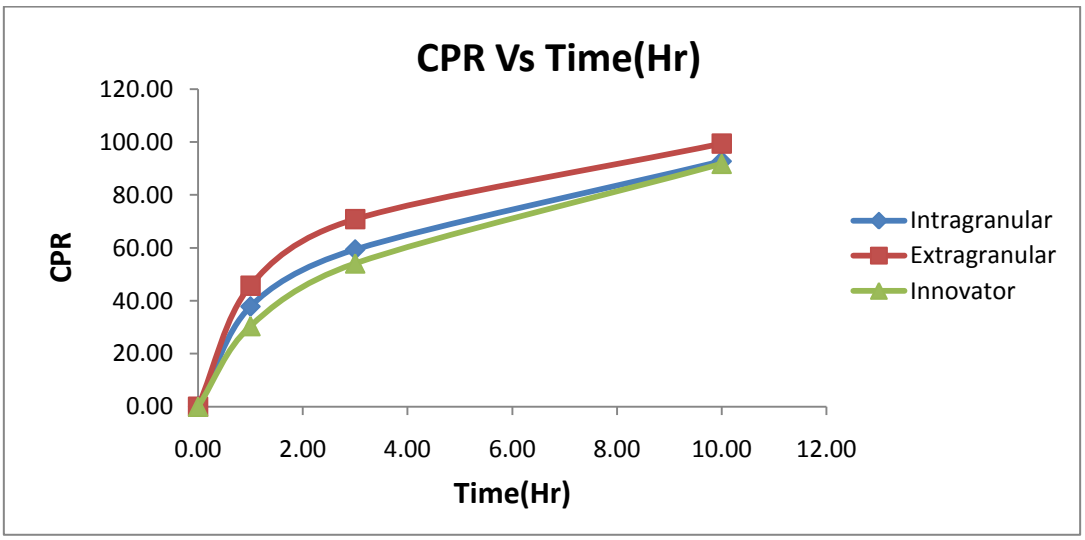


Figure No.: 16 CPR Vs Time (Hr)

Conclusion:

In 500/01A batch HPMC K100MCR was taken totally intragranularly. The release was found decreasing **(Figure: 16)** but some tableting problems like Capping, high friability were observed as compare to other tablets. This may be due to formation of very hard granules.

In 500/02A batch HPMC K100MCR was taken totally extra granularly. Here release was not decrease sufficiently and also tableting problems like high friability was observed as compared to other tablet batches.

Thus the batch containing Polymers with both Intragranular as well as extra granular were prepared which produces tablets with desired release property.

5.4.3 TRIALS BY TAKING POLYMER INTRAGRANULAR AS WELL AS EXTRAGRANULAR

Problems like hard granules, capping, friability was observed when HPMC K100MCR was taken totally intra granularly.Problems like friability, the insufficient retardation of release of drug were observed by taking HPMC K100MCR totally extra granularly. So further trials were done by taking polymer intragranularly as well as extra granularly to nullify problems[56].

Intragranular part of polymer was taken to retard the initial drug release.Extra granular part of polymer was taken to retard the release of drug at later part of dissolution.

Formula:

Sr. No	**Ingredients**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	%w/w	**Qty/Tab (Mg)**	**%w/w**
Batch No.		**500/01**		**500/02**		**500/03**	
	Intra granularly						
1	DCPT070	500	62.5	500	62.5	500	62.5
2	HPMC K 100 MCR	80	10	80	10	80	10
3	MCC 102	79	-	79	-	79	-
4	PVP K 30	40	5	40	5	40	5
	Extra granularly						
5	Mg Stearate	21	2.625	21	2.625	21	2.625
6	**HPMC K 15M**	-	-	**80**	**10**	-	-
7	**HPMC K 100MCR**	**80**	**10**	-	-	-	-
8	**Carbopol 71G**	-	-	-	-	**80**	**10**
	Total weight(mg)	800		800		800	

Process Parameters:

Granulation Parameters:

Process	**Dry mixing**	**Binder addition**	**Kneading**
Impeller	Medium	Medium	Medium
Load in miliampier	2.04	2.07	2.22
Chopper	Slow	Off	Slow
Load in miliampier	0.47	-	0.47
Time	5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/01**	**500/02**	**500/03**
LOD (%)	1.90	1.90	1.90
Bulk density (g/ml)	0.46	0.4623	0.4536
Tapped density (%)	0.6708	0.6721	0.6532
Carr's Index (%)	28.57	28.59	27.77
Hausner's ratio	1.46	1.46	1.44

Particle size distribution of granules:

Batch No.	**500/01**		**500/02**		**500/03**	
Sieve(#)	**Weight**	**% Retained**	**Weight**	**% Retained**	**Weight**	**% Retained**
30	0	0.00	0	0.00	0	0.00
40	2.62	19.74	1.59	11.20	2.37	16.83
60	1.95	14.69	3.03	21.34	2.76	19.60
80	1.27	9.57	1.27	8.94	1.69	12.00
100	2.81	21.18	2.81	19.79	2.84	20.17
Base	4.62	34.82	5.5	38.73	4.42	31.39
Total	13.27	100.00	14.2	100.00	14.08	100.00

Compression details:

Parameters	**500/01**	**500/02**	**500/03**
Hardness (N)	150±10	150±10	150±10
Weight Uniformity	Pass as per USP	Pass as per USP	Pass as per USP
Weight of tablets(mg)	801.50	804.16	805.56
Friability (%)	0.1744	0.292	0.182
Thickness(mm)	5.20	5.22	5.21

Analytical Results:

App II (paddle) vol- 1000ml, 100 RPM Phosphate buffer pH 6.8	**Cumulative % Drug Release**			
	0 Hr	**1 Hr**	**3 Hr**	**10 Hr**
Acceptance criteria	0%	20-40%	45-65%	>85%
500/01	0	38.73	66.91	92.50
500/02	0	46.36	74.58	102.71
500/03	0	38.73	54.19	89.89
Innovator	0	30.46	54.15	91.80

