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# Extended Release Formulation

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**ABSTRACT:**

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral Extended release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence, in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate extended release system in order to achieve plasma concentration profile up to 24 hrs.

The extended release formulations are the type of formulations which will improves the therapeutic index of drug concentration.These formulations makes the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. Here an attempt was made to formulate the Delayed Drug release in to the systemic circulation. Which will give detailed information about the formulation and formulation requirements to develop the ideal Delayed drug release formulation.

## 1. INTRODUCTION AND PATENT SUMMARY

### 1.1 INTRODUCTION

In recent years in association with progress and innovation in the field of pharmaceutical technology there has been an increasing effort to develop prolonged release dosage forms. The prolonged release dosage forms have

many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced drug efficacy can be prolonged and the incidence of adverse effects can be decreased. Extended release drug formulations have been used since 1960's. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet from which the drug is slowly released. This formulation helps to avoid the side effects associated with low concentration and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

**Advantages:**

Extended release products having many advantages.

1. The extended release formulations may maintain therapeutic concentrations over prolonged periods.
2. The use of extended release formulations avoids the high blood concentration.
3. Extended release formulations have the potential to improve the patient compliance.
4. Reduce the toxicity by slowing drug absorption.
5. Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
6. Minimize the local and systemic side effects.
7. Improvement in treatment efficacy.
8. Minimize drug accumulation with chronic dosing.
9. Usage of less total drug.
10. Improvement the bioavailability of some drugs.
11. Improvement of the ability to provide special effects.

    Ex: Morning relief of arthritis through bed time dosing.

**Disadvantages:**

1. High cost of preparation.
2. The release rates are affected by various factors such as, food and the rate transit through the gut.
3. Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
4. Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
5. The larger size of extended release products may cause difficulties in ingestion or transit through gut.

**1.2 PATENT SUMMARY:**

Patent no 3087790 describes a combination of HPMC and HPC which is used to control the release rate of a pharmaceutically active compound. It explains the ratio of drug and solubilize preferable range is 1:2 to1:6. The - API was dissolved in cremophor RH 40 and than solution obtained was mixed carefully with material aluminium silicate. The mixture was granulated with HPMC and dried. SSF was added as a lubricant and tablets were prepared by compression.

US patent no 5439687 describes the pharmaceutical dosage forms having a linear release rate of the zero-order for the once daily oral administration of calcium antagonist of the dihydropyridine type characterized by a homogenous matrix containing 2-50% by weight of HPMC as well as customary excipients compatible with the formulation such as lipophilic liberation controllers, fillers, lubricants and optionally film coatings.

US Patent no 5846563 describes a sustained release excipient that is suitable for providing when combined with a medicament a sustained release formulation that provides therapeutically effective blood levels of the medicament for example 12 to 24 hrs.

**Drugs, which are suitable for, extended release formulation:**

**I. Physiochemical Properties of the drug:**

**a) Aqueous Solubility:**

Lower limit solubility for such product is reported to be 0.1 mg/ml. As the drug must be in solution form before absorption, drug having low aqueous solubility usually suffers oral bioavailability problem due to limited GI transit time of undissolved drug and limited solubility at absorption site. So these types of drug are undesirable. Drug having extreme aqueous solubility are undesirable for ER because, it is too difficult to control release of drug from the dosage form. Physiological pH dependent solubility i.e. variation in solubility at different GI pH are undesirable (e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine) as it will yield variation in dissolution rate. A drug with good aqueous solubility, pH independent solubility is desirable for oral new drug delivery system

**b) Partition Co-efficient:**

As biological membrane is lipophilic in nature through which the drug has to pass though, so partition co-efficient of drug influence the bioavailability of drug very much. Drug having lower partition co-efficient values less than the optimum activity are undesirable for oral ER drug delivery system, as it will have very less lipid solubility and the drug will be localized at the first aqueous phase it come in contact e.g. Barbituric acid. Drug having higher partition co-efficient value greater than the optimum activity are undesirable for oral ER drug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane. The value of partition co-efficient at which optimum activity is observed is approximately 1000:1 in 1-octano/water system.

**c) Drug Stability *in-vivo*:**

As most of ER Drug delivery system is designing to release drug over the length of the GIT, hence drug should be stable in GI environment. So drug, which is unstable, can't be formulated as oral ER drug delivery system, because of bioavailability problem.

e.g. - Nitroglycerine.

**d) Protein Binding:**

The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half life and thus sometimes ER drug delivery system is not required for this type of drug.

**e) Drug pKa & Ionization at Physiological pH:**

As we know only unionized drug are absorbed and permeation of ionized drug is negligible, since its rate of absorption is 3 to 4 times less than that of the unionized drug. pKa range for acidic drug where ionization is pH sensitive is around 3.0 – 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be non-ionized at the site to an extent 0.1 – 5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system.

e.g.:- Hexamethonium.

**f) Mechanisms and Sites of Absorption:**

Drug absorption by carrier mediated transport and those absorbed through a window are poor candidate for oral ER drug delivery system e.g. – several B vitamins. Drugs absorbed by passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral ER drug delivery system.

**g) Molecular Size and diffusivity:**

With large molecular size are poor candidate for oral ER drug delivery system because it the ability of the drug to diffuse polymeric membrane is a function of its diffusivity (or diffusion co-efficient). Diffusivity depends on size shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug i.e.-100 to 400 Dalton, through flexible polymer range from $10^{-6}$ to $10^{-9}$ $cm^2$/sec. For drugs having molecular weight > 500 Daltons the diffusion co-efficient in many polymers are very less i.e. less than $10^{-12}$ $cm^2$/sec. Drugs is very difficult to control release rate of medicament from dosage form e.g. proteins and peptides.

**h) Dose Size:**

If a product has dose size >0.5g it is a poor candidate for oral ER drug delivery system, because increase in bulk of the drug, thus increases the volume of the product.

**II. Biological Properties of Drug: -**

**a) Absorption:**

For oral ER drug delivery system the rate of drug absorption (ka) should be more -API than that of the rate of drug release (kr) from the dosage form i.e. kr <<< ka. Drug that are slowly absorbed or absorbed with a variable absorption rate of elimination of drug are poor candidate for oral ER drug delivery system. Some possible reasons for a low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis, and metabolism or its site of absorption.

**b) Distribution:**

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral ER drug delivery system e.g. Chloroquine.

**c) Metabolism:**

Drug, which extensively metabolized is not suitable for ER drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption of first-pass effect is poor candidate for ER delivery, since it could be difficult to maintain constant blood level e.g. levodopa, nitroglycerine.

**d) Half-life of Drug:**

A drug having biological half-life between 2 to 8 hours is best suited for oral ER drug delivery system. As if biological half-life < 2hrs the system will require unacceptably large rate and large dose and biological half-life >8hours formulation of such drug into oral ER drug delivery system is unnecessary.

**e) Margin of safety:** As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral ER drug delivery system due to technological limitation of control over release rates.

**f) Plasma Concentration Response Relationship:**

Generally pharmacological response of drug depends on plasma drug concentration rather than size and dose. But some drugs pharmacological activity is independent of plasma concentrations, which are poor candidate for oral ER drug delivery system

E.g. Reserpine

**g) Concentration Dependency on Transfer of Drug:**

Transfer of drug from one compartment to other by zero kinetic process then such drugs are poor candidate for oral ER delivery system, it should be first order kinetics.

**Types of Extended release formulation**:

Many current oral extended release systems are available

1. Dissolution-controlled release system.
2. Diffusion-controlled release system.
3. Osmotic pump system.
4. Erosion controlled release systems.

**1. Dissolution controlled release systems:**

In dissolution controlled extended release systems the rate of dissolution in the gastrointestinal juices of the drug or another ingredients is the release controlling process. Sparingly water-soluble drug can form a preparation of a dissolution controlled extended release type. Reduced drug solubility can be accomplished by preparing poorly soluble salts or derivatives of the drug. An alternative means to achieve extended release based on dissolution is to incorporate the drug in a slowly dissolving carrier.

Dissolution controlled extended release systems can also be obtained by covering drug particles with a slowly dissolving coating. The release of the drug from such units occurs in two steps,

1) The liquid that surrounds the release unit dissolves the coating (rate limiting dissolution step).

2) The solid drug is exposed to the liquid and subsequently dissolves sustained release oral products employing dissolution as the rate limiting step are in principle the simplest to prepare. A drug with a slow dissolution rate is inherently sustained. Some example of these drugs includes digoxin, griseofulvin, and salicylamide. Others, such as aluminum aspirin, ferrous sulfate, and benzphetamine paomate, produce such forms when in contact with the absorption pool contents. Steroids have been reports to undergo transformation into less soluble polymorphs during dissolution in the absorption pool.

For those drugs with high water solubility and therefore high dissolution rate, one can decrease solubility through appropriate salt of derivative formation. Unfortunately, forms such as these do not meet the criterion of constant availability rate because their surface area decreases with time. Nevertheless, sustained drug release can be achieved by coating drug particles or granules with materials of varying thickness or by dispersing them in a polymeric matrix.

The basic principle of dissolution control is as follows. If the dissolution process is diffusion layer controlled, where the rate of diffusion from the solid surface through an unstirred liquid film to the bulk solution is rate limiting, the flux J is given by:

$J = -D (dc/dx)$

Where D is the diffusion coefficient and dc/dx is the concentration gradient from the solid surface to the bulk solution. The flux can also be defined as the flow rate to material (dm/dt) trough a unit area (A), thus one has the equation:

$J = (1/A)\ dm/dt$

If the concentration gradient is linear and the thickness of the diffusion layer is h,

$dc/dx = (Cb – Cs)/h$

Where Cs is the concentration at the solid surface and Cb is the concentration in the bulk solution. By combining the above equation, the flow rate of material is given by

$dm/dt = -(DA/h)(Cb–Cs) = kA(Cs – Cb)$

Where k is the intrinsic dissolution rate constant.

The above equation predicts constant dissolution rate. If the surface area, diffusion co-efficient, diffusion layer thickness, and concentration difference are kept constant. However, as dissolution proceeds, all of the, parameters the surface area especially, may change.

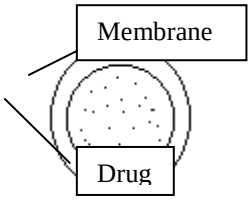



**Figure- 1 Dissolution control of drug release via thickness and dissolution rate of the membrane barrier coat.**

Most suitable dosage forms for this mechanism is compressed tablets containing coated particles. E.g. Ethyl cellulose, Nylon, Acrylic resins. Release depends on drug solubility and pore structure membrane. Constant release resulted when GI fluid passes through barrier to dissolve drug.

