# "Development of controlled release coating system for highly soluble drug matrix tablets of an anti-diabetic category (PH0168)"

**A THESIS SUBMITTED TO**

## NIRMA UNIVERSITY

**IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF**

## MASTER OF PHARMACY

**IN**

## PHARMACEUTICAL TECHNOLOGY & BIOPHARMACEUTICS

**BY**

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**UNDER THE GUIDANCE OF**

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# *CERTIFICATE*

*This is to certify that* ***Mr.Tushar R. Bambharoliya*** *has prepared his thesis entitled "Development of controlled release coating system for highly soluble drug matrix tablets of an anti-diabetic category (PH0168)", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He has carried out the work at the Formulation & development, Alembic Research Centre, Vadodara.*


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**Date : 30th April, 2011**

# *DECLARATION*

*I declare that the thesis "Development of controlled release coating system for highly soluble drug matrix tablets of an anti-diabetic category (PH0168)", has been prepared by me under the guidance of Industrial guide Dr. Girish Achliya, Group leader, Alembic research center, Vadodar & Academic guide Prof. (Dr.) Tejal A. Mehta, Professor & Head, Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.*

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***-Albert Einstein.***

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Date : 30th April, 2011

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A controlled release (CR) formulation is designed to modify the properties of a drug, by slowing down the rate of drug release from the dosage form. The aim of such an approach is to extend the absorption time of drug within the GI tract, thus prolonging the duration of the therapeutic action of the drug[1].

Other important Advantage[2]

- Achievement of steady drug concentrations within the therapeutic range.
- Decrease of the frequency of administration.
- Reduction of adverse effects.
- An improvement in patient compliance.

Drug with short elimination half life as well as that are administered in large doses is good candidate for CR delivery. The Drug PH0168 used in present investigation is used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Drug PH0168 has short half life of 6 hrs. To reduce the frequency of administration and to improve the patient compliance, a controlled release formulation of Drug PH0168 is desirable.

Hence in the present work an attempt has been made to develop controlled release coating system (Core-coat technology) for highly soluble drug matrix tablets of Drug PH0168. The drug release for extended duration, particularly for water soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such water soluble drugs, hydrophobic polymers are suitable along with a hydrophilic matrix for developing controlled release dosage forms.

The present study was planned with an objective of development of stable & equivalent dosage form of Drug PH0168 in comparison with its UK innovator formulation

The following strategy was adopted in present investigation

- To develop a controlled release coating system for highly soluble drug matrix tablets of an anti-diabetic category.
- Optimization of dissolution profile in-line with UK innovator's formulation.

The innovator's formulation was present in 500, 750, and 1000 mg strengths. To develop generic product, it is essential to match dissolution profile with respect to similarity factor (f2 values). By core-coat technology the attempts was made to get desired release profile of all strengths with similarity factor greater than 50.

Now, the innovator pharmaceutical product is that which was first authorized for marketing, usually as a patented drug, on the basis of documentation of efficacy, safety & quality. Innovator product are protected by a patent, usually patent protection are given for 20 years from the date of submission of the patent.
This provides protection to the innovator of such products & to generate revenue & make

good initial cost incurred by the organization in research, development and marketing expenses to develop new drug, so innovator product is costly.

On other side generic product is having therapeutic equivalence (comprising pharmaceutical equivalence and bioequivalence) to the innovator product, thus ensuring comparable efficacy and safety profile.

Innovator product plays an important role in medication, but generics are their cost effective alternatives[3].Thus, the aim of present investigation is to develop cost effective & industrially feasible generic formulation of selected anti diabetic drug.

## 2.1 Introduction to Matrix tablet[2,4,5,6,7,8]

The term modified-release dosage form is used to describe products that alter the timing and rate of release of drug substance. A modified-release dosage form is defined "as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms. The USP/NF presently recognizes several types of modified-release dosage forms such as:

1. Oral Dosage Forms

- Modified release dosage forms
- Extended release e.g. controlled release, sustained release and prolonged release
- Delayed release e.g. enteric-coated tablets.

2. Intramuscular Dosage Forms

- Depot injections
- Water-immiscible injections e.g. oils

3. Subcutaneous Dosage Forms

- Implants

4. Transdermal Delivery Systems

- Patches, creams, etc.

5. Targeted Delivery Systems.

Controlled release drug delivery system is capable of achieving the benefits over the conventional dosage forms as:

**Drawbacks Associated with Conventional Dosage Forms:**

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration which may lead to under medication or over medication.

- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occurs.

**Advantages of Controlled Release Drug Delivery Systems**

Therapeutic advantage: Reduction in drug plasma level fluctuation; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

- Reduction in adverse side effects and improvement in tolerability: Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms.
- Patient comfort and compliance: Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.
- Reduction in healthcare cost: The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product. With reduction in side effects, the overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increase as we approach the maximum safe concentration.
- Avoid night time dosing: It is also good for patients to avoid the dosing at night time.

**Matrix Tablets**

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

- **Classification Of Matrix Tablets**

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

- **Hydrophobic Matrices (Plastic matrices):**

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

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

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

- **Lipid Matrices:**

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

- **Hydrophilic Matrices:**

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

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

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

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

3.Polymers of acrylic acid; corbopol 934, the most used variety.