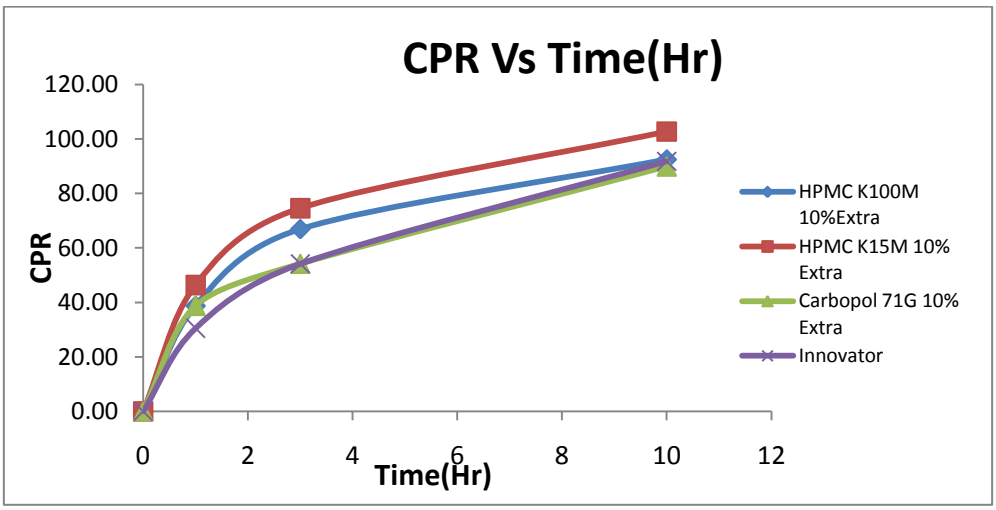


Figure No.: 17 CPR Vs Time (Hr)

Discussion:

In Batch 500/01 & 500/03 the all compression parameters are nearly similar. But still it was found to retard the drug release at initial point of dissolution (1hr and 3hr).So further batch was prepared by increasing concentration of HPMC K100 M and Carbopol 71G from 10% to 11.25 % extra granularly.

In batch 500/02 friability was higher as compared to Batch No. 500/01,500/03.This strongly indicates that still need to retard the release of drug so further batch was prepared by increasing concentration of HPMC K15 M from 10% to 15%

5.4.4 POLYMER OPTIMIZATION BATCH

It was observed that there is still need to retard the drug release so batches were prepared by increasing concentration of all three polymers which can match dissolution profile with innovator product.

Formula:

Sr No	**Ingredient**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	%w/w	**Qty/Tab (Mg)**	**%w/w**
Batch No.		**500/04**		**500/05**		**500/06**	
	Intra granularly						
1	DCPT070	500	62.5	500	62.5	500	62.5
2	HPMC K 100 MCR	80	10	80	10	80	10
3	MCC 102	q.s.	-	q.s.	-	q.s.	-
4	PVP K 30	40	5	40	5	40	5
	Extra granularly						
5	Mg Stearate	21	2.625	21	2.625	21	2.625
6	HPMC K 15MCR	-	-	120	**15**	-	-
7	HPMC K 100MCR	90	**11.25**	-	-	-	-
8	Carbopol 71G	-	-	-	-	90	**11.25**
	Total weight	800		800		800	

Process Parameters:

Granulation Parameters:

Process	**Dry mixing**	**Binder addition**	**Kneading**
Impeller	Medium	Medium	Medium
Load in miliampier	2.04	2.07	2.22
Chopper	Slow	Off	Slow
Load in miliampier	0.47	-	0.47
Time	5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/04**	**500/05**	**500/06**
LOD (%)	1.87	1.87	1.87
Bulk density (g/ml)	0.457	0.46	0.4563
Tapped density (%)	0.657	0.667	0.6523
Carr's Index (%)	28.54	27.12	27.45
Hausner's ratio	1.458	1.442	1.46

Particle size distribution of granules:

Batch No.	**500/04**		**500/05**		**500/06**	
Sieve(#)	**Weight**	**% Retained**	**Weight**	**% Retained**	**Weight**	**% Retained**
30	0	0.00	0	0.00	0	0.00
40	2.55	17.88	1.39	9.62	2.37	16.83
60	1.95	13.67	3.04	21.04	2.76	19.60
80	1.14	7.99	1.27	8.79	1.69	12.00
100	2.81	19.71	3.44	23.81	2.84	20.17
Base	5.81	40.74	5.31	36.75	4.42	31.39
Total	14.26	100.00	14.45	100.00	14.08	100.00

Compression details:

Parameters	**500/04**	**500/05**	**500/06**
Hardness (N)	150±10	150±10	150±10
Weight Uniformity	pass	pass	pass
Weight of tablets(mg)	795.60	803.4	802.60
Friability (%)	0.226	0.182	0.131
Thickness(mm)	5.19	5.48	5.28

Analytical Results:

App II (paddle) vol- 1000ml, 100 RPM Phosphate buffer pH 6.8	**Cumulative % Drug Release**			
	0 Hr	**1 Hr**	**3 Hr**	**10 Hr**
Acceptance criteria	0%	20-40%	45-65%	>85%
500/04	0	33.64	59.25	92.46
500/05	0	33.64	66.89	95.04
500/06	0	31.09	56.69	89.14
Innovator	0	30.46	54.15	91.80

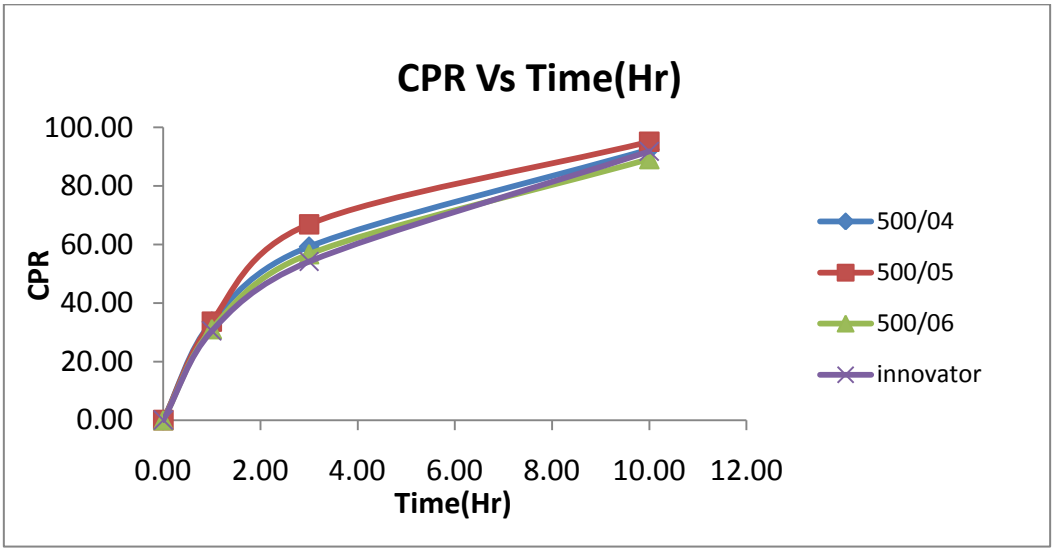


Figure No.: 18 CPR Vs Time (Hr)

Discussion:

The results of Batch No. 500/04 and 500/05 showed strong need to control drug release (Figure 18). So, Batch with increasing concentration of HPMC K100MCR from 11.25% to 12%and HPMC K15MCR from 15% to 17.5 was taken.