**2) Diffusion Controlled Release:**

There are basically two types of diffusion-controlled systems, which have been developed over the past two decades: reservoir devices and matrix devices. In diffusion controlled extended release systems the transport by diffusion of dissolved drug in pores filled with gastric or intestinal juice or in a solid (normally polymer) phase is the release controlling process.

Depending on the part of the release unit in which the drug diffusion takes place, diffusion controlled release systems are divided into matrix systems (also referred to as monolithic systems) and reservoir systems. In matrix systems diffusion occurs in pores located within the bulk of the release unit, and in reservoir systems diffusion takes place in a thin water-insoluble film or membrane, often about 5-20 µm thick, which surrounds the release unit. Diffusion through the membrane can occur in pores filled with fluid or in the solid phase that forms the membrane.

Drug is release from a diffusion controlled release unit in two steps-

1. The Liquid that surrounds the dosage from penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.

2. The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released, or, alternatively, the dissolved drug will partition into the membrane surrounding the dose unit and diffuse in the membrane.

A dissolution step is thus normally involved in the release process but the diffusion step is the rate-controlling step.

The rate at which diffusion will occur depends on four variables:

- The concentration gradients over the diffusion distance.
- The area.
- The distance over which diffusion occurs.
- The diffusion co-efficient of the drug in the diffusion medium.

Some of these variables are used to modulate the release rate in the formulation.

**3) Osmotic pump system:**

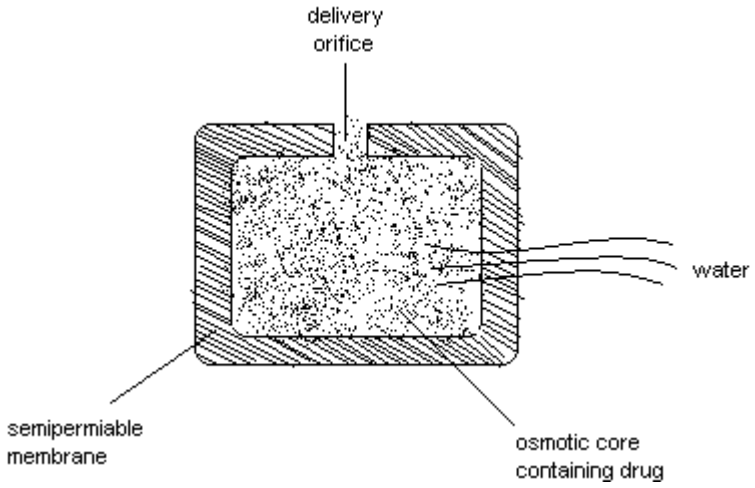
The rate of drug release in these products is determined by the constant inflow of water across semipermiable membrane into a reservoir, which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains a small hole from which dissolved drug is pumped at a rate determined by the rate of entrance of water due to osmotic pressure. The advantage of this type of product is that the constant release is unaltered by the environment of the gastrointestinal tract. The rate of release can modified by altering the osmotic agent and the size of the hole.

$$\frac{dm}{dt} = \frac{Ak\pi_s s}{h}$$

A =membrane area

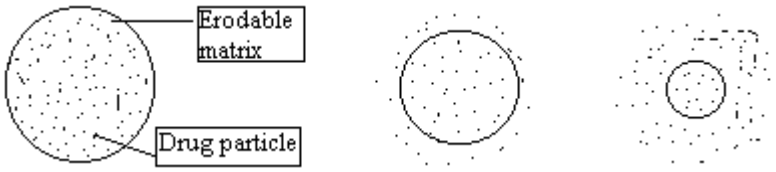
k =membrane permeability

h =membrane thickness




**4) Erosion controlled release systems:**

In erosion controlled extended release systems that rate of drug release is controlled by the erosion of a matrix in which the drug release is controlled by the erosion of a matrix in which the drug is dispersed. The matrix is normally a tablet, i.e. the matrix is formed by a tab letting operation, and the system can thus be described as a single unit system. The erosion in its simplest form can be described as a continuous liberation of matrix material (both drug and excipients) from the surface of the tablet, i.e. surface erosion. The consequence will be a continuous reduction in tablet weight during the course of the release process.




$t = 0$ $t = t_1$ $t = t_2$

**(t = time)**

**Mechanism of drug release from a erosion based matrix tablet**

Drug release from an erosion system can thus be described in two steps.

1. Matrix material, in which the drug is dissolved or dispersed, is liberated from the surface of the tablet.

2. The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

The eroding matrix can be formed from different substances. One example is lipids or waxes, in which the drug is dispersed. Another example is polymers that gel in contact with water (Hydroxy ethyl cellulose). The gel will subsequently erode and release the drug dissolved or dispersed in the gel. Diffusion of the drug in the gel may occur in parallel.

## 2. OBJECTIVES AND PLAN OF WORK

### 2.1 OBJECTIVE OF THE STUDY

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral Extended release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence, in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate extended release system for in order to achieve even plasma concentration profile up to 24 hrs.

Reason for the selection of -API as a model drug

- -API is a potent antihypertensive.
- Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to extend the drug release.
- Bioavailability after oral administration is 20% Silent features to design formulation in extended release tablets are,
- Less risk of dose dumping.
- Less inter and intra subject variability.
- High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.
- Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.

- Transport of drug is independent of gastric emptying.

**2.2 PLAN OF WORK**

1. Formulation and evaluation of Extended release tablets.

➢ Through literature survey on the drug

➢ Selection of suitable excipients and different parameters of excipients.

➢ Study the mechanism of drug release from the matrix tablets.

2. Preformulation studies:

1) -API characterization

➢ Physical characterization

➢ Solubility studies

➢ Physico-mechanical characterization

2) Drug-excipients Compatibility studies

3. Formulation development

➢ Wet granulation approach

➢ Evaluation of Extended release tablets by

- Thickness.
- Hardness.
- Weight variation.
- Disintegration time.
- Assay and content uniformity.
- In-vitro drug release.

➢ Comparison of these formulations.

➢ Coating of the formulation.

## 3. LITREATURE REVIEW

**Prisant LM.Bottini B:** Novel controlled release drug delivery systems have been used in the treatment of hypertension. Potential advantages include reduced dosing frequency, enhanced compliance and convenience reduced toxicity and decreased total dose. It is possible that future research will prove that the agents that provide complete 24 hours control, may reduce the cardiovascular events associated with the early morning blood pressure surge.

**H. Kranz** (2004) et al; studied the development of a multi particulate extended release formulation for a weakly basic drug. The objective of this study was to achieve pH independent release of drug from multiple units extended release mini matrix tablet based on the polymeric matrix former and organic acid.

**Paolo Giunchedi:** This research investigated the use of sodium alginate for the preparation of hydrophilic matrix tablets intended for prolonged drug release using ketoprofen as a model drug. The matrix tablets prepared by direct compression using sodium alginate, HPMC in different combinations and ratio s. Invitro release and erosion studies of the matrix tablets were carried out in usp phosphate buffer (7.4) only the matrices containing the highest quantity of HPMC (20%) maintained their capacity to release ketoprofen for a prolonged time.

**Sabel:** A polymeric device releasing biologically active, water-soluble materials having a molecular weight of less than 1000 in a controlled, continuous and linear manner over an extended period of time. In soluble biocompatible polymers are used so that the device is implantable. The device is made based on diffusion of fluid into a polymeric matrix containing dispersed biologically active molecules to yield a polymer device which can be placed in a fluid environment.

**Krogel and R-Bodmeier:** A multifunctional drug delivery system based on HPMC matrices (tablets) placed with in an impermeable polymeric cylinder was developed. The release behavior of the different devices was investigated as a function of HPMC viscosity grade, HPMC content, type of drug, matrix weight, and addition of various fillers. The drug release increased with a reduced HPMC viscosity grade. Higher aqueous drug solubility

decreased HPMC content and increased surface area of the matrix. The lag time prior to the drug release could be controlled through the erosion matrix.

**Cheil.Li:** Hypromellose is most commonly used in the fabrication of hydrophilic matrices. It provides the release of drug to prolong its therapeutic effect. This review provides chemical, thermal and mechanical properties of hypromellose, hydration of the polymer matrices, the mechanism of drug release and the influence of tablet geometry on drug release rate. The effect of dissolution media and the influence of both the external environment and microenvironment pH with in the gel matrix on the properties of the polymer are also discussed.

**Eun-Jung Kim:** A solvent wetting method was used to prepare -API solid dispersion in the presence of various carriers. The amount of ethanol used to prepare solid dispersions did not have a significant effect on dissolution rate of -API. The Polyvinyl pyrolidine (PVP) and hydroxypropyl methyl cellulose (HPMC) were used as carriers. The dissolution rates of -API in PVP, HPMC solid dispersion was much faster than those for the corresponding physical mixtures. However the dissolution profile was found to depend on the carriers used. the dissolution rate of -API increased slowly for solid dispersion prepared using HPMC,whereas -API initial dissolution rates were observed for solid dispersion prepared using PVP.Increases in dissolution rates were partly dependent on the ratio of -API to carriers. No significant changes in crystal form were observed by X- ray diffraction spectroscopy or thermal analysis.

**DANG-HAN WON:** solid dispersion of -API was formulated with HPMC and surfactants by the conventional solvent evaporation method and supercritical antisolvent precipitation method. The solid dispersion particles were characterized by particle size DSC, XRD, solubility and dissolution studies. The effect of drug and polymer ratio on the solubility of -API was also studied. The physical state of -API changed from crystalline form to amorphous form during CSE and SAS process conformed by DSC or XRD data. The equilibrium solubility of the -API solid dispersion prepared by the SAS process was 1.5-20 µg/ml.while the maximum solubility was 35-110 µg/ml. the solid dispersion from the SAS process showed a high dissolution rate of over 90% within 2 hour. The SAS process system may be used to enhance the solubility or to produce oral dosage forms with high dissolution rate.

**Lynne. S. Taylor: -** The ability of various polymers to inhibit the crystallization of amorphous -API was studied in amorphous molecular dispersions. Spin-coated films of -API with polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), and hydroxypropylmethylcellulose (HPMC) were prepared and used for measurement of the nucleation rate and to probe drug-polymer intermolecular interactions. Bulk solid dispersions were prepared by a solvent evaporation method and characterized using thermal analysis. It was found that each polymer was able to significantly decrease the nucleation rate of amorphous -API even at low concentrations (3-25% w/w). Each polymer was found to affect the nucleation rate to a similar extent at an equivalent weight fraction. For HPMC and HPMCAS, thermal analysis indicated that the glass transition temperature ($T_g$) of the solid dispersions were not significantly different from that of -API alone, whereas an increase in $T_g$ was observed for the PVP containing solid dispersions. Infrared spectroscopic studies indicated that hydrogen bonding interactions were formed between -API and each of the polymers. These interactions were stronger between -API and PVP than for the other polymers. It was speculated that, at the concentrations employed, the polymers reduce the nucleation rate through increasing the kinetic barrier to nucleation.