- **Biodegradable Matrices:**

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

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

- **Mineral Matrices:**

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

**B. On the Basis of Porosity of Matrix**

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

- **Macroporous Systems:**

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

- **Microporous System**:

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

- **Non-porous System:**

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

**Advantages of Matrix Tablets**

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

**Disadvantages of the matrix systems:**

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

**Table1: Polymers used in Matrix Tablets**

| Hydrogels | Soluble polymers | Biodegradable polymers | Non biodegradable polymers | Muco-adhesive polymers | Natural gums |
|---|---|---|---|---|---|
| Polyhydroxy ethyle methylacrylate (PHEMA) | Polyethylene glycol (PEG) | Polylactic acid (PLA) | Polydimethyl siloxane (PDS) | Poly carbophil | Xanthan gum |
| Cross-linked polyvinyl alcohol (PVA) | Polyvinyl alcohol (PVA) | Polyglycolic acid (PGA) | Polyether urethane (PEU) | Sodium carboxy methyl cellulose | Guar gum |
| Cross-linked polyvinyl pyrrolidone (PVP) | Polyvinyl pyrrolidone (PVP) | Polycaprolactone (PCL) | Polyvinyl chloride (PVC) | Polyacrylic acid | Karaya gum |
| Polyethylene oxide (PEO) | Hydroxypropyl methyl cellulose (HPMC) | Polyanhydrides | Cellulose acetate (CA) | Tragacanth | - |
| Polyacrylamide (PA) | - | Polyorthoesters | Ethyl cellulose (EC) | Methyl cellulose | - |

## 2.2 Introduction to Coating[9]

- Polymeric film coatings are frequently used to control drug release from solid pharmaceutical dosage forms providing different types of drug release behavior, e.g. zero order kinetics, pulsatile and sigmoidal patterns.
- To obtain a particular, desired release profile which is adapted to the pharmacokinetic/pharmacodynamic characteristics of the drug and type of pharmacotreatment, different formulation and processing parameters can be varied, such as the coating level, type of polymer and type and amount of added plasticizer.
- However, the variation of these parameters is generally restricted and it is sometimes difficult to adjust optimized release kinetics. For instance, too low and too high coating levels must be avoided to prevent accidental film rupturing (and subsequent dose dumping) and too long processing times. The type of polymer used should be known to be non-toxic; otherwise time-and costintensive toxicity studies are required. Too high amounts of added plasticizers lead to intense sticking of the coated dosage forms, whereas too low amounts result in too brittle films.
- An interesting possibility to overcome these restrictions is based on the use of blends of two types of polymers, which are known to be non-toxic and exhibit different physic chemical characteristics [e.g., water and drug permeability, mechanical stability and solubility along the gastro-intestinal tract (GIT)]
- By simply varying the polymer:polymer blend ratio, the resulting film coating properties can effectively be altered, and broad ranges of drug release patterns be provided. Interestingly, not only the slope of the release curves can be varied, but also their shape, due to changes in the underlying drug release mechanisms. Importantly, the use of polymer blends as controlled release coating materials is not only restricted to the facilitated adjustment of desired drug release kinetics, the presence of a second type of macromolecules can also help to improve film formation in the case of aqueous polymer dispersions and to provide appropriate mechanical film coating stability when osmotically active pellet/capsule/tablet cores generate considerable hydrostatic pressure within the systems during drug release.


**Figure1:** Schematic presentation of the strategy to use polymer blends as coating materials or controlled drug delivery systems: by simply varying the blend ratio of two known, non-toxic polymers with different physicochemical characteristics, broad ranges of film coating properties (e.g., permeability for drug and water, mechanical stability and solubility along the GIT) can be provided.

- The use of polymer blends as coating materials for controlled drug delivery systems can offer major **advantages**, including:

  (i) facilitated adjustment of desired drug release patterns, mechanical properties and drug release mechanisms,

  (ii) improved film formation and storage stability, and

  (iii) the possibility to develop novel strategies for site specific drug delivery within the gastro intestinal tract (e.g., colon targeting).

- Different types of classification schemes can be used for polymer blends, based for instance on the chemical structure, thermal properties, miscibility or solubility of the macromolecules. In this article, the systems are classified according to their solubility along the gastro-intestinal-tract (GIT), distinguishing:

  (i) polymers that are insoluble throughout the GIT ("GIT insoluble polymers"),

  (ii) polymers that are soluble throughout the GIT ("GIT-soluble polymers"),

  (iii) enteric polymers, and

  (iv) enzymatically degradable polymers.