The dissolution profile of 500/06 is almost similar to innovator product(Figure 18) but further optimization Batch with decreasing concentration of Carbopol 71G from 11.255 to 11% was used to check effect of lower concentration on dissolution profile.

5.4.5 POLYMER OPTIMIZATION BATCH

The results of all this studies still shows strong need to retard the drug release in Batch No.: 500/04 and 500/05. So batch prepared by increasing Concentration of HPMC K 100MCR

Further batch with Decreasing Concentration of Carbopol 71G was prepared to check the effect of low concentration of carbopol 71G on dissolution profile.

Formula:

Sr No	**Ingredient**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	**%w/w**
Batch No.		**500/07**		**500/08**		**500/09**	
	Intra granularly						
1	DCPT070	500	62.5	500	62.5	500	62.5
2	HPMC K 100 MCR	80	10	80	10	80	10
3	MCC 102	q.s.	-	q.s.	-	q.s.	-
4	PVP K 30	40	5	40	5	40	5
	Extra granularly						
5	Mg Stearate	21	2.625	21	2.625	21	2.625
6	**HPMC K 15MCR**	-	-	**140**	**17.5**	-	-
7	**HPMC K 100MCR**	**96**	**12**	-	-	-	-
8	**Carbopol 71G**	-	-	-	-	**88**	**11**
	Total weight(mg)	800		800		800	

Process Parameters:

Granulation Parameters:

Process	**Dry mixing**	**Binder addition**	**Kneading**
Impeller	Medium	Medium	Medium
Load in miliampier	2.04	2.07	2.22
Chopper	Slow	Off	Slow
Load in miliampier	0.47	-	0.47
Time	5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/07**	**500/08**	**500/09**
LOD (%)	1.90	1.90	1.90
Bulk density (g/ml)	0.463	0.45	0.45
Tapped density (%)	0.66	0.67	0.65
Carr's Index (%)	28.51	28.5	27.73
Hausner's ratio	1.452	1.45	1.44

Particle size distribution of granules:

Batch No.	**500/07**		**500/08**		**500/09**	
Sieve(#)	**Weight**	**% Retained**	**Weight**	**% Retained**	**Weight**	**% Retained**
30	0	0.00	0	0.00	0	0.00
40	2.59	18.07	1.39	9.62	2.37	17.00
60	1.79	12.49	3.04	21.04	3.14	22.53
80	1.28	8.93	1.27	8.79	1.5	10.76
100	2.81	19.61	3.44	23.81	2.84	20.37
Base	5.86	40.89	5.31	36.75	4.09	29.34
Total	14.33	100.00	14.45	100.00	13.94	100.00

Compression details:

Parameters	500/07	500/08	500/09
Hardness (N)	150±10	150±10	150±10
Weight Uniformity	Pass as per USP	Pass as per USP	Pass as per USP
Weight of tablets(mg)	795.60	799.24	803.4
Friability (%)	0.226	0.234	0.182
Thickness(mm)	5.19	5.19	5.48

Analytical Results:

App II (paddle) vol- 1000ml, 100 RPM Phosphate buffer pH 6.8	Cumulative % drug Release			
	0 Hr	**1 Hr**	**3 Hr**	**10 Hr**
Acceptance criteria	0%	20-40%	45-65%	>85%
500/07	0	**32.11**	**58.99**	**100.85**
500/08	0	**31.86**	**58.48**	**98.82**
500/09	0	37.46	65.38	99.36
Innovator	0	30.46	54.15	91.80

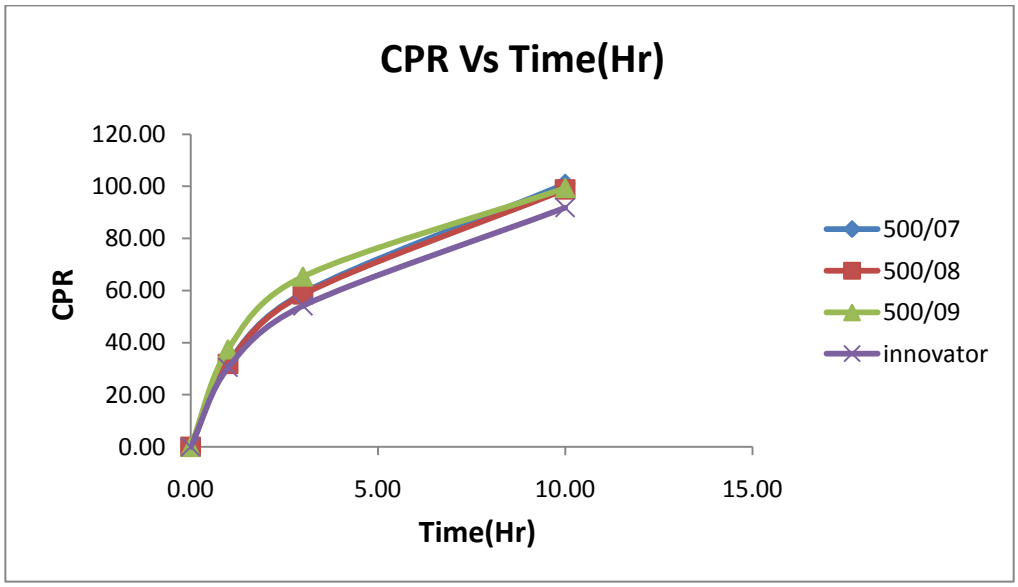


Figure No.: 19 CPR Vs Time (Hr)

Discussion:

The dissolution Profile of Batch No. 500/07 and 500/08 matched with dissolution profile of Innovator product. So these batches are selected as optimized batches for HPMC K100MCR and HPMC K15MCR respectively.