**NAKAJIMA:** The relationship between the plasma drug concentration and the antihypertensive effect of -API was analyzed by an ion-channel binding model which takes into consideration the slow association/dissociation process of a drug at the calcium channel. The in vitro dissociation constant (K_d) of -API to the calcium channel in the heart of rats was determined, and was compared to the in vivo dissociation constant (D_<d, calc>) estimated by the pharmacodynamic analysis of the concentration-effect data in Japanese essential hypertensive patients obtained from literature. The relative relationship between K_d and K<d, calc> of -API was substantially identical with eight other calcium channel blocking agents reported previously. This result suggested the possibility that we can predict the pharmacodynamic behavior of newly developed calcium channel blocking agents from the in vitro K_d value and plasma concentration-time profile in human using the ion-channel binding model.

**WESTBERG.B:** The efficacy of and tolerance to -API given as extended-release (ER) tablets once daily (o.d) and the plain tablets twice daily (bid) were compared in this study. After a 4-week period on placebo and a beta-blocker,

102 patients who had a diastolic blood pressure (DBP) in the supine position greater than 95 mm Hg were randomized to treatment with -API ER tablets 10 mg o.d. (n = 50) or plain tablets 5 mg bid. (n = 52). If the DBP was greater than 90 mm Hg after 2 weeks, the dose was doubled. The total treatment time on -API was 6 weeks. Blood pressure (BP) was measured 2 h after the dose and at the end of the dosing interval, i.e., 24 h after ER and 12 h after plain tablets. Both formulations reduced BP significantly (15/12 mm Hg in the ER and 13/11 mm Hg in the plain tablet group, at the end of the dosing interval). No differences in BP reduction were seen between the groups. The proportion of responders was 71% on ER and 65% on plain tablets 24 and 12 h, respectively, after dose intake, and greater than 90% in both groups, when measured 2 h after dose. Ankle swelling and flushing were the most frequently reported adverse events. Eight patients (three on ER) were withdrawn, most of them due to vasodilatory side effects. -API ER once daily was as effective and tolerable as plain tablets b.i.d.

**SCHOLZEJ: -**The aim of the study was to identify the most appropriate dosage combination of ramipril and -API ER for mild to moderate supine diastolic blood pressure was taken in randomized. The patients were randomized to 12-groups. Although the greatest reductions in blood pressure were observed with ramipril and -API ER (10\10mg). Consideration of the anti hypertensive efficacy and safety factors suggest that the ramipril--API ER (5\5mg) combination has the best efficacy ratio of the combinations tested. The incidence of adverse effects with ramipril--API-ER combination therapy was similar to that with -API monotherapy but peripheral edema, tachycardia and vasodilatation occurred less frequently with combination dose. The combination of ramipril--API ER (5/5mg) can be considered to be most suitable option for Hypertensive patients with an inadequate response to either of the monocomponents.

**WERNER WEITSCHIES**: - Gastrointestinal motility and transport as well as concomitant food intake are factors that are known to pharmacokinetics derived after intake of ER dosage forms. In this study the gastrointestinal transit and the *in-vivo* drug release of magnetically labeled ER tablets containing -API were monitored together with the drug absorption phase of pharmacokinetics under fasting and fed conditions in 6 healthy volunteers using magnetic maker monitoring. It was found that the in vivo drug release profiles of the tablets compared well under fasting and

fed conditions. However the plasma concentration profiles were strongly influenced by concomitant food intake. This could be attributed to elongated residence of the tablets in proximal parts of the stomach resulting in delayed drug absorption and the occurrence of the late high plasma peak concentrations. The study shows that increased plasma peak drug concentration after intake of extended release formulations together with food can be explained by poor mixing in the proximal parts of the stomach and not necessarily due to failure of the formulation to control the drug release.

**DRUG AND POLYMER PROFILE**

**4.1 DRUG PROFILE**

**-API**

-API is a calcium antagonist (calcium channel blocker). -API is a dihydropyridine derivative

**Melting point :** 145°c

**Bioavailability :** 20%

**Half-life :** 14 hr

**Protein binding :** 99%

**Description :** -API is a slightly yellowish, crystalline powder

**Solubility :** It is insoluble in water and is freely soluble in dichloromethane and ethanol.

**Mechanism of Action:**

API is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers). It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependent Ca++ currents in vascular smooth muscle and cultured rabbit atrial cells and blocks potassium-induced contracture of the rat portal vein.

*In vitro* studies show that the effects of -API on contractile processes are selective, with greater effects on vascular smooth muscle than cardiac muscle. Negative inotropic effects can be detected *in vitro*, but such effects have not been seen in intact animals. The effect of -API on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance in man, with a modest reflex increase in heart rate. With the exception of

a mild diuretic effect seen in several animal species and man, the effects of -API are accounted for by its effects on peripheral vascular resistance.

**Pharmacokinetics and Metabolism:**

Following oral administration, -API is almost completely absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of -API is approximately 20 percent. Mean peak concentrations following the administration of -API are reached in 2.5 to 5 hours. Both peak plasma concentration and the area under the plasma concentration time curve (AUC) increase linearly with doses up to 20 mg. -API is greater than 99 percent bound to plasma proteins.

Following intravenous administration, the plasma concentration of -API declined triexponentially with mean disposition half-lives of 4.8 minutes, 1.5 hours and 9.1 hours. The mean contributions of the three individual phases to the overall AUC were 15, 40 and 45 percent, respectively, in the order of increasing $t_{½}$.

Following oral administration of the immediate-release formulation, the plasma level of -API also declined polyexponentially with a mean terminal $t_{½}$ of 11 to 16 hours. The mean peak and trough steady-state plasma concentrations achieved after 10 mg of the immediate-release formulation given once a day to normal volunteers were 20 and 0.5 nmol/l respectively. The trough plasma concentration of -API in most individuals was substantially below the concentration needed to effect a half-maximal decline in blood pressure ($EC_{50}$) [4-6 nmol/l for -API], thus precluding once a day dosing with the immediate- release formulation.

Following administration of a 10-mg dose of -API, the extended-release formulation, to young, healthy volunteers, mean peak and trough steady-state plasma concentrations of -API were 7 and 2 nmol/l, respectively. Corresponding values in hypertensive patients (mean age 64) after a 20-mg dose of -API were 23 and 7 nmol/l. Since the $EC_{50}$ for -API is 4 to 6 nmol/l, a 5- to 10-mg dose of -API in some patients, and a 20-mg dose in others, would be expected to provide an antihypertensive effect that persists for 24 hours.

**Geriatric Use:** Plasma concentrations of -API, after a single dose and at steady state, increase with age. Mean clearance of -API in elderly hypertensive (mean age 74) was only 45% of that of young volunteers (mean age 26).

At steady state mean AUC for young patients was 39% of that for the elderly. Data for intermediate age ranges suggest that the AUCs fall between the extremes of the young and the elderly.

**Hepatic Dysfunction:**

In patients with hepatic disease, the clearance of -API was reduced to about 60% of that seen in normal young volunteers. Renal impairment does not alter the plasma concentration profile of -API; although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive. Animal studies have demonstrated that -API crosses the blood-brain barrier and the placenta.

**Cardiovascular Effects:**

Following administration of -API, a reduction in blood pressure generally occurs within 2 to 5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50% of peak reductions. The antihypertensive effect is dose dependent and correlates with the plasma concentration of -API.

A reflex increase in heart rate frequently occurs during the first week of therapy; this increase attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic dosing. Beta-blocking agents inhibit the increase.

-API when administered alone or in combination with a beta-blocking agent does not affect the P-R interval of the ECG. -API alone or in combination with a beta-blocking agent has been shown, in clinical and electro physiologic studies, to have no significant effect on cardiac conduction (P-R, P-Q, and H-V intervals).

In clinical trials in hypertensive patients without clinical evidence of left ventricular dysfunction, no symptoms suggestive of a negative inotropic effect were noted; however, none would be expected in this population.

**Renal/Endocrine Effects:**

API decreases renal vascular resistance while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis, and kaliuresis have been observed during the first week of therapy. No significant effects on serum

electrolytes were observed during short- and long-term therapy. In clinical trials in patients with hypertension, increases in plasma noradrenaline levels have been observed.

**Clinical Studies:**

API produces dose-related decreases in systolic and diastolic blood pressure as demonstrated in six placebo-controlled, dose response studies using either immediate-release or extended-release dosage forms. These studies enrolled over 800 patients on active treatment, at total daily doses ranging from 2.5 to 20 mg. In those studies -API was administered either as monotherapy or was added to beta-blockers. The results of the 2 studies with -API given once daily as monotherapy are shown in the table below:

**Indications and usage:**

API is indicated for the treatment of hypertension.

API may be used alone or concomitantly with other antihypertensive agents.

**CONTRAINDICATIONS**

API is contraindicated in patients who are hypersensitive to this product.

**PRECAUTIONS**

**Hypotension**

API, like other calcium antagonists, may occasionally precipitate significant hypotension and, rarely, syncope. It may lead to reflex tachycardia that in susceptible individuals may precipitate angina pectoris.

**Heart Failure**

Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with API have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using -API in patients with heart failure or compromised ventricular function, particularly in combination with a beta-blocker.

**Patients with Impaired Liver Function:** Patients with impaired liver function may have elevated plasma concentrations of -API and may respond to lower doses of -API therefore, a starting dose of 2.5 mg once a day is

recommended. These patients should have their blood pressure monitored closely during dosage adjustment of – API.

**Peripheral Edema**

Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose and age dependent. Frequency of peripheral edema ranged from about 10% in patients under 50 years of age taking 5 mg daily to about 30% in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

**Drug Interactions**

**Erythromycin:**

Co administration of -API with erythromycin resulted in approximately 2.5-fold increase in the AUC and Cmax, and about 2-fold prolongation in the half-life of -API.

**Grapefruit juice**

Co administration of -API with grapefruit juice resulted in more than 2-fold increase in the AUC and Cmax, but no prolongation in the half-life of -API.

**Cimetidine**

Co administration of -API with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the Cmax, of -API.

**Beta-Blocking Agents**

A pharmacokinetic study of -API in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of -API. The AUC and Cmax of metoprolol, however, were increased approximately 31 and 38%, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with -API and were well tolerated.

**Digoxin:**

When given concomitantly with -API the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

**Anticonvulsants**

In a pharmacokinetic study, maximum plasma concentrations of -API were considerably lower in epileptic patients on long-term anticonvulsant therapy (e.g., phenytoin. carbamazepine, or Phenobarbital) than in healthy volunteers. In such patients, the mean area under the -API plasma concentration-time curve was also reduced to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

**Pregnancy**

**Teratogenic Effects**

Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3, and 4.6 mg/kg/day (from 0.8 to 8 times the maximum recommended human dose on a mg/m2 basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given -API

In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed, but an abnormal position of the distal phalanges was noted in about 40% of the fetuses.