- Blends of polymer

  (i)Blends of GIT-insoluble polymers

  (ii)Blends of GIT-insoluble and GIT-soluble polymers

(iii)Blends of GIT-insoluble and enteric polymers

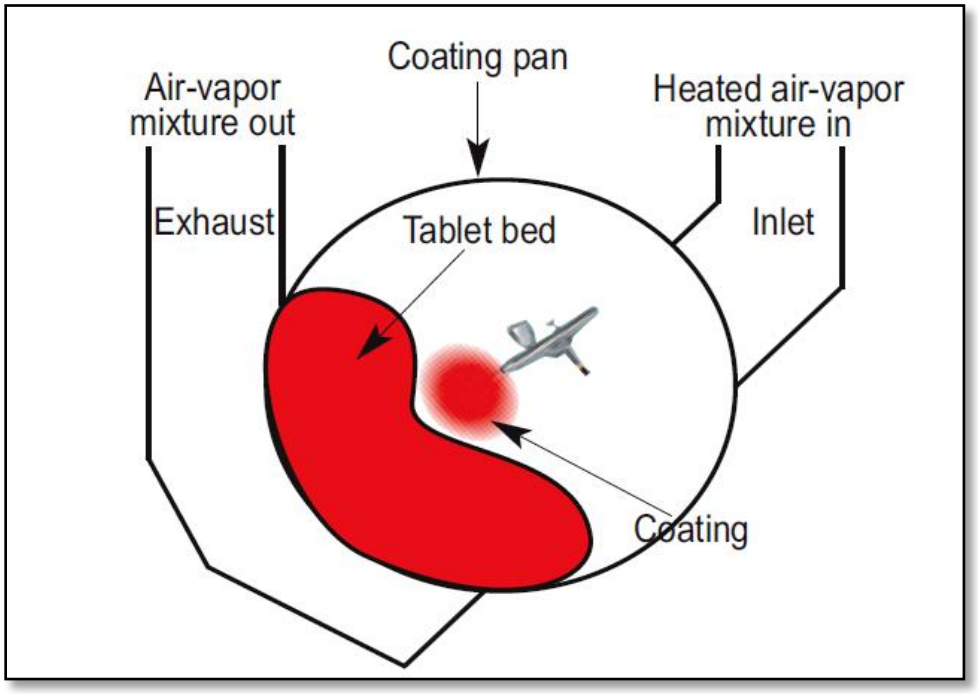
(iv)Blends of GIT-insoluble and enzymatically degradable polymers .

- **Blends of GIT-insoluble and GIT-soluble polymers**
  - **Ethylcellulose** is a frequently used GIT-insoluble polymer in controlled drug delivery systems. However, if applied as a film coating material, perfectly formed membranes result in very low drug release rates because ethylcellulose is poorly permeable for most drugs. To overcome this restriction, **water-soluble polymers** can be added to ethylcellulose coatings.For example,

    polyethylene glycol (PEG),
    polyvinyl pyrrolidone (PVP) and
    hydrophilic cellulose ethers, such as hydroxypropyl methylcellulose (HPMC)
    have been proposed.

- Upon contact with aqueous media, these additives hydrate and potentially leach out from the polymeric membranes, resulting in more permeable films and increased drug release rates. In contrast to low molecular weight water-soluble additives, these polymers are generally not considered as “true pore-formers”, because they do often not completely leach out from the coatings, and do not create well-defined porous structures.
- The so far most frequently used water-soluble, macromolecular additive for ethylcellulose-based film coatings is hydroxypropyl methylcellulose (HPMC). Ethylcellulose: HPMC coatings are for instance used in osmotically controlled drug delivery systems. In these devices, the water permeability of the surrounding polymeric membranes is of fundamental importance.
- As pure ethylcellulose films exhibit a water permeability which is much smaller than that of cellulose acetate-based films, HPMC has been added to the coatings. However, attention must be given, because the initially semipermeable ethylcellulose:HPMC membranes become also permeable for the drug at high HPMC contents.
- In addition to the film coating's permeability for the drug (and water), also the mechanical stability of the polymeric membrane is decisive for the resulting drug release kinetics. This could be explained by the decreasing mechanical stability of the polymeric films, facilitating the formation of cracks and flaws within the filmcoatings through which the drug can rapidly diffuse out. Thus, the permeability of a polymeric controlled release film coating can strongly depend on the mechanical pressure it is exposed to.

- **Figure2: A simple diagram of a tablet coating system**



## 2.3 Introduction to Excipient[10,11]

## 1.Hypromellose

**Nonproprietary Names**

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP: Hypromellose

**Synonyms**

*Benecel MHPC*; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

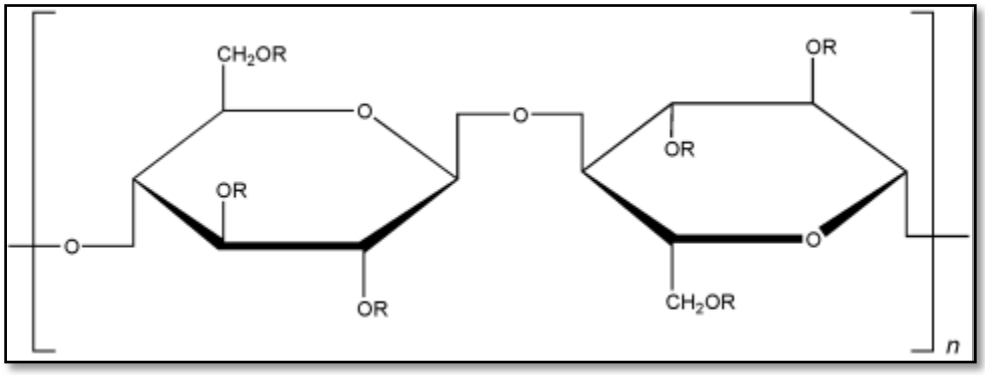
**Chemical Name and CAS Registry Number**