The Cumulative % release of Batch No. 500/09 increased as carbopol 71G concentration decreased. Thus Batch 500/06 selected as optimized batch for carbopol 71G

5.4.6 TRIAL TO CHECK COMBINATION EFFECT OF POLYMER

The required drug release was obtained in previous batches. However, to further determine better batch, it was decided to see the effect of combination of polymers as researchers reported use of combination of polymers very advantageous[57, 58]

Formula:

Sr No	**Ingredients**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	%w/w	**Qty/Tab (Mg)**	**%w/w**
Batch No.		**500/10**		**500/11**		**500/12**	
	Intra granularly						
1	DCPT070	500	62.5	500	62.5	500	62.5
2	HPMC K 100 MCR (10%)	80	10	80	10	80	10
3	MCC 102	q.s.	-	q.s.	-	q.s.	-
4	PVP K 30	40	5	40	5	40	5
	Extra granularly						
5	Mg Stearate	21	2.625	21	2.625	21	2.625
7	**HPMC K 100MCR**	**45**	**5.625**	**27**	**3.375**	**63**	**7.875**
8	**Carbopol 71G**	**45**	**5.625**	**63**	**7.875**	**27**	**3.375**
	Total weight	800		800		800	

Process Parameters:

Granulation Parameters:

Process	**Dry mixing**	**Binder addition**	**Kneading**
Impeller	Medium	Medium	Medium
Load in miliampier	2.04	2.07	2.22
Chopper	Slow	Off	Slow
Load in miliampier	0.47	-	0.47
Time	5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/10**	**500/11**	**500/12**
LOD (%)	1.92	1.92	1.92
Bulk density (g/ml)	0.4621	0.45	0.4567
Tapped density (%)	0.645	0.668	0.6562
Carr's Index (%)	28.523	28.545	27.7321
Hausner's ratio	1.447	1.45	1.4453

Particle size distribution of granules:

Batch No.	**500/10**		**500/11**		**500/12**	
Sieve(#)	**Weight**	**% retained**	**Weight**	**% retained**	**Weight**	**% retained**
30	0	0.00	0	0.00	0	0.00
40	2.62	19.74	1.59	11.20	2.37	16.83
60	1.95	14.69	3.03	21.34	2.76	19.60
80	1.27	9.57	1.27	8.94	1.69	12.00
100	2.81	21.18	2.81	19.79	2.84	20.17
Base	4.62	34.82	5.5	38.73	4.42	31.39
Total	13.27	100.00	14.2	100.00	14.08	100.00

Compression details:

Parameters	500/10	500/11	500/12
Hardness (N)	150±10	150±10	150±10
Weight Uniformity	Pass as per USP	Pass as per USP	Pass as per USP
Weight of tablets(mg)	805.56	801.58	799.29
Friability (%)	0.233	0.212	0.245
Thickness(mm)	5.20	5.11	5.19

Analytical Results:

App II (paddle) vol- 1000ml, 100 RPM Phosphate buffer pH 6.8	Cumulative % Drug Release			
	0 Hr	1 Hr	3 Hr	10 Hr
Acceptance criteria	0%	20-40%	45-65%	>85%
500/10	0	41.88	69.22	100.14
500/11	0	44.81	75.21	100.17
500/12	0	42.09	76.16	99.67
Innovator	0	30.46	54.15	91.80

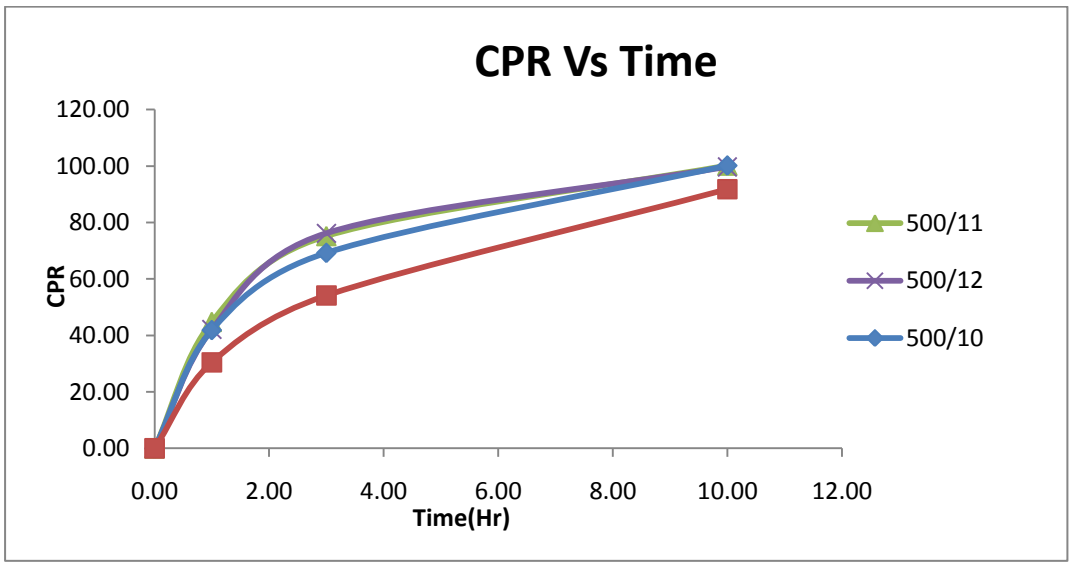


Figure No. 21: CPR Vs Time (Hr)

Discussion:

In all three batches the release of drug was found increasing by combination of polymers compared to use of individual polymers. This may be due to improper formation of matrix when use in combination. So, it was concluded that combination is not advantageous.

5.4.7 TRIALS TO CHECK EFFECT OF BINDER

Now further trials were taken to see the effect of binder on Dissolution profile of DCPT070

If there is effect of binder on drug release then Batch No.: 500/01 that is HPMC K100MCR 10% extra granularly with PVP K30 in higher concentration 7.5% may give the similar type of release as batch No: 500/07

So, Binder optimization was done for both Batch No. 500/01 as well as 500/07 with varying concentration of binder concentration.

Formula:

Sr. No	**Ingredients**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	**%w/w**	**Qty/Tab (Mg)**	**%w/w**
Batch No.		**500/13**		**500/01**		**500/14**	
	Intra granularly						
1	DCPT070	500	62.5	500	62.5	500	62.5
2	HPMC K 100 MCR	80	10	80	10	80	10
3	MCC 102		-	79	-		-
4	PVP K 30	**20**	**2.5**	**40**	**5**	**60**	**7.5**
	Extra granularly						
5	Mg Stearate	21	2.625	21	2.625	21	2.625
6	HPMC K 15MCR	-	-	-	-	-	-
7	HPMC K 100MCR	**80**	**10**	**80**	**10**	**80**	**10**
8	Carbopol 71G	-	-	-	-	-	-
	Total weight(mg)	800		800		800	

Process Parameters:

Granulation Parameters:

Process	**Dry mixing**	**Binder addition**	**Kneading**
Impeller	Medium	Medium	Medium
Load in miliampier	2.04	2.07	2.22
Chopper	Slow	Off	Slow
Load in miliampier	0.48	-	0.48
Time	5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/13**	**500/01**	**500/14**
LOD (%)	1.99	1.97	1.95
Bulk density (g/ml)	0.459	0.46	0.45
Tapped density (%)	0.657	0.667	0.6523
Carr's Index (%)	28.54	27.12	27.45
Hausner's ratio	1.458	1.442	1.46

Particle size distribution of granules:

Batch No.	**500/13**		**500/01**		**500/14**	
Sieve(#)	**Weight**	**% Retained**	**Weight**	**% Retained**	**Weight**	**% Retained**
30	0	0.00	0	0.00	0	0.00
40	2.55	17.88	1.39	9.62	2.37	16.83
60	1.95	13.67	3.04	21.04	2.76	19.60
80	1.14	7.99	1.27	8.79	1.69	12.00
100	2.81	19.71	3.44	23.81	2.84	20.17
Base	5.81	40.74	5.31	36.75	4.42	31.39
Total	14.26	100.00	14.45	100.00	14.08	100.00

Compression details:

Parameters	**500/13**	**500/01**	**500/14**
Hardness (N)	150±10	150±10	150±10
Weight Uniformity	pass	pass	pass
Weight of tablets(mg)	800.08	803.4	800.12
Friability (%)	0.275	0.182	0.198
Thickness(mm)	5.19	5.48	5.28

Analytical Results:

App II (paddle) vol-1000ml, 100 RPM Phosphate buffer pH 6.8	**Cumulative % Drug Release**			
	0 Hr	**1 Hr**	**3 Hr**	**10 Hr**
Acceptance criteria	0	20-40%	45-65%	>85%
500/13	0	41.60	69.09	100.90
500/01	0	33.64	66.89	95.04
500/14	0	42.01	68.38	100.90
Innovator	0	30.46	54.15	91.80

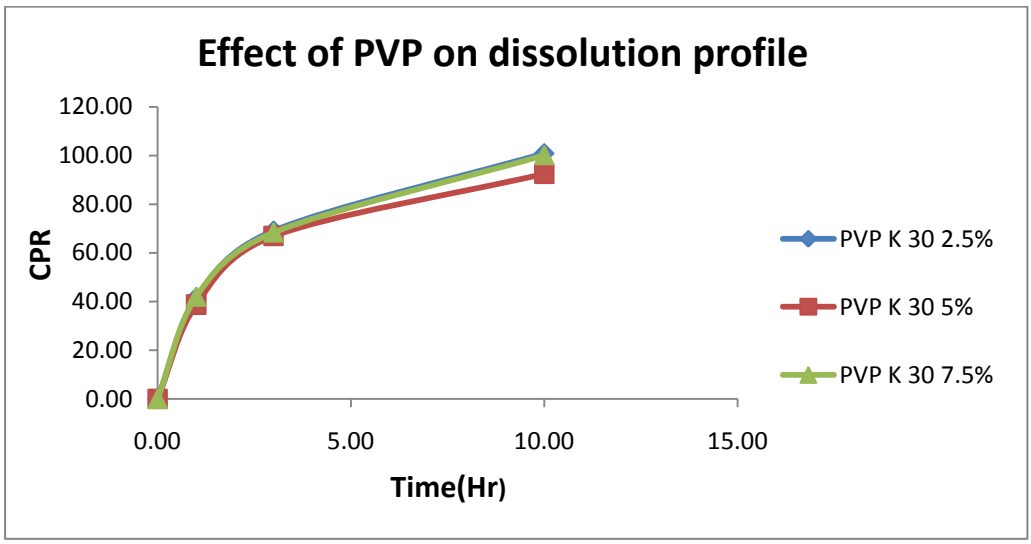


Figure No.: 22 CPR Vs Time (Hr)

Formula:

Sr No	Ingredient	Qty/Tab (Mg)	%w/w	Qty/Tab (Mg)	%w/w	Qty/Tab (Mg)	%w/w
Batch No.		**500/15**		**500/07**		**500/16**	
	Intra granularly						
1	DCPT070	500	62.5	500	62.5	500	62.5
2	HPMC K 100 MCR	80	10	80	10	80	10
3	MCC 102		-	79	-		-
4	PVP K 30	**20**	**2.5**	**40**	**5**	**60**	**7.5**
	Extra granularly						
5	Mg Stearate	21	2.625	21	2.625	21	2.625
6	HPMC K 15MCR	-	-	-	-	-	-
7	HPMC K 100MCR	**96**	**12**	**96**	**12**	**96**	**12**
8	Carbopol 71G	-	-	-	-	-	-
	Total weight(mg)	800		800		800	

Process Parameters:

Granulation Parameters:

Process	**Dry mixing**	**Binder addition**	**Kneading**
Impeller	Medium	Medium	Medium
Load in miliampier	2.04	2.07	2.22
Chopper	Slow	Off	Slow
Load in miliampier	0.48	-	0.48
time	5min	1min 30 sec	1min

Characterization of granules:

Parameters	**500/15**	**500/07**	**500/16**
LOD (%)	1.99	1.90	1.95
Bulk density (g/ml)	0.459	0.463	0.45
Tapped density (%)	0.657	0.66	0.6523
Carr's Index (%)	28.54	28.51	27.45
Hausner's ratio	1.458	1.452	1.46

Particle size distribution of granules:

Batch No.	**500/15**		**500/07**		**500/16**	
Sieve(#)	**Weight**	**% retained**	**Weight**	**% retained**	**Weight**	**% retained**
30	0	0.00	0	0.00	0	0.00
40	2.55	17.88	2.59	18.07	2.37	16.83
60	1.95	13.67	1.79	12.49	2.76	19.60
80	1.14	7.99	1.28	8.93	1.69	12.00
100	2.81	19.71	2.81	19.61	2.84	20.17
Base	5.81	40.74	5.86	40.89	4.42	31.39
Total	14.26	100.00	14.33	100.00	14.08	100.00

Compression details:

Parameters	**500/15**	**500/07**	**500/16**
Hardness (N)	150±10	150±10	150±10
Weight Uniformity	pass	pass	pass
Weight of tablets(mg)	810.301	795.60	799.63
Friability (%)	0.399	0.226	0.211
Thickness(mm)	5.18	5.19	5.23

Analytical Results:

App II (paddle) vol- 1000ml, 100 RPM Phosphate buffer pH 6.8	**Cumulative % Drug Release**			
	0 Hr	**1 Hr**	**3 Hr**	**10 Hr**
Acceptance criteria	0	20-40%	45-65%	>85%
500/15	0	33.08	60.67	101.37
500/07	0	32.11	58.99	100.85
500/16	0	31.35	57.21	97.28
Innovator	0	30.46	54.15	91.80