**Nonteratogenic Effects**

A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (8 times the maximum human dose on a mg/m2 basis) and above.

Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (2.1 times the maximum human dose on a mg/m2 basis). This effect occurred only in pregnant rabbits and regressed during lactation.

Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If -API is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of -API on labor and delivery and on the mammary glands of pregnant females.

**Nursing Mothers**

It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from -API in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**ADVERSE REACTIONS**

In controlled studies in the United States and overseas, approximately 3,000 patients were treated with -API as either the extended-release formulation.

The most common clinical adverse events reported with -API administered as monotherapy at the recommended dosage range of 2.5 mg to 10 mg once a day were peripheral edema and headache. Peripheral edema was generally mild, but it was age and dose related and resulted in discontinuation of therapy in about 3% of the enrolled patients. Discontinuation of therapy due to any clinical adverse event occurred in about 6% of the patients receiving -API principally for peripheral edema, headache, or flushing.

The following adverse events have been reported from clinical trials and from Post Marketing Surveillance.

**Table no: 1**

| Frequency | System Organ Class | Adverse drug reaction |
|---|---|---|
| Common | Central and peripheral nervous system: | Headache |
| | Skin: | Flush |
| | Vascular (extra cardiac): | Peripheral oedema |
| Uncommon | Cardiovascular system: | Tachycardia, palpitations |
| | Central and peripheral nervous system: | Dizziness, paraesthesiae |
| | Gastrointestinal: | Nausea, abdominal pain |
| | Skin: | Rash, pruritis |
| | General: | Fatigue |
| Rare | Cardiovascular system: | Syncope |
| | Gastrointestinal: | Vomiting |
| | Musculo-skeletal: | Arthralgia, myalgia |
| | Psychiatric: | Impotence/sexual dysfunction |
| | Skin: | Urticaria |
| Very rare | Gastrointestinal: | Gingival hyperplasia, gingivitis |
| | Hepatic: | Increased liver enzymes |
| | Skin: | Photosensitivity reactions, leucocytoclastic vasculitis |
| | Urinary system: | Pollakisuria |
| | General: | Hypersensitivity reactions eg. angioedema, fever |

**Clinical Laboratory Test Findings**

Serum Electrolytes— No significant effects on serum electrolytes were observed during short- and long-term therapy.

Serum Glucose— No significant effects on fasting serum glucose were observed in patients treated with -API in the U.S. controlled study.

Liver Enzymes— 1 of 2 episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

**OVERDOSAGE**

Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg -API together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Over dosage might be expected to cause excessive peripheral vasodilatations with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to over dosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether -API can be removed from the circulation by hemodialysis.

To obtain up-to-date information about the treatment of overdose, consult your Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

**DOSAGE AND ADMINISTRATION**

The recommended starting dose is 5 mg once a day. Depending on the patient's response, the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than 2 weeks. The recommended dosage range is 2.5 to 10 mg once daily. In clinical trials, doses above 10 mg daily showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events. Modification of the recommended dosage is usually not required in patients with renal impairment.

-API should regularly be taken either without food or with a light meal -API should be swallowed whole and not crushed or chewed.

**Geriatric Use**

Patients over 65 years of age are likely to develop higher plasma concentrations of -API In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (2.5 mg daily). Elderly patients should have their blood pressure closely monitored during any dosage adjustment.

**Patients with Impaired Liver Function**

Patients with impaired liver function may have elevated plasma concentrations of -API and may respond to lower doses of -API extended-release tablets; therefore, patients should have their blood pressure monitored closely during dosage adjustment of -API extended-release tablets.

**4.2 EXCIPIENTS PROFILE**

**HYDROXY PROPYL METHYL CELLULOSE:**

**Synonym** : Hypromellose, Methocel, Methylcellulose.

**Chemical name** **:** Cellulose, 2-hydrxy propyl methyl ether.

**Functional category** **:** Tablet binder, suspending agent, coating agent, thickening agent, viscosity increasing agent.

**Applications in pharmaceutical formulation:**

- HPMC is widely used in oral, ophthalmic and topical formulations
- HPMC id primarily used as tablet binder and as a matrix for use in extended release tablet formulation.
- Lower viscosity grades used in aqueous film coating solutions while higher viscosity grades are used with organic solvents.
- HPMC is also used as a suspending agent and thickening agents in topical formulations.
- HPMC at concentrations between 0.45%-1.0%w/w may be added as a thickening agent to vehicles for eye drops
- Also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments.

**Description:**

HPMC is an odorless and tasteless, white or creamy with fibrous or granular powder.

**Solubility:**

Soluble in cold water forming a viscous colloidal solutions practically insoluble in chloroform, ethanol but soluble in mixtures of ethanol. Certain grades of HPMC are soluble in aqueous acetone solution.

**Viscosity:**

A wide range of viscosity types is commercially available. Aqueous solutions are most commonly prepared. Increasing concentration also produce more viscous solutions.

**Stability and storage conditions:** HPMC powder is stable material. Solutions are stable at $P^H$ 3-11. Aqueous solutions are comparatively enzyme resistant providing good viscosity stability during long-term storage. Hypromellose powder should be stored in a well-closed container**.**

**HYPROMELLOSE ACETATE SUCCINATE:**

**Synonym** **:** Aqoat, Aqoat AS-MF/MG, 2-hydroxypropylmethyl ether acetate succinate.

**Chemical name** **:** cellulose, 2-hydroxypropylmethyl ether.

**Functional category** **:** component of controlled release or sustained release.

**Applications in pharmaceutical formulation:**

- Hypromellose acetate succinate is commonly used in oral pharmaceutical formulations as film coating as well as enteric coating material for tablets. It will insoluble in gastric fluid but swell and dissolve rapidly in the upper intestine.
- It may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained release properties.

**Description:** Hypromellose acetate succinate is a white to off white powder or granules. It has a faint acetic acid like odour and barely detectable taste.

**Solubility:** It is practically insoluble in ethanol (95%), hexane and xylene. On the addition of acetone or mixture of ethanol and dichloromethane (1:1) a clear or turbid viscous liquid is produced.

**Stability and storage conditions**:

Hypromellose acetate succinate is stable for four years after manufacturing. It should be stored in well-closed container in a cool dry place.

**HYPROMELLOSE PHTHALTE:**

**Synonyms** **:** Cellulose phthalate hydroxypropyl methyl ether.

Methyl hydroxyl propyl cellulose phthalate.

**Chemical name** **:** Cellulose, hydrogen 1,2-benzene dicarboxylate.

**Functional category** **:** coating agent

**Applications in pharmaceutical formulation**:

- Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating agent for tablets or granules. It will insoluble in gastric fluid but swell and dissolve rapidly in the upper intestine.
- Tablets coated with Hypromellose phthalate disintegrate more rapidly than tablets coated with cellulose acetate phthalate.
- It may be used alone or in combination with other soluble or insoluble binder in the preparation of granules with sustained drug release properties. Since Hypromellose phthalate is tasteless and insoluble in saliva. It can also be used as a coating agent to mask the unpleasant taste of some tablet formulations.

**Description:**

Hypromellose phthalate occurs as white to slightly off white free flowing flakes or as a granular powder. It is odorless or with a slightly acidic odour and has a barely detectable taste.

**Stability and storage conditions:** Hypromellose phthalate is chemically and physically stable at ambient temperature for at least 3-4 years. It is stable on exposure to UV light for up to 3months at 25°C and 70°RH. Stored in cool, dry place should be brought to room temperature before opening.

**HYDROXYPROPYL CELLULOSE**

**Synonym** **:** Klucel, methocel, hydroxypropyl ether.

**Chemical name** **:** Cellulose, 2-hydroxypropyl ether

**Functional category** **:** Coating agent, emulsifying agent, suspending agent, tablet binder, thickening agent, viscosity increasing agent.

**Applications in pharmaceutical formulations:**

- Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.
- HPC is primarily used in tableting as a binder, film coating and extended release matrix former.
- Concentrations of 15-35%w/w HPC may be used as to produce tablets with an extended drug release.
- The addition of anionic surfactant similarly increases the viscosity of HPC and hence decreases the release rate of the drug.
- HPC is also used in micro encapsulation process and as a thickening agent.

| USE | CONCENTRATION (%) |
|---|---|
| Extended release –matrix former | 15-35 |
| Tablet binder | 2-6 |
| Tablet film coating | 5 |

**Description:** It is a white to slightly yellow –colored, odorless and tasteless powder.

**Solubility:** HPC is freely soluble in water forming a smooth clear colloidal solution. It is soluble 1 in 2 parts of methanol. Practically insoluble in aliphatic hydrocarbons.

**Stability and storage:** HPC powder is stable material. Aqueous HPC solutions have optimum stability at pH6.0 to 8.0. Ultraviolet light will decrease the stability of HPC.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

**LACTOSE**

**Synonym** **:** Capsulac, Lactohale, Microtose.

**Chemical name** **:** ß-D-galactopyranosyl-(1-4) ß-D-glycopyranose

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

**Functional category:** Diluent.

**Applications in pharmaceutical formulations:**

Lactose is widely used as a diluent in tablets and capsules. It is also used as a diluent in dry powder inhalations.

Various Lactose grades are commercially available that have different physical properties. Usually fine grades of Lactose used in the preparation of tablets.

Lactose is also used in combination with sucrose (approximately1:3) to prepare sugar coating solutions.

The amorphous Lactose hardness profile.

Direct compression grades of lactose may also combined with MCC or starch usually requires a tablet lubricant.

**Description:** Lactose occurs as white to off white crystalline particles or powder. It is odor less and slightly sweet tasting. Several different forms of lactose are commercially available.

**Stability and storage conditions:**

Lactose develops brown coloration on storage. The color stabilities of various lactose's also differ. Lactose should be stored in a well-closed container in a cool, dry place.

**CREMOPHOR RH 40:**

**Synonym** **:** Eumulgin HRE 40, PEG-40 hydrogenated castor oil.

**Chemical name** **:** Poly ethoxylated caster oil

**Functional category** **:** Emulsifying agent, solubilizing agent, wetting agent.

**Applications in pharmaceutical formulations:** It can be used to solubilize vitamins, essential oils and certain drugs.

In aerosol it can be used to improve the solubility of the propellant in the aqueous phase.

It is also used as an emulsifier of fatty acids and alcohols.

**Description:** Cremophor RH 40 is a white, semisolid paste that liquefies at 30. It has a very faint characteristic odor and a slight taste in aqueous solution.