Cellulose hydroxypropyl methyl ether [9004-65-3]

**Empirical Formula and Molecular Weight**

The PhEur 2005 describes hypromellose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to thenonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

**Structural Formula**




where R is H, CH3, or CH3CH(OH)CH2

**Functional Category**

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

**Applications in Pharmaceutical Formulation or Technology**

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder,1 in film-coating,2–7 and as a matrix for use in extended-release tablet formulations.8–12 Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.
- Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of filmcoating materials that are commercially available include *AnyCoat C*, *Spectracel*, and *Pharmacoat*. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

- Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

**Description**

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

**Typical Properties**

**Acidity/alkalinity:**

pH = 5.5–8.0 for a 1% w/w aqueous solution.

**Ash:**

1.5–3.0%, depending upon the grade and viscosity.

**Autoignition temperature:**

360°C

**Melting point:**

browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

**Moisture content:**

hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Solubility:**

soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades

of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

**Specific gravity:**

1.26

**Viscosity (dynamic):**

a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

**Table2: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C.**

| Methocel Product | USP 28 designation | Nominal viscosity (mPa s) |
|---|---|---|
| Methocel K100 Premium LVEP | 2208 | 100 |
| Methocel K4M Premium | 2208 | 4000 |
| Methocel K100M Premium | 2208 | 100,000 |
| Methocel E10M Premium CR | 2906 | 10000 |
| Methocel E3 Premium LV | 2906 | 3 |
| Methocel E5 Premium LV | 2906 | 5 |
| Metolose 60SH | 2910 | 50,4000,10000 |
| Metolose 65SH | 2906 | 50,400,1500,4000 |

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol (95%), glycol, or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

**Stability and Storage Conditions**

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.13 However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

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

**Incompatibilities**

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

## 2.Carboxymethylcellulose Sodium

**Nonproprietary Names**

BP: Carmellose sodium

JP: Carmellose sodium

PhEur: Carmellosum natricum

USP: Carboxymethylcellulose sodium

**Synonyms**

*Akucell*; *Aquasorb*; *Blanose*; cellulose gum; CMC sodium; E466; *Finnfix*; *Nymcel*; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; *Tylose CB*.

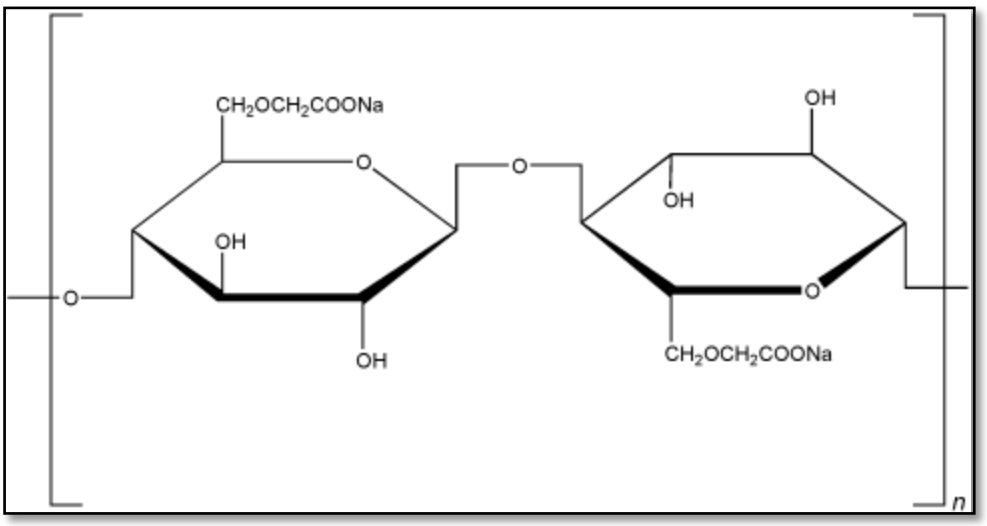
**Chemical Name and CAS Registry Number**

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

**Empirical Formula and Molecular Weight**

The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

**Structural Formula**




Structure shown with a degree of substitution (DS) of 1.0.

**Functional Category**

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

**Applications in Pharmaceutical Formulation or Technology**

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration. Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant, and to stabilize emulsions.

Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out. Carboxymethylcellulose sodium is additionally one of the main ingredients of self-adhesive ostomy, wound care, and dermatological patches, where it is used as a muco-adhesive and to absorb wound exudate or transepidermal water and sweat. This muco-adhesive property is used in products designed to prevent post-surgical tissue adhesions; and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair. Encapsulation with carboxymethylcellulose sodium can affect drug protection and delivery. There have also been reports of its use as a cytoprotective agent.