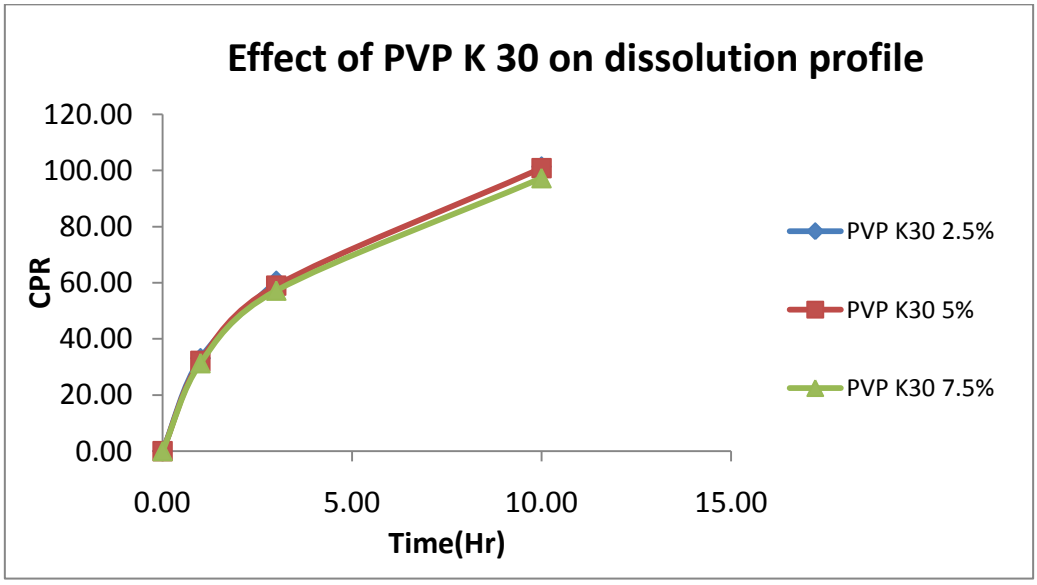


Figure No. : 23 CPR Vs Time (Hr)

Discussion:

The figure 22 shows the dissolution profile of batch No. 500/13,500/01,500/14 containing PVP K30 2.5%, 5%, and 7.5% respectively. It was observed that dissolution profile is quite similar.

The figure 23 shows the dissolution profile of batch No. 500/15,500/07,500/16 containing PVP K30 2.5%, 5%, and 7.5% respectively. It was observed that dissolution profile is quite similar.

Similarity factors found between batches are:

Batch No.	F2 Value
500/01 & 500/13	70.65
500/01 & 500/14	72.26
500/13 & 500/14	97.93

Batch No.	F2 Value
500/07 & 500/15	93.7
500/07 & 500/16	85.6
500/15 & 500/16	78.9

Discussion:

Table shows that similarity factor between all three batches are greater than 50 so all three batches are considered to be similar. So there is no significant effect of binder on drug dissolution profile.

The possible reasons highly solubility high dose of drug that is 500mg therefore the drug release may be unaffected by binder concentration.

Batch No. 500/07(HPMC K 100MCR 10% Intra granular & 12% Extra granular) was selected as best batch.

5.4.8 SELECTION OF BEST BATCH FROM OPTIMIZED BATCHES

Dissolution Profile of Optimized Batch:

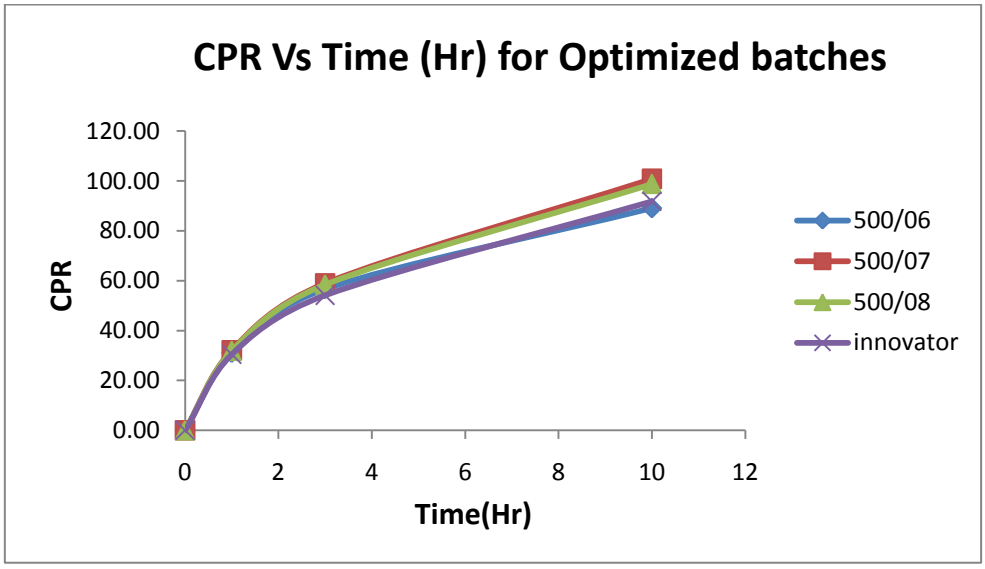


Figure No. : 20 CPR Vs Time (Hr)

F2 value comparison of optimized batch with innovator product

Batch No.	F2 Value
500/06	87.0
500/07	68.0
500/08	72.4

Batch No.	t Value	t critical
500/06	0.46	2.35
500/07	0.07	2.35
500/08	0.07	2.35

Looking to the results of t values of all three batches are less than the t critical. So there were no significant changes in optimized batches than innovator product.

As per the result of f2 value comparison with innovator product the f2 value obtained for batch No. 500/06 was higher than Batch No. 500/07, 500/08 but there is larger variation in drug release by changing small amount of carbopol 71G. This may make problem during scale up and development of commercial batch.

The f2 values of Batch No. 500/07 & Batch No. 500/08 were almost similar. But in batch No.: 500/08 concentration of HPMC K15MCR required to retard release was higher as compared to Batch No.: 500/07 containing HPMC K100MCR.

The Cost of both HPMC K100MCR and HPMC K15MCR is nearly similar.

Thus looking to drug release obtained and cost of product finally Batch No. 500/07(HPMC K 100MCR 10% Intra granular & 12% Extra granular) was selected as best batch.