**Stability and storage conditions:** It should be stored in a well-filled, air tight container, protected from light, in a cool dry place.

**SODIUM STEARYL FUMARATE:**

**Synonym** **:** Fumaric acid, sodium salt.

**Chemical formula** **:** $C_{22}$ $H_{39}$ Na $O_4$

**Functional category** **:** Tablet and capsule lubricant.

**Applications in pharmaceutical formulations:**

Sodium steryl fumarate is used as a lubricant in tablet and capsule formulations. The concentration of SSF is 0.5 to 2%. It is also used in certain food preparations.

**Stability and storage conditions:**

At ambient temperature SSF is stable for up to 3 years in amber glass bottles. The bulk material should be stored in a well closed-container in a cool, dry place.

**COLLOIDAL SILICON DIOXIDE:**

**Synonyms** **:** Aerosil, colloidal silica, cab-o-sil.

**Chemical formula** **:** $Sio_2$

**Functional category** **:** Adsorbent, anticaking agent, glidant, suspending agent, viscosity improving agent.

**Applications in pharmaceutical formulations**:

Colloidal silicon dioxide improves the flow properties of the dry powders. Aerosil also act as a thickening agent and suspending agent in gels and semisolid preparations.

In aerosols Aerosil is used to promote particulate suspension, eliminate hard settling.

It is also used as a tablet disintegrant.

Aerosil is frequently added suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation.

**Description:** It is a light, loose, bluish-white colored, odorless, tasteless, nongritty amorphous powder.

**Solubility:** Practically insoluble in organic solvents, water and acids. It is soluble in hot solutions of alkali hydroxide.

**Stability and storage conditions:** Aerosil is hygroscopic but absorbs large quantities of water without liquefying. Aerosil should be stored in well-closed container.

**MICROCRYSTALINE CELLULOSE:**

**Synonym** **:** Avicel, celphere, emocel

**Empirical formula :**

**Functional category :** Adsorbent, Suspending Agent, Diluent, Disintigrant.

**Applications in pharmaceutical formulations:**

MCC is widely used in pharmaceutical formulation as a binder, diluent in tablet and capsule preparations.

It also used as a disintegrant and lubricant.

**Description:**

It is a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available different particle sizes and moisture grades that have different properties and applications

**Solubility:** MCC is slightly soluble in 5%sodium hydroxide solution. Practically insoluble in water, dilute acids and most organic solvents.

**Stability and storage conditions:**

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

**4.3 LIST OF EQUIPMENTS USED**

**Table no: 2**

| S. No. | Equipments | Make |
|---|---|---|
| 1. | Digital Weighing Balance | Mettler Toledo |
| 2. | Rapid mixer granulator | Saral |
| 3. | Mechanical Stirrer | Remi |
| 4. | Tray dryer | Mevish pharma Eng. |
| 5. | Moisture content | Mettler Toledo |
| 6. | Oscillating granulator | Cad mach |
| 7. | Tablet Compression Machine | Cad mach |
| 8. | Tablet Hardness Tester | Dr. Schleuninger's |
| 9. | Friabilator (USP) | Electro lab |
| 10. | Disintegration | Electro lab |
| 11. | Dissolution Apparatus | Electro lab |

**LIST OF CHEMICALS USED**

**Table no: 3**

| Sr. No. | Chemicals | Manufacturer |
|---|---|---|
| 1. | -API | Cadila health care |
| 2 | Cremophor RH 40 | BASF |
| 3. | Isopropyl Alcohol | Merck limited |
| 4. | Hydroxypropyl methyl cellulose | Dow chemical |
| 5. | Hydroxy propyl cellulose | Dow chemical |
| 6. | Lactose Anhydrous | DMV International |
| 10 | Microcrystalline cellulose | FMC biopolymer |

| | | |
|---|---|---|
| 11. | Sodium steryl fumarate | JRS pharma |
| 12. | Aerosil 200 | Degussa |
| 13. | Opadry white | Colorcon |

## 5. PREFORMULATION STUDIES:

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms that can be mass-produced. The type of information needed will depend on the dosage form to be developed.

The first step in any tablet design or formulation activity is careful consideration of the Preformulation data. It is important that the formulation have a complete physicochemical profile of the active ingredients available prior to initiating formulation development activity. Usually data shown below on the drug substances necessary for preformulation study.

1) Stability: drug – excipients stability

2) Physico-mechanical properties

3) Chemical Properties: Assay, Dissolution, and Related substances.

### 5.1. Organoleptic Characteristics

The color, odor, and taste of the drug were characterized and recorded using descriptive terminology; the results were shown in the table no. 4

**Table-4: Results of Organoleptic properties.**

| Properties | Results |
|---|---|
| Description | Yellow Crystalline |
| Taste | Slightly bitter |
| Odour | Odorless |
| Colour | Yellowish |

**5.1.2 Microscopic Examinations**

In this study, pure drug was examined under compound microscope for crystal morphology. The results were shown in table no: 5

Microscopic examination:

**Table No. -5**

| **Properties** | **Observation** |
|---|---|
| Crystal Structure and characteristics. | Irregular crystal shaped structure of various sizes. |

**5.2 Physico – mechanical characterization**

**a) Density measurement: -**

Different types of density calculation were done to characterize the -API and its flow property. Generally two types of density are determination i.e. bulk density and tapped density. The methods followed for calculation of the above two densities are determined by the following way.

- **Bulk Density**:

An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula. The results were shown in table no.7

***Bulk density = Weight of powder / Bulk volume***

- **Tapped Density**

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula. The results were shown in table no: 7

*Tapped density = Weight of powder / Tapped volume*

**b) Flow properties**

- **Carr's Index [Compressibility Index]: -**

It is one of the most important parameter to characteristic the nature of powders and granules. It can be calculated from the following equation: *Carr's index = Tapped density - Bulk density / Tapped density X 100*

**Table No -6**

| **% Compressibility** | **Flow ability** |
|---|---|
| 5-15 | Excellent |
| 12-16 | Good |
| 18-21 | Fair-passable |
| 23-35 | Poor |
| 33-38 | Very poor |
| >40 | Very very poor |

The results of compressibility index was shown in the table no.6

- **Haussner's Ratio:-**

Haussner's ratio is an important character to determine the flow property of powder and granules. This can be calculation by the following formula-

Hausner's ratio = Tapped density / Bulk density

Haussner's ratio of -API is represented in Table No -7

Value < 1.25 indicate good flow (=20% Carr)

While > 1.50 indicate poor flow (=35% Carr)

Between 1.25 and 1.5, adding glidant will improve flow. The index of Carr is a one point determination and does not reflect the ease or speed with which consolidation occur. Indeed some materials have high index suggesting poor flow but may consolidate rapidly, which is essential for uniform filling on tablet machines when the power flows at nearly equal to bulk density in to the die and consolidates to approaching tapped density prior to compression.

*Hausner's ratio = Tapped density / Bulk density*

The result of Hausner's ratio was shown in the table.

**Physico – mechanical characterization**

**Table No.7**

| **Properties** | **Observations** |
|---|---|
| Bulk density (gm/ml**)** | 0.255 ± 0.010 |
| True density (gm/ml) | 0.536 ± 0.062 |
| Haussner's Ratio | 1.545 |
| Carr's/Compressibility Index (%) | 35.29% |

**5.2.1 Melting point range:**

Melting point was determined, using hot stage melting point apparatus and differential scanning colorimeter. The result was tabulated in Table-No 8

**Table No.8: Melting point range.**

| **Experiment** | **Observation** |
|---|---|
| Melting Point Range | 140-145°c |

**5.2.3 Moisture Content:**

Halogen moisture analyzer determined moisture content. The result of moisture content was tabulated in Table No.9

**Table No.9: Moisture content.**

| **Experiment** | **Observation** |
|---|---|
| Moisture content (%) | 0.105-0.115% w/w |

**5.2.4 Hygroscopicity:**

Weighed quantity of the pure drug was taken in a Petridish and the initial weight of Petridis with the drug was recorded. Then, it was kept openly in environment chamber maintained at 75% RH. The weight of the Petridish

was measured periodically and the weight gain or loss was calculated in reference to the initial weight of the Petridish. The results obtained were tabulated in the Table No.10

**Hygroscopity:**

**Table No.10**

| **Experiment** | **Observation** |
|---|---|
| Hygroscopic | Non- hygroscopic |

**5.3 Drug Excipients Compatibility Study**

**Protocol for drug-excipients compatibility**

(a) Drug: Excipients Ratio

1. -API alone.
2. -API +HPMC 50 cps+ HPMC 15cps(1:2:2)
3. -API + HPC (1:1)
4. -API +Lactose Anhydrous (1:2)
5. -API +Aluminium silicate (1:1)
6. -API +Cremophor (1:2)
7. -API+HPMC E4M + HPMC 6 cps (1:2:2)
8. -API+MCC 101+ MCC 102 (1:2:2)
9. -API+ Aerosil (1:0.5)
10. -API + SSF (1:0.5).

(b) Pack details

Amber colored glass vials with rubber stopper and aluminum seal

(c) Storage condition

1. Initial sample at room temperature. (25ºC / 30% RH).
2. 40ºC / 75% RH.
3. 50ºC / 80% RH

(d) Testing Frequency

1. $2^{nd}$ week for sample charged at 40ºc
2. $4^{th}$ week sample charged at 50ºC / 80%RH.

(e) Test to be performed

1. Physical observation.
2. DSC of initial sample compare with charged samples.

## Procedure

-API and excipients are to be thoroughly mixed in predetermined ratio given in table no. And passed through the sieve no.40. In case of polymer used in the formulations are in dispersion forms instead of dispersion dry polymers whose dispersion is used in formulation were kept for stability conditions. The blend was to be filled in ambered colored glass vials and are closed with gray rubber stoppers and sealed with aluminum seal and charged in to condition at 40º c and 50º C / 80%RH. Similarly -API shall also be kept at all condition as per the sample. Samples to be withdrawn for analysis within two day of sampling date as per the compatibility study plan.

## Physical observation

Physical observation of sample was done at every week for any colour change or lumps formation and flow, the results of the physical observation were shown in table No.

There is no color change and no lumps observed in sample charged at 50ºC/80%RH for 1 month and 40ºc for 15 days.

**Table No-11:** Results of the physical observation

| **Initial** | **Physical observation** | | | |
|---|---|---|---|---|
| | **1st Week** | **2nd week** | **3rd week** | **4th week** |
| Light yellow | + | + | + | + |
| Light yellow | + | + | + | + |
| Light yellow | + | + | + | + |
| Light yellow | + | + | + | + |
| Light yellow | + | + | + | + |
| Light yellow | + | + | + | + |
| Light yellow | + | + | + | + |

***+ sign indicate that there is no change in colour and no lump formation***

## 6. DEVELOPMENT OF ER TABLETS:

The main objective of this project is to develop extended release tablets of Anti hypertensive drug to reduce Hypertension. Following administration of -API, a reduction in blood pressure generally occurs within 2 to 5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50% of peak reductions. The antihypertensive effect is dose dependent and correlates with the plasma concentration of -API.