Carboxymethylcellulose sodium is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

**Use Concentration (%)**

Emulsifying agent 0.25–1.0

Gel-forming agent 3.0–6.0

Injections 0.05–0.75

Oral solutions 0.1–1.0

Tablet binder 1.0–6.0

**Description**

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular powder.

**Typical Properties**

**Dissociation constant:**

p*K*a = 4.30

**Melting point:**

browns at approximately 227°C, and chars at approximately 252°C

**Moisture content:**

Typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%.

**Solubility:**

practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS).

**Viscosity:**

Various grades of carboxymethylcellulose sodium are commercially available that have differing aqueous viscosities; *see* Table III. Aqueous 1% w/v solutions with viscosities of 5–13 000 mPa s (5–13 000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity. Prolonged heating at high temperatures will depolymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxymethylcellulose solutions is fairly stable over a pH range of 4–10. The optimum pH range is neutral.

**Table3: Viscosity of aqueous carboxymethylcellulose sodium 1% w/v solutions. (Measurements made with a Brookfield LVT viscometer at 25°C.)**

| Grade | Viscosity (mPa s) | Spindle | Speed |
|---|---|---|---|
| Low viscosity Akucell AF 0305 | 10-15 | #1 | 60 rpm |
| Medium viscosity Akucell AF 2785 | 1500-2500 | #3 | 30 rpm |
| High viscosity Akucell AF 3085 | 8000-12000 | #4 | 30 rpm |

**Stability and Storage Conditions**

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under highhumidity conditions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water. Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9.

The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities**

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%). Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

**Safety**

Carboxymethylcellulose sodium is used in oral, topical, and some parenteral formulations. It is also widely used in cosmetics, toiletries, and food products, and is generally regarded as a nontoxic and nonirritant material. However, oral consumption of large amounts of carboxymethylcellulose sodium can have a laxative effect; therapeutically, 4–10 g in daily divided doses of the medium- and high-viscosity grades of carboxymethylcellulose sodium have been used as bulk laxatives. The WHO has not specified an acceptable daily intake for carboxymethylcellulose sodium as a food additive since the levels necessary to achieve a desired effect were not considered to be a hazard to health.

## 3. Microcrystaline cellulose:

**Nonproprietary Names**

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

**Synonyms**

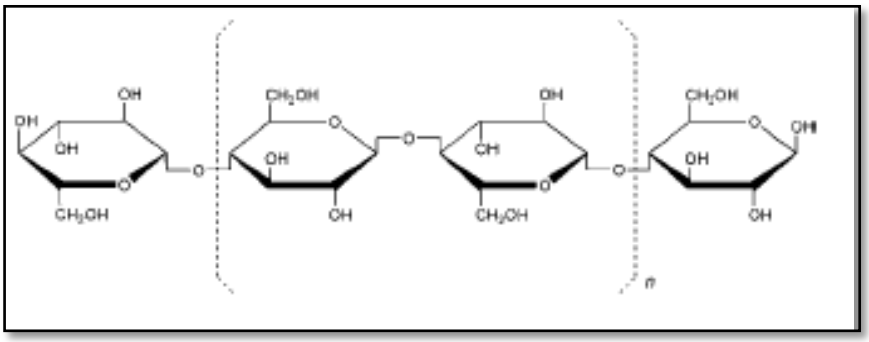
Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

**Empirical Formula and Molecular Weight**

(C6H10O5)n _36 000

where n _ 220.

**Structural Formula**



**Functional Category**

- Adsorbent
- suspending agent
- tablet and capsule diluent
- tablet disintegrant.

**Description**

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

**Applications in Pharmaceutical Formulation or Technology**

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-

compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

**Typical Properties**

**Melting point**: chars at 260–2708C.

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

**Table4 : Characterization of different grades of microcrystalline cellulose**

| Grade | Nominal mean particle size (µm) | Particle size analysis | | Moisture content (%) |
|---|---|---|---|---|
| | | Mesh size | Amount retained (%) | |
| Avicel PH-101 | 50 | 60 | ≤ 1.0 | ≤ 5.0 |
| | | 200 | ≤ 30.0 | |
| Avicel PH-102 | 100 | 60 | ≤ 8.0 | ≤ 5.0 |
| | | 200 | ≥ 45.0 | |
| Avicel PH-103 | 50 | 60 | ≤ 1.0 | ≤ 3.0 |
| | | 200 | ≤ 30.0 | |
| Avicel PH-105 | 20 | 400 | ≤ 1.0 | ≤ 5.0 |
| Avicel PH-200 | 180 | 60 | ≥ 10.0 | ≤ 5.0 |
| | | 100 | ≥ 50.0 | |

**Incompatibilities**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

## 4.ETHYL CELLULOSE

**Nonproprietary Names**

BP: Ethylcellulose

PhEur: Ethylcellulosum

USPNF: Ethylcellulose

**Synonyms**

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

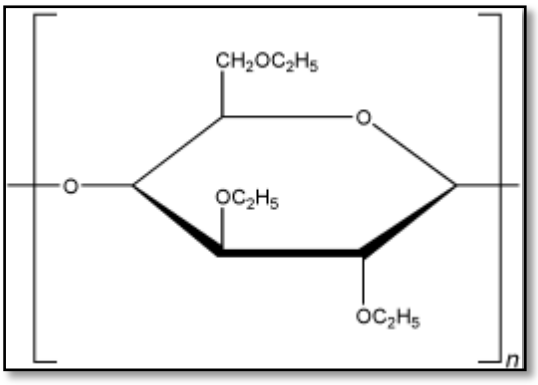
**Chemical Name and CAS Registry Number**

Cellulose ethyl ether [9004-57-3]

**Empirical Formula and Molecular Weight**

Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

**Structural Formula**




**Functional Category**

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

**Applications in Pharmaceutical Formulation or Technology**

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation.