5.5 CALCULATION OF SIMILARITY AND DISSIMILARITY FACTORS OF BEST BATCH

F-1 ANALYSIS(DISIMILARITY FACTOR)					
Time(Hr)	**500/07**	**Innovator Product**	**Rt-Tt**		
0.00	0.00	0.00	0.00		
1.00	32.11	30.46	1.65		
3.00	58.99	54.15	4.84		
10.00	100.85	91.80	9.06		
				SUM(Rt-Tt)	15.55
				SUM(Rt)	176.40
				SUM(Rt-Tt)/SUM(Rt)	0.09
				F1=	8.82

F2 ANALYSIS(SIMILARITY FACTOR)				
Time(Hr.)	**500/07**	**Innovator product**	**Rt-Tt**	**$(Rt-Tt)^2$**
0.00	0.00	0.00	0.00	0.00
1.00	32.11	30.46	-1.65	2.74
3.00	58.99	54.15	-4.84	23.45
10.00	100.85	91.80	-9.06	82.03
			$SUM(Rt-Tt)^2$	108.22
			N=	6.00
			$1/N\ [SUM(Rt-Tt)^2]$	18.04
			$1+1/N\ [SUM(Rt-Tt)^2]$	19.04
			$\{1+1/N\ [SUM(Rt-Tt)^2]\}^{-0.5}$	0.23
			$\{1+1/N\ [SUM(Rt-Tt)^2]\}^{-0.5}*100$	22.92
			$Log\{\{1+1/N\ [SUM(Rt-Tt)^2]\}^{-0.5}*100\}$	1.36
			$50*Log\{\{1+1/N\ [SUM(Rt-Tt)^2]\}^{-0.5}*100\}$	68.01

Discussion:

Similarity factor is > 50 and dissimilarity factor is less than 20. So it is concluded that developed product is similar to that of marketed product.

5.6 DOSE DUMPING STUDY:

Definition: [59, 60]

"Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form is often referred to as "dose dumping**"**

Purpose:

Some modified-release (MR) oral dosage forms contain drugs and excipients which are highly soluble in ethanol, leading to concerns that these products might dose-dump if co-administered with alcoholic beverages. Such dose-dumping could pose a significant risk to patients, either because of increased toxicity or diminished efficacy or both. This study assesses the performance of an in vitro assay to determine the potential for alcohol-induced dose-dumping of generic modified release drug products.

Methods:

The assay was implemented for several MR drug products under review at the Office of Generic Drugs (OGD). The assay employs USP Apparatus I or II and 900 ml of 0.1 N HCl media containing ethanol (v/v) at: 0%; 5%; 20%; and 40%, sampling every 15 minutes until 2 hours. Applicants conduct these studies on all drug product strengths.

The dissolution results are categorized as:

Case I: If at 2 hours, % dissolved of the generic product in 40% ethanol is ≤ in 0% ethanol, the generic product is considered robust (does not dose-dump); if not

Case II: At 2 hours, % dissolved of the generic product in ethanol solution is less or comparable to that of the reference, the potential for dose-dumping is similar for the two products and the generic product is acceptable; if not

Case III: The generic product releases more drugs in ethanol than the reference and is unacceptable.

Results:

To date, the OGD reviewed 22 submissions, representing 7 different drugs, containing results of in vitro dose-dumping in alcohol studies. Of these 22 studies, 12 (54.6%), 9 (40.9%), and 1 (4.5%) were categorized as Case I, II, and III, respectively. Similar trends in study outcome were observed for the various strengths of each drug product line tested.

Conclusion:

The study data indicate that the in vitro dose-dumping in alcohol assay recommended by the Agency is adequately discriminating to assess the potential for ethanol to alter the rate of drug release for a variety of MR drug products. Also, most of the generic products studied so far showed ruggedness against alcohol-induced dose-dumping.

Dose dumping Studies of final Batches

Dissolution apparatus : Type II (paddle)