**In process Quality Control Parameters during Compression**

Compressed tablets may be characterized by a number of specifications. These include size, shape, thickness, and Weight, hardness, and disintegration time and dissolution characteristics.

### Hardness:

The resistance to the tablet to chipping, abrasion or breakage under condition of storage, transportation and handling before usage depends upon its hardness. The most widely used apparatus to measure tablet hardness or crushing strength is the Schleuniger digital tester. This and other newer electrically operated test equipment eliminates the operator variability inherent in the measurement i.e. it measure the force required to break the tablet when the force is applied diametrically to the tablet. The force is measured in kilograms when used in production, hardness of 4 kg is considered to be minimum for a satisfactory tablet. Hardness determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tablet compression machine.

**Friability:**

Tablet friability measurement is made by use of the Roche friabilator. Rather than a measurement of the force required to crush a tablet, the instrument is design to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. A number of tablets are weighed and place in apparatus where they are exposed to rolling and repeated shocks resulting from freefalls with the apparatus. After a given number of rotations the tablets are weighed and the loss in weight indicates the ability of the tablet to withstand the type of wear.

**Thickness:**

The thickness of the tablet from production run to production is carefully controlled. Thickness can vary with no change in weight due to difference in the dosing of the granulation and the pressure applied to the tablets as well as the speed of the tablet compression. Tablet thickness also becomes an important characteristics packaging. If thickness varies throughout the lot, the result will vary in the count. Thickness is determined with Vanier calipers in millimeters. ± 5% may be allowed, depending upon the size of the tablet.

**Weight variation:**

The volumetric fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill adjusted to give the desired tablet weight. After the tablet machine is in operation the weights of the tablets were checked routinely to ensure that proper weight of tablet are being made.

**Disintegration:**

To release the drug component from the tablet, it must disintegrate. So disintegration time is noted after added six tablets in each cylinder of DT apparatus containing water at 37±0.5 $^0$C.

**In vitro dissolution study**

**Dissolution Parameter**

| | |
|---|---|
| **Medium** | **:** 500 mL; pH 6.5, Phosphate buffer with 1 % Sodium lauryl sulphate |
| **Apparatus** | **:** USP-2 (Paddle) |
| **RPM** | **:** 50 |
| **Time** | **:** 2, 6, 10 hours |
| **Temperature** | **:** 37°C ± 0.5°C |

**Preparation of medium** *(pH 6.5, Phosphate buffer with 1 %SLS)***: -** Dissolve 28.4 g of sodium dihydrogen orthophosphate monohydrate ($NaH_2PO_4.H_2O$), 13.9 g of disodium hydrogen orthophosphate ($Na_2HPO_4$) and 50 g of sodium lauryl sulfate in 5 liters of purified water. Adjust the pH to 6.5 with 10 % sodium hydroxide solution.

**Standard preparation:** Transfer an accurately weighed quantity of about 25 mg of -API USPRS/working standard to a 100 mL volumetric flask. Add about 50 mL of alcohol and syndicate to dissolve. Make volume up to the mark with alcohol and mix. Dilute 2.0 mL of this solution to 25.0 mL with dissolution medium and mix.

**Sample preparation**: Set the dissolution parameters of the instrument as mentioned above. Place one tablet each in a specially made quadrangular basket (refer annexure I and II). Place the tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two Teflon nuts, 3.2 cm from the center of the vessel. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade. Orient the large side of the basket tangentially to the flow stream with the tablet standing on its edge. Program for withdrawal of sample after 2 hours, 6 hours and 10 hours the buffer stage. At each withdrawal point, withdraw about 10 mL of solution from zone midway between the surface of the dissolution medium and top of the rotating paddle is not less than 1 cm from the vessel wall. Compensate the volume withdrawn with dissolution medium into each vessel at each time point. Filter the solution through 0.45 µm Millipore PVDF filter; collect the filtrate by discarding first few mL of the filtrate.

**Assay**

**Note: -**Prepare standard and sample preparations fresh prior to analysis.

**Buffer solution**: Dissolve 6.9 g of monobasic sodium phosphate in 400 mL of water in a 1000-mL volumetric flask. Add 8.0 mL of 1 M phosphoric acid, dilute with Milli Q water to volume, and mix.

**Mobile phase:** Prepare a filtered and degassed mixture of buffer solution, acetonitrile and methanol in the ratio of (40: 40: 20). Make adjustment if necessary.

**Diluent:** Use mobile phase as diluent**.**

**Resolution solution:** Dissolve 150 mg of sample in a mixture of 25 mL of tertiary butyl alcohol and 25 mL of 1 N perchloric acid, add 10 mL of 0.1 M ceric sulfate, mix, and allow standing for 15 minutes. Add 3.5 mL of 10 N sodium hydroxide, and neutralize with 2 N sodium hydroxide. Shake the mixture with 25 mL of methylene chloride in a separator. Draw off the lower layer, and evaporate it to dryness under a stream of nitrogen on a water

bath. Dissolve 10 mg of residue (-API oxidation product) and 5 mg of -API USPRS/working standard in mobile phase, dilute with mobile phase to 100.0 mL, and mix. Dilute 1.0 mL of the resulting solution to a 100.0 mL with diluent and mix.

**Standard preparation:** Transfer an accurately weighed quantity of about 15 mg of -API USPRS/working standard to a 50-mL volumetric flask. Add about 25 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix.

Prepare two independent sample preparations.

**Sample preparation***:* Transfer an accurately weighed quantity of about 30 mg of sample to a 100-mL volumetric flask. Add about 50 mL of diluent and sonicate to dissolve. Make volume up to the mark with diluent and mix.

**Chromatographic system**

| | |
|---|---|
| Column | : Kromasil C18, (15 cm x 4.6 mm), 5 µm |
| Detector | : 254 nm |
| Flow rate | : 1.0 mL/minute |
| Injection volume | : 40 µL for standard preparation and sample preparation and 20 µL for resolution solution |

**Developmental trial by Wet granulation approach:** Objective to design formulation by wet granulation was to improve the flow of powder by increasing particle size and sphericity. Wet granulation forms the granules by binding the powders together with an adhesive. It improves and increases the uniformity of powder density and improves cohesion during and after compression.

The wet granulation technique employs a solution, suspension or slurry containing a binder which is usually added to powder mixture however the binder may be incorporated dry into the powder mixture and the liquid may be added by itself. The liquid plays a key role in the granulation process. Liquid bridges are developed between particles and the tensile strength of these bonds increases as the amount of liquid added is increased. So we can improve the hardness of tablets using wet granulation strategies.

**Table no: 12**

| Sr.No. | Ingredients | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| **Drug solution preparation** | | | | | |
| 1 | -API | 10 | 10 | 10 | 10 |
| 2 | Cremophor RH 40 | 20 | 20 | 20 | 20 |
| 3 | IPA | qs | qs | qs | qs |
| **Binder solution preparation** | | | | | |
| 4 | HPC(Klucel- LF) | -- | -- | 22.5 | 22.5 |
| 5 | Povidone K 90 | -- | 18 | -- | -- |
| 6 | IPA | -- | qs | qs | qs |
| **Dry mixing** | | | | | |
| 7 | HPC(Klucel- LF) | 90 | 90 | -- | -- |
| 8 | Lactose Anhydrous | 45 | 45 | 45 | 45 |
| 9 | HPMC E4M | -- | -- | 45 | 45 |
| 10 | HPMC K 100 | -- | -- | -- | -- |
| 11 | HPMC E6 | 135 | 135 | -- | 160 |
| 12 | Avicel PH 101 | 141 | 123 | 231 | 138.5 |
| **Lubrication** | | | | | |
| 13 | Avicel pH 102 | -- | -- | 67.5 | -- |
| 14 | Sodium stearyl fumrate | 4.5 | 4.5 | 4.5 | 4.5 |
| 15 | ColloidalSilicon Dioxide (Aerosil-200) | 4.5 | 4.5 | 4.5 | 4.5 |

**Manufacturing Procedure:**

**1-Dispensing:** Dispensed raw materials quantities as per mentioned in the formula.

**2-Preparation of Drug Solution*:*** Dissolve the Cremophor RH 40 in Isopropyl Alcohol with stirring till clear solution obtain. Add -API to this solution with stirring till clear solution obtained.

**3-Preparation of Binder solution:** Add hydroxy propyl cellulose to the Isopropyl Alcohol with continuous stirring to get homogeneous dispersion.

**4-Dry mixing:** Mix Lactose Anhydrous, Hypromellose 50 cps, Hypromellose 15 cps and Sodium aluminium silicate in High speed rapid mixture granulator for 10 min.

**5-Adsorption of -API solution:** Add -API solution to the dry mixed blend with slow impeller speed. Finally it with impeller slow and chopper fast for 2 min to get uniform distribution of drug.

**6-Wet granulation:** Add the binder solution to the blend with slow impeller speed. Finally mix it with fast impeller and chopper for 2 to 5 minutes.

**7-Drying:** Dry the granules in Tray dryer with inlet temperature is 55° C to 60° C for around 2 Hr to achieve LOD between 0.5 to 1.5 % w/w.

**8-Milling**: Sift the dried granules with Colloidal silicon dioxide through oscillating granulator equipped with 20 mm screen to get uniform size granules.

**9-Compression:** Compress the blend into tablets using B-Tooling 16- station compression machine.

**Observations**

**Table no: 13**

| **Flow properties of the lubricated blend** | | | | |
|---|---|---|---|---|
| **Observation** | **$F_1$** | **F2** | **$F_3$** | **$F_4$** |
| | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** |
| **Tapped density(g/ml)** | 00.76± 0.004 | 00.71± 0.066 | 00.74 ± 0.009 | 00.77± 0.013 |
| **Bulk density (g/ml)** | 00.65± 0.004 | 00.51± 0.001 | 00.56 ± 0.010 | 00.65± 0.001 |
| **Compressibility Index (%)** | 13.94± 0.081 | 28.00± 0.811 | 24.54 ± 0.802 | 15.74± 0.416 |
| **Hausner's Ratio** | | | | |
| **Moisture content** | 01.16± 0.001 | 01.38± 0.015 | 01.31 ± 0.034 | 01.18± 0.005 |
| **(%MC)** | 01.14± 0.010 | 01.16± 0.020 | 01.21 ± 0.101 | 01.23± 0.110 |
| **Physical parameters of ER tablets** | | | | |
| **Tablet thickness(mm)** | 5.28 ± 0.184 | 5.35 ± 0.143 | 5.37± 0.126 | 5.38± 0.140 |
| **Weight (mg)** | 450 ± 0.378 | 450 ± 0.305 | 450 ± 0.152 | 450 ± 0.200 |
| **Hardness (Kp)** | 4.6 ± 0.305 | 4.70 ± 0.200 | 7.66 ± 0.157 | 8.93 ± 0.152 |
| **Friability (%)** | 00.21± 0.014 | 00.61 ± 0.055 | 00.63± 0.015 | 00.59± 0.020 |

**Discussion:**

- B.No.$F_1$ taken with HPMC and HPC hardness found at lower side.
- For improve the hardness purpose in B.NO F2 taken with PVP K 90 but hard ness was not satisfied.
- In B.NO F3 was taken with 10% HPMC E 4M and microcrystalline cellulose to achieved good hardness. But in this trail dissolution is completed with in one hour.
- In B.NO F4 10% HPMC E 4M, microcrystalline cellulose and HPMC 6 cps 35% are taken In this trial hard ness will come satisfactory but the dissolution results are faster than target.