**Table5 : Uses of ethylcellulose.**

| Use | Concentration(%) |
|---|---|
| Microencapsulation | 10.0-20.0 |
| Sustained-release tablet coating | 3.0-20.0 |
| Tablet coating | 1.0-3.0 |
| Tablet granulation | 1.0-3.0 |

Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. High-viscosity grades of ethylcellulose are used in drug microencapsulation.Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethylcellulose is additionally used in cosmetics and food products.

**Description**

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder

**Typical Properties**

**Glass transition temperature:**

129–133°C

**Moisture content:**

ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily

**Solubility:**

ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).

**Specific gravity:**

1.12–1.15 g/cm$^3$

**Viscosity:**

the viscosity of ethylcellulose is measured typically at 25°C using 5% w/v Ethylcellulose dissolved in a solvent blend of 80% toluene : 20% ethanol (w/w). Grades of ethylcellulosewith various viscosities are commercially available. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPa s (7–100 cP). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity.

**Stability and Storage Conditions**

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range. Ethylcellulose should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

**Incompatibilities**

Incompatible with paraffin wax and microcrystalline wax.

**Safety**

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys. Ethylcellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material.

## 5. Polyethylene Glycol-4000

**Nonproprietary Names:**

BP: Macrogols

JP: Macrogol 4000

PhEur: Macrogola

USPNF: Polyethylene glycol

**Synonyms:**

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

**Chemical Name:**

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

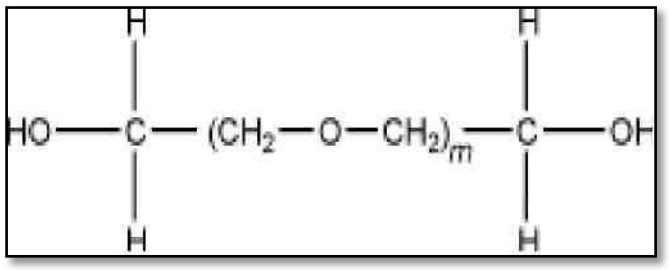
**Molecular Weight**:

3000–4800

**Emperical formula:**

HOCH2(CH2OCH2)mCH2OH where m represents the average number of oxyethylene groups. Alternatively, the general formula H(OCH2CH2)nOH may be used to represent polyethylene glycol, where n is a number m in the previous formula + 1. m= 8.7 n= 9.7

**Structural formula:**




**Description:**

It occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.

**Functional Category:**

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

**Application:**

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.

It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms. Polyethylene glycols are useful as

plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents.

It has also been used in insulin-loaded microparticles for the oral delivery of insulin. It has been used in inhalation preparations to improve aerosolization. Polyethylene glycol nanoparticles have been used to improve the oralbioavailability of cyclosporine.

**Description**

white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor.

**Typical Properties**

**Melting point:**

50–58°C for PEG 4000.

**Moisture content:**

Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades e.g. PEG 4000 and above, are not hygroscopic.

**Viscosity (kinematic) [mm2/s (cSt)] (PhEur 2005)**

102–158

**Viscosity (kinematic) [mm2/s (cSt)] (98.9°C ± 0.3°C from the USPNF 23)**

110–158

**Stability and Storage Conditions:**

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant. If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation. Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

**Incompatibilities**

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents. The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

**Safety**

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low. Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Liquid polyethylene glycols may be absorbed when taken orally, but the higher molecularweight polyethylene glycols are not significantly absorbed from the gastrointestinal tract.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.

## 6. Magnesium stearate:

**Nonproprietary Names**

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

**Synonyms**

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

**Empirical Formula and Molecular Weight**

C36H70MgO4 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur 25 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

**Structural Formula**

[CH3(CH2)16COO]2Mg

**Functional Category**

Tablet and capsule lubricant.