Volume: 900ml

RPM : 100

Dissolution medium : 0.1N HCl + 40% ethanol

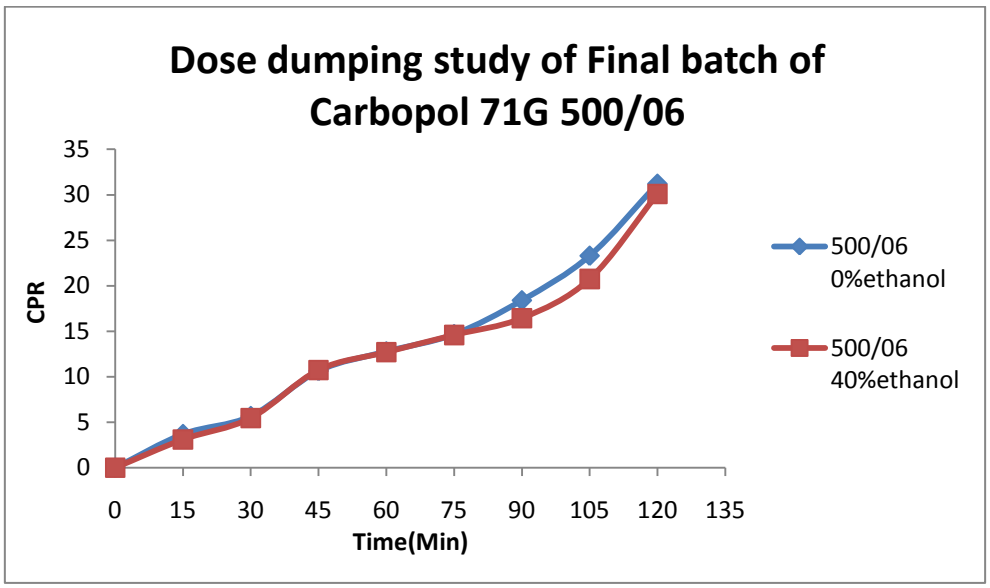


Figure No. : 24 Dose dumping study of Final batch of Carbopol 71G 500/06

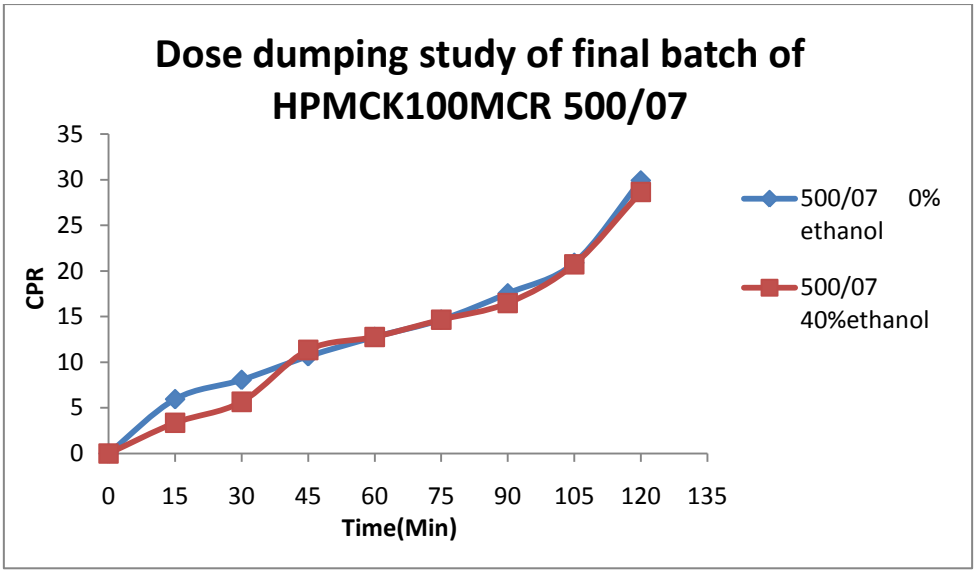


Figure No.: 25 Dose dumping study of final batch of HPMCK100MCR 500/07

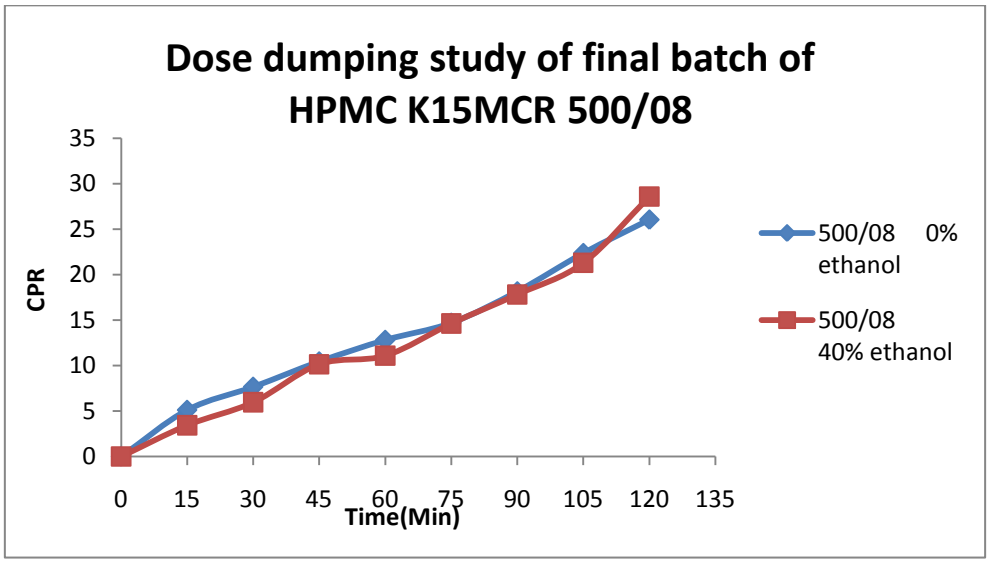


Figure No.: 26 Dose dumping study of final batch of HPMC K15MCR 500/08

Discussion:

All three batches comes under the case I(figure 24,25,26) that is % dissolved of the generic product in 40% ethanol at 2 hours is less than %dissolved in 0% ethanol at 2 hours. So, all the three batches were considered robust (does not dose-dump).

5.7 CALCULATION OF DRUG RELEASE KINETICS

Zero-Order Kinetics: [61]

Zero order as cumulative amount of drug released vs time,

$$C = K_0 t$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of drug remaining vs time,

$$Log\ C = Log\ Co - kt / 2.303$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi Model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = K t^{1/2}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmayer Peppas Model:

Korsmeyer et al's equation log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$M t / M \infty = K t^{n}$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers.

For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion.

$0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion.

n= 0.89 is indicative of Case-II Transport or typical zero-order release.

Results of release parameters of best batch 500/07:

Sr. No.	MODEL	MULTIPLE R	R SQUARE	INTERCEPT	SLOPE	FISCHER RATIO	SSR
1	**Zero order**	0.9448	0.8926	16.6737	8.9468	16.6185	587.6315
2	**First order**	0.9934	0.9869	1.9832	-0.1262	75.4494	31.3965
3	**Higuchi model**	0.9744	0.9494	11.9659	12.1929	112.6279	13821.8466
4	**Kosmeyer-pepas model**	**0.9980**	0.9961	-0.4840	**0.4962**	253.8272	**10.2671**
5	**Weibull model**	0.9712	0.9432	-0.5146	1.3852	16.6037	301.0801
6	**Hixson-crowel model**	0.9955	0.9910	-0.1335	0.5627	220.4027	260.2786

Discussion:

Result shows that the release kinetics of Batch No. 500/07 fit into Kosmeyer pepas model as it have highest multiple R value that is 0.9980 and lowest Sum of square of residual that is 10.2671.

Value of exponent n is between 0.45 and 0.89 that is 0.4962. The release mechanism is Anomalous diffusion that is drug release occur by fickian diffusion as well as swelling of polymer.

8. SUMMARY

Preformulation Studies:

All physical and chemical parameters of DCPT 070 were similar to the reported parameters.Excipients used in formulations are compatible with the DCPT 070.

Identification of DCPT 070:

DCPT 070 shows wavelength maxima at 233nm.that conclude that the given drug is DCPT070.

DCPT 070 shows linearity within the calibration curve concentration range.

Selection and Optimization of Polymers:

HPMCK100MCR, HPMC K15MCR, Carbopol 71G were selected as release retarding polymers.

Various trials were taken to optimize the polymer concentration.

Among which the Batch with 10% HPMC K100MCR intra granularly & 12% HPMC K100MCR extra granularly selected as best batch. (Batch No. 500/07)

Optimization of Binder concentration:

There was no effect of binder on dissolution profile of DCPT 070 because DCPT 070 is highly water soluble.

Dose dumping Study:

Dose dumping study was carried out to check the effect of alcohol on dissolution profile of DCPT070 and thereby minimize the side effects if tablets taken with alcoholic beverages.

All batches were robust. (No dose dumping was observed)

Calculation of similarity and dissimilarity factors:

Similarity factor is > 50 and dissimilarity factor is less than 20 so; the product is considered similar to the marketed product.

Application of dissolution model:

The release of best batch fit into the Kosmeyer peppas model. So release mechanism may be anomalous diffusion.

Stability Studies:

All stability study data were found satisfactory in all three packing.

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