**Table no: 14**

| Sr.No. | Ingredients | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|
| **Drug solution preparation** | | | | | |
| 1 | -API | 10 | 10 | 10 | 10 |
| 2 | Cremophor RH 40 | 20 | 20 | 20 | 20 |
| 3 | IPA | qs | qs | qs | qs |
| **Binder solution preparation** | | | | | |
| 4 | HPC(Klucel- LF) | 22.5 | 22.5 | 22.5 | 22.5 |
| 5 | Povidone K 90 | -- | -- | - - | -- |
| 6 | IPA | qs | qs | qs | qs |
| **Dry mixing** | | | | | |
| 7 | HPC(Klucel- LF) | -- | -- | -- | -- |
| 8 | Lactose Anhydrous | 45 | 45 | 45 | 45 |
| 9 | HPMC E4M | 56 | 67.5 | -- | -- |
| 10 | HPMC K 100 | -- | -- | 157.5 | 135 |
| 11 | HPMC E6 | 160 | 160 | 90 | 112.5 |
| 12 | Avicel PH 101 | 127.5 | 116 | 96 | 96 |
| **Lubrication** | | | | | |
| 13 | Avicel pH 102 | -- | -- | -- | -- |
| 14 | Sodium stearyl fumerate | 4.5 | 4.5 | 4.5 | 4.5 |
| 15 | Colloidal Silicon Dioxide | 4.5 | 4.5 | 4.5 | 4.5 |

**Manufacturing Procedure:**

**1-Dispensing**: - Dispensed raw materials quantities as per mentioned in the formula.

**2-Preparation of Drug Solution: -** Dissolve the Cremophor RH 40 in Isopropyl Alcohol with stirring till clear solution obtain. Add -API to this solution with stirring till clear solution obtained.

**3-Preparation of Binder solution: -** Add Hydroxy propyl cellulose to the Isopropyl Alcohol with continuous stirring to get homogeneous dispersion.

**4-Dry mixing: -** Mix Lactose Anhydrous, and different grades of Hypromellose and microcrystalline cellulose in High speed rapid mixture granulator for 10 min.

**5-Adsorption of -API solution: -** Add -API solution to the dry mixed blend with slow impeller speed. Finally it with impeller slow and chopper fast for 2 min to get uniform distribution of drug.

**6-Wet granulation: -** Add the binder solution to the blend with slow impeller speed. Finally mix it with fast impeller and chopper for 2 to 5 minutes.

**7-Drying: -** Dry the granules in Tray dryer with inlet temperature is 55° C to 60° C for around 2 Hr to achieve LOD between 0.5 to 1.5 % w/w.

**8-Milling**: - Sift the dried granules with Colloidal silicon dioxide through oscillating granulator equipped with 20 mm screen to get uniform size granules

**9-Compression: -** Compress the blend into tablets using B-Tooling 16- station compression machine.

## Observation

## Table no: 15

| Flow properties of the lubricated blend | | | | |
|---|---|---|---|---|
| **Observation** | **$F_5$** | **F6** | **F7** | **$F_8$** |
| | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** |
| **Tapped density(g/ml)** | 00.61 ±.006 | 00.71 ± .011 | 00.65 ±0.006 | 00.72 ± 0.006 |
| **Bulk density (g/ml)** | 00.47±0.005 | 00.55 ±0.013 | 0.48 ± 0.004 | 00.53 ± 0.014 |
| **Compressibility Index (%)** | 22.24 ± 1.654 | 22.34 ±0.719 | 25.97 ±0.973 | 26.17 ± 2.650 |
| **Hausner's Ratio** | 01.28 ± 0.026 | 01.28 ±0.030 | 01.31 ±0.017 | 10.32 ± 0.050 |
| **Moisture content (%)** | 01.04 ± 0.055 | 01.11± 0.043 | 00.09± 0.049 | 01.17 ± 0.055 |
| **Physical parameters of ER tablets** | | | | |
| **Tablet thickness(mm)** | 5.30 ± 0.184 | 5.38 ± 0.243 | 5.29 ± 0.226 | 5.40 ± 0.240 |
| **Weight (mg)** | 450 ± 0.378 | 450 ± 0.305 | 450 ± 0.152 | 450 ± 0.200 |
| **Hardness (Kp)** | 8.6 ± 0.305 | 8.60 ± 0.200 | 8.66 ± 0.157 | 09.93± 0.152 |
| **Friability (%)** | 00.21± 0.014 | 00.61± 0.055 | 00.63± 0.015 | 00.59± 0.020 |

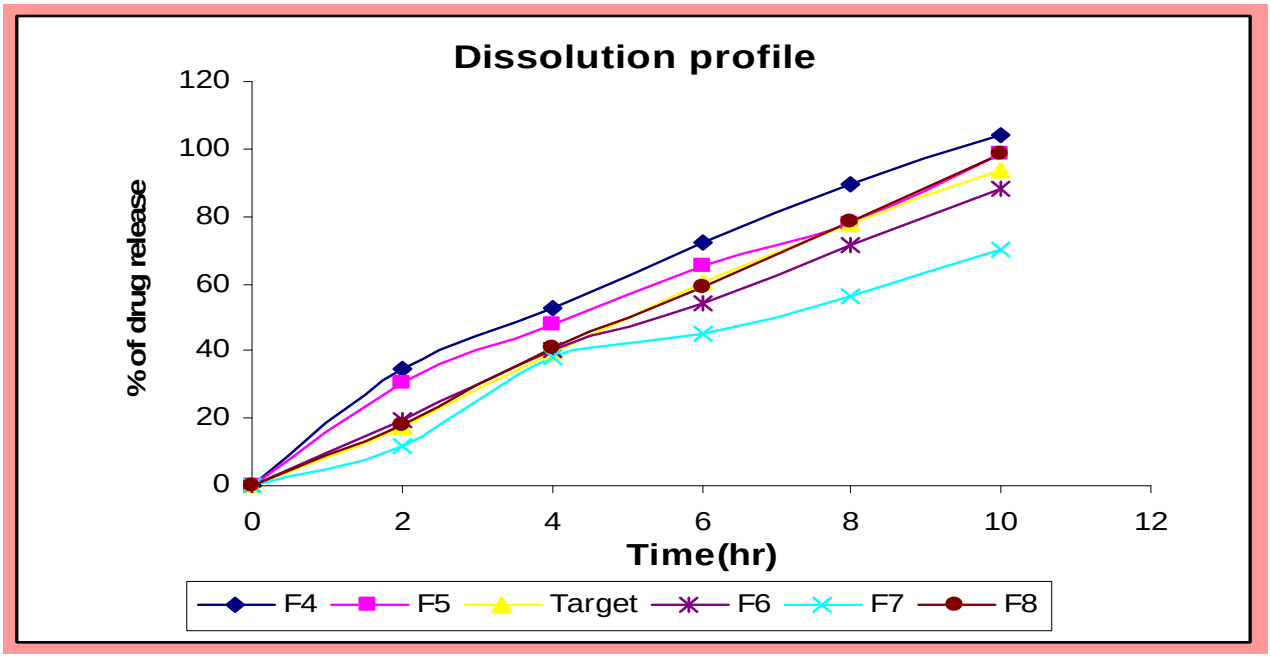
## DISCUSSION

- In B.NO F5 12% HPMC E 4M, microcrystalline cellulose and HPMC 6 cps 35% are taken. In this trial hard ness will come satisfactory but the dissolution results are slight faster than target.
- In B.NO F6 15% HPMC E 4M are taken in this trail the dissolution results are matching with target.
- In B.NO F7 trail HPMC E 4M replace with 35% HPMC K 100 in this trail the dissolution rate is slower than target.
- In F8 B.NO trail taken with 25% HPMC E6and 30% HPMC K100 in this trail the dissolution rate is match with target.
- Hence this formula was selected as a lead formula for coating trails.

**TABLE NO: 16**

| Time(hr) | Target | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 17.2 | 80 | 34.6 | 30.8 | 19.7 | 12.1 | 18.1 |
| 4 | 39.6 | 89.8 | 52.7 | 48.2 | 40.4 | 38 | 41.2 |
| 6 | 60.2 | 95 | 72.2 | 65 | 54.2 | 45.1 | 59.1 |
| 8 | 77.5 | 98.6 | 89.5 | 77.8 | 71.6 | 56 | 78.6 |
| 10 | 93.6 | 99.5 | 104 | 98.8 | 88.4 | 70 | 98.8 |

**TABLE NO: 17**



**DEVELOPMENT OF COATING FORMULA:**

Film coating is a high sophisticated process. The first film-coated tablet became commercially available in 1954. The technology advanced with the introduction of the semi synthetic cellulose derivatives and synthetic acrylic polymers.

Film coating applied for several reasons.

- Taste masking and moisture protection.
- Light protecting coating.
- Improved the product appearance.
- Improved the mechanical resistance of the coated product.
- Modified drug release.

The properties and performance of the final coat is strongly affected by the polymer properties and the formulation parameters. According to the interesting aspect for the specific use the polymer may be classified as

- Protective coating.
- Functional coating.

**Protective coating:** Thin films of water soluble polymers are often applied for taste or odour masking, to improve the stability of the moisture sensitive products or better mechanical resistance of the product.

E.g. HPMC, PVP, PVA

**Functional coating:** Film coatings which are applied to achieve a certain desired release profile of the incorporated drug. These are generally called as functional coating or modified release coating. Those intended to protect the drug from the acidic environment of the gastric medium(generally called as enteric coating) extended release coatings in contrast are requested to control the release of the drug over a prolonged period of time. During coating process parameters to be considered are

- Pan rotation speed

- Inlet temperature
- Product temperature
- Spray rate
- Atomization

**Preparation of aqueous coating solution:**

Weighed accurately opadry white (50gm) Added slowly into 450ml purified water Stirred for 45 minutes. The tablets were coated in NEOCOATA Coating machine under controlled conditions.