**Applications in Pharmaceutical Formulation or Technology**

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

**Description**

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

**Typical Properties**

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

**Flash point:** 2508C

**Flowability:** poorly flowing, cohesive powder.

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

**Solubility:**

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

Specific surface area: 1.6–14.8m2/g

**Incompatibilities**

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

## 3.1 Literature review on Matrix tablet

**Basak Subal Chandra et al**[12] using drug PH0168 formulated a hydrophobic matrix sustained release tablet employing wax materials and the sustained release behavior of the fabricated tablet was investigated. Sustained release matrix tablets containing 500 mg drug were developed using different bees wax combinations. The tablets were prepared by wet granulation technique. The formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The resulting formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. Statistically significant differences were found among the drug release profile from different bees wax combination matrices. The results of dissolution studies indicated that formulations F-III, FIV and F-V (bees wax and cetyl alcohol combination matrices), exhibited drug release pattern very close to theoretical release profile. Applying kinetic equation models, the mechanism of release of the drug from the three formulations was found to be followed Higuchi model, as the plots showed high linearity, with correlation coefficient (R2) value of 0.98 or more. Tablet matrices containing cetyl alcohol gave better release of the drug than other materials studied. However, the rate of release varied with amount of cetyl alcohol in the matrix. The ‘n’ value lies below 0.5 (Korsmeyer- Peppas model) demonstrating that the mechanism controlling the drug release was the quasi Fickian. Therefore, the results of the kinetic study obtained permit us to conclude that the fabricated hydrophobic matrix tablets, in this case, delivers the drug through diffusion dominated mechanism.

**Mura Paola et al**[13] had incorporated Didanosine, a nucleoside analog used in the treatment of acquired immuno deficiency syndrome (AIDS), directly into compressed monolythic matrices whose excipients were mixtures at different ratios of a methacrylic resin (Eudragit RSPM) and an ethylcellulose (Ethocel 100), both water-insoluble and pH-independent polymers. Technological characterization (drug particle morphology, mean weight, diameter, thickness and hardness of tablets) was carried out and in vitro drug release behaviour was measured using the USP basket apparatus. The effect of varying the Eudragit–Ethocel ratio, as well as the drug–polymeric matrix ratio, was evaluated. The results showed the suitability of Eudragit–Ethocel mixtures as matrix-forming material for didanosine sustained release formulations. Combination of the moderate swelling properties of Eudragit RSPM with the

plastic properties of the more hydrophobic Ethocel 100 allowed suitable modulation of didanosine release.

**Cao Qing-Ri et al**[14] studied the effect of incorporating pharmaceutical excipients on the in vitro release profiles and the release mechanism of monolithic hydroxypropylmethylcellulose (4000 cps) matrix tablets (m-HPMC tablets) in terms of mimicking the dual drug release character of bi-layered TylenolR ER tablets. they also compared the in vitro release profiles of optimized m-HPMC matrix tablet and TylenolR ER tablet in water, pH 1.2 gastric fluid, and pH 6.8 intestinal fluid, and in vivo drug bioavailabilities in healthy human volunteers. Acetaminophen was used as the model drug. The m-HPMC tablets were prepared using a wet granulation method followed by direct compression. Release profiles and swelling rates of m-HPMC tablets were found to be highly influenced by the types and amounts of pharmaceutical excipients incorporated. Starch 1500 (PrejelR) and sodium lauryl sulfate (SLS) played a key role in determining the dissolution rate of m-HPMC tablets. Additional excipients, i.e., microcrystalline cellulose (AvicelR PH101) and NaH2PO4 were used to tune the release profiles of m-HPMC tablets. The effect of pharmaceutical excipients on drug release from HPMC-based matrix tablets was found to be mainly due to a change in hydrophilic gel expansion and on physical interactions between the drug and HPMC. The optimized m-HPMC tablet with a balanced ratio of PrejelR, SLS, AvicelR PH101, and NaH2PO4 in the formulation showed dual release profiles in water, pH 1.2 gastric fluid, and pH 6.8 intestinal fluid in vitro. Dual release was defined as immediate drug release within few minutes followed by extended release over 8 h. The similarity factors of m-HPMC tablets and bi-layered TylenolR ER tablets were 79.8, 66.1, and 82.7 in water, gastric fluid and intestinal fluid, respectively, indicating the equivalence of the two release profiles. No significant in vivo bioavailability differences were observed in healthy human volunteers. The developed m-HPMC tablet with dual release characteristics can be easily prepared using a conventional high-speed tablet machine and could provide an alternative to commercially available bilayered TylenolR ER tablets.

**Prathvipathy R. et al**[15] used pseudoephedrine hydrochloride as a model drug to prepare direct compression sustained release tablets with ethylcellulose (EC). Initially, different viscosity grades of EC were studied. An increase in viscosity grade resulted in a marginal to moderate increase in the release rate. However, lower viscosity grades produced harder tablets. The highly compressible 10 cp grade was used to study the effect of drug loading, particle size, compression force, and magnesium stearate concentration on release properties. The rate of drug release decreased with a decrease in the drug concentration in the matrix. Except for tablets prepared with EC having a particle size fraction 250-420 and 177-250/xm, drug release up to 80% exhibited a square root of time dependency and tablets remained intact during dissolution. Tablets prepared with either the EC 250-420 or 177-250 Izm particle size fraction eroded. The square of the release rate is proportional to drug concentration in the matrix, indicating that the release of pseudoephedrine hydrochloride from EC matrices is primarily matrix-controlled.

**Verhoeven J. et al**[16] used microporous polypropylene powder (Accurel) for the formulation of a matrix tablet of furosemide. The formulation of the matrix tablet was based on known absorption data of furosemide in the literature. Six male volunteers participated in an in-vivo study, in which they received a 60 mg matrix tablet, a 60 mg oral solution and an i.v. bolus injection of 40 mg furosemide. The bioavailability of furosemide calculated from the AUCs and from numerical deconvolution was resp. 76.6 f 14.9 and 73.8 + 17.5% ($P < 0.05$) for the oral solution and 40.0 rt 17.8 and 37.9 f 19.4% ($P < 0.05$) for the matrix tablet. Peak diuretic effects were similar to the effects of a regular furosemide tablet. The high diuretic efficacy of the matrix tablet is remarkable (compared to the oral solution and the i.v. injection) although the bioavailability is relatively low. The possibility of controlled-release dosing for furosemide has been discussed from a pharmacological point of view. The pharmacodynamic response was studied in relation to the furosemide concentrations in the urine.

## 3.2 Literature review on functional coating

**Lee Beom-Jin et al**[17] formulated a dual drug-loaded hydroxypropylmethylcellulose (HPMC) matrix tablet simultaneously containing drug in inner tablet core and outer coated layer using drug-containing aqueous-based polymeric Eudragit® RS30D dispersions. Effects of coating levels, drug loadings in outer layers, amount and type of five plasticizers and talc concentration on the release characteristics were evaluated on the characteristics in simulated gastric fluid for 2 h followed by a study in intestinal fluids. Melatonin (MT) was selected as a model drug. The surface morphology of dual drug-loaded HPMC tablets using scanning electron microscope (SEM) was smooth, showing the distinct coated layer with about 75-μm coating thickness at the 15% coating level. Unlike the uncoated and conventionally coated HPMC tablet, the dual drug-loaded HPMC matrix tablet gave a biphasic linear release, showing a zero-order for 4 h (first) followed by another zero-order release when fitted using linear regression (r2=0.99). As the coating levels (15, 25%) increased, the release rate was further decreased. The biphasic release profiles of dual drug-loaded HPMC matrix tablet was unchanged except when 25% coating level containing 0.5% drug concentration was applied. As the drug concentration in polymeric coating dispersion increased (0.25–1.0%), the amount of drug released increased. The time for the first linear release was also advanced. However, the biphasic release pattern was not changed. The biphasic release profiles of dual drug-loaded HPMC matrix tablet were highly modified, depending on the amount and type of five plasticizers. Talc (10–30%) in coating dispersion as an anti-sticking material did not affect the release profiles. The current dual drug-loaded HPMC matrix tablet, showing biphasic release profiles may provide an alternative to deliver drugs with circadian rhythmic behaviors in the body but needs to be further validated in future in human studies. The dual drug-loaded coating method is also interesting for the modified release of poorly water-soluble drugs because solubilizers and other additives can be added in drug-containing polymeric coating dispersions.

**Lin Wen-Jen et al**[18] develop a microporous-controlled delivery system for theophylline via coating a blend of PCL and PEG on the surface of tablets, where PCL was the major component of film coating material and PEG was acted as a leachable pore-forming agent when contacting with an aqueous medium. The influences of the type of solvent, the amount of PEG, and the thickness of films on the mechanical and thermal properties of coating films and drug release performance were investigated. The DSC thermograms and FTIR spectra indicated both PCL and PEG remained independently in the blended films. The mechanical data showed a decrease tendency as increase in the amount of PEG in the blends due to highly crystalline character of PEG. Slower evaporation rate of acetone than dichloromethane enhanced phase separation between PCL and PEG during film formation, and resulted in the pore size in films prepared from acetone larger than from dichloromethane. The release rate of coated tablets were increased by increasing the amount of pore-forming agent, and the corresponding values from tablets coated in dichloromethane were less than in acetone. Much denser structure and smaller pore size of films formed from dichloromethane contributed to this result. The release of drug from tablets coated in acetone showed a profile more close to a zero-order constant release profile. The penetration of water into drug core played an important role in influencing drug release pattern.

**Fan T.Y. et al**[19] develop new pulsatile release tablets, which can suppress drug release in stomach and release the drug rapidly after a predetermined lag time of about 3 h in intestine, the use of tablets with ethylcellulose / Eudragit L as a coating film and cross-linked polyvinylpyrrolidone in the core tablets was investigated. The release of diltiazem hydrochloride (DIL) as a model drug in the core tablets was investigated in vitro. The lag time (*t* ) was prolonged with an increase of the coating 10 level, whereas the drug release rate was almost constant, irrespective of the coating level. The water-uptake study and electron microscope photographs suggested the mechanism of pulsatile release of drug. Pulsatile release tablets containing 60 mg DIL with 4.4 h of lag time (*t* ) in vitro were administrated to eight volunteers. The mean plasma concentration curves 10 showed 4.9 h of lag time (*t* ), 8.0 h of time to maximum concentration (*t* ) and 3.1 h of time between *t* and *t* (*t* ) lag max max lag psi in vivo. Relative bioavailability was 1.05 for pulsatile release tablets compared to conventional tablets.

**During T. et al**[20] highlights the development of an Aquarius SRX coating system, an ethylcellulose