**Pan speed** : 5 RPM
**Pan size** : 3 KG
**Spray rate** : 2 RPM
**Inlet temp** : 47°c
**Exhaust temp** : 22°c

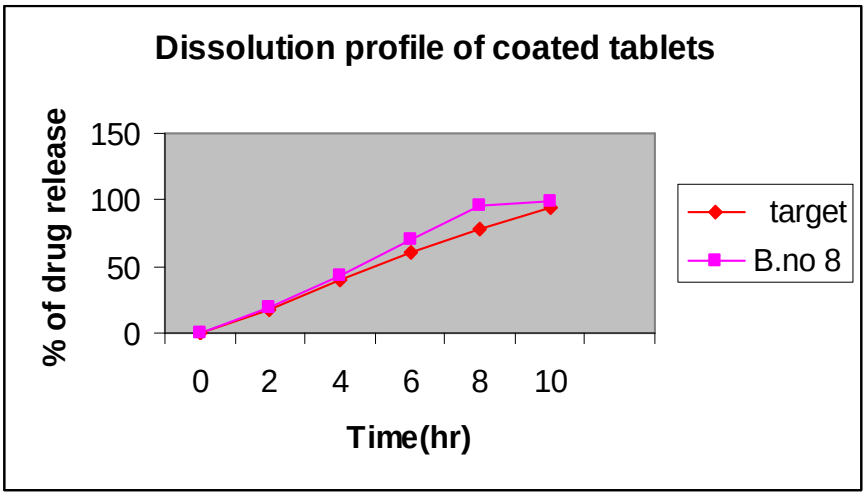
**Dissolution parameter**

**Apparatus** : USP Type II (Paddle method)
**RPM** : 50 rpm
**Media** : 500 ml; pH 6.5, Phosphate buffer with 1 % SLS
**Temperature** : 37 ± 0.5 $^{0}$C

**Table no: 18**

| **Time in hours** | **% Drug release** | |
|---|---|---|
| | **Target** | **F8** |
| 0 | 0 | 0 |
| 2 | 17.2 | 17.9 |
| 4 | 39.6 | 42 |
| 6 | 60.2 | 59.5 |
| 8 | 77.5 | 79 |
| 10 | 93.6 | 99 |

**Table no: 19**




**REPRODUCIBILITY BATCH:**

Trial $F_8$ formula was selected as lead formula for the reproducibility batch.

**Formula** **Batch Size: 1000 Tablets**

**Table no: 20**

| Sr.No. | Ingredients | F8 | % | Category |
|---|---|---|---|---|
| **Drug solution preparation** | | | | |
| 1 | -API | 10 | 2.2 | Active ingredient |
| 2 | Cremophor RH 40 | 20 | 4.4 | Solubelizer |
| 3 | IPA | Qs | -- | Solven |
| **Binder solution preparation** | | | | |
| 4 | HPC(Klucel- LF) | 22.5 | 5 | Binder |
| 5 | IPA | -- | -- | Solvent |
| **Dry mixing** | | | | |
| 6 | Lactose Anhydrous | 45 | 10 | Filler |
| 7 | HPMC K 100 | 135 | 30 | Polymer |
| 8 | HPMC E6 | 112.5 | 25 | Polymer |

| | | | | |
|---|---|---|---|---|
| 9 | Avicel PH 101 | 96 | 21.3 | Filler |
| **Lubrication** | | | | |
| 10 | Sodium stearyl fumrate | 4.5 | 1 | Lubricant |
| 11 | Colloidal Silicon Dioxide | 4.5 | 1 | Glidant |
| Core tablet weight | | 450 mg | 100% | |

**Manufacturing Procedure:**

**1-Dispensing**: - Dispensed raw materials quantities as per mentioned in the formula.

**2-Preparation of Drug Solution: -** Dissolve the Cremophor RH 40 in Isopropyl Alcohol with stirring till clear solution obtain. Add -API to this solution with stirring till clear solution obtained.

**3-Preparation of Binder solution: - Add** Hydroxy propyl cellulose to the Isopropyl Alcohol with continuous stirring to get homogeneous dispersion.

**4-Dry mixing:-** Mix Lactose Anhydrous, and different grades of Hypromellose and microcrystalline cellulose in High speed rapid mixture granulator for 10 min.

**5-Adsorption of -API solution:-** Add -API solution to the dry mixed blend with slow impeller speed. Finally it with impeller slow and chopper fast for 2 min to get uniform distribution of drug.

**6-Wet granulation: -** Add the binder solution to the blend with slow impeller speed. Finally mix it with fast impeller and chopper for 2 to 5 minutes.

**7-Drying: -** Dry the granules in Tray dryer with inlet temperature is 55° C to 60° C for around 2 Hr to achieve LOD between 0.5 to 1.5 % w/w.

**8-Milling**: - Sift the dried granules with Colloidal silicon dioxide through oscillating granulator equipped with 20 mm screen to get uniform size granules

**9-Compression: -** Compress the blend into tablets using B-Tooling 16- station compression machine.

**Coating Formula:**

| Formulation designation | Opadry white (mg) | % Coat relative to the core |
|---|---|---|
| F8 | 9 | 2% |

After completion of the coating the tablet weight is 460mg

**Physical Parameters of the Tablets:**

**Table No - 21**

| Test | Observation |
|---|---|
| Tablet thickness (mm) | 5.2-5.3 |
| Weight (mg) | 459 |
| Hardness (kp) | 8-9 |
| Friability (%) | 02 |

**Dissolution Results of reproducibility data of trial $F_8$**

**Dissolution parameter**

**Apparatus** : USP Type II (Paddle method)

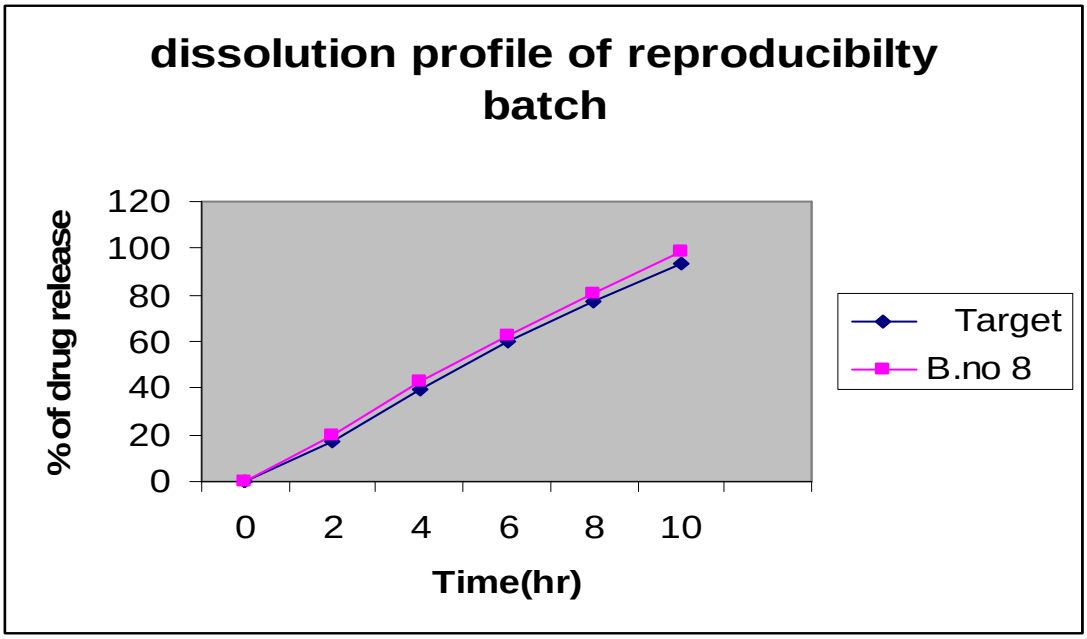
**RPM** : 50 rpm

**Media** : 500 ml; pH 6.5, Phosphate buffer with 1 % SLS

**Temperature** : 37 ± 0.5 $^0$C

| Time in hours | % Drug release | |
|---|---|---|
| | Target | F8 |
| 0 | 0 | 0 |
| 2 | 17.2 | 19.7 |
| 4 | 39.6 | 41 |
| 6 | 60.2 | 62.5 |
| 8 | 77.5 | 80.8 |
| 10 | 93.6 | 98.5 |

**Table no: 22**




**Discussion:**

- During compression Blend flow was found satisfactory, all physical parameters of the core tablets were found good.
- During coating, All Product and Process Parameters were found satisfactory.
- Dissolution profile of reproducibility data was same as previously prepared trial of $F_8$

**7. CONCLUSION**

API is a calcium channel blocker widely used in the treatment of Hypertension. According to BCS -API is class-II drug it's having low solubility and high permeability. The Preformulation studies are important step in the development of dosage form. There is no interaction of the drug with excipients. The overall objective of preformulation testing was found that -API having good flow and poor compressible, melting point 140-145 $^0$C, moisture content within controlled limit and -API was non hygroscopic. pH 6.5+1% SLS phosphate buffer was used as dissolution medium.

Wet granulation approaches were used for the prototype development of extended release tablet to produce the quality product consistency. From trials of $F_1$ and F2 it was concluded that low hardness was found.

To achieve required hardness HPMC E 4 M (10%) and microcrystalline cellulose is using in the F3 trial. In this trail hardness was improved but in this trail the dissolution is completed with in one hour. For controlling the dissolution time the trail F4 and F5 is taken with HPMC E6 in this trail the dissolution time is slightly faster than target. To achieve good dissolution results purpose in trial F6 taken with 15% HPMC E4 M in this trails the dissolution results were matching with target. The trail F7 is taken with 35% HPMC K 100 and 20% of the HPMC E6 in this trail the dissolution results are slower than the target. The trail F8 was taken with 30% HPMC K 100 and 25% of the HPMC E6 in this trail the dissolution results are matching with target. The trail F8 formula is taking for the coating trails.

Film coating is applied for tablets. The aim of the film coating is to improve the appearance of the tablet and improve the mechanical strength of the tablet. Opadry white is selected for coating of the tablets 2% coating will applied to tablets. To check the reproducibility of the formula one batch was planned there was no change in the dissolution profile of the tablets.

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I am sure words form poor substitutes when I acknowledge my parents, my brothers, my sister, and friends, who have been a pillar of strength behind me, whose inspiration and sacrifice made this course a success.

Last but not least, I thank Almighty, for all the blessings. He has showered blessings on me in every step I have taken.

At this ecstatic moment my apologies to all those I forgot to acknowledge.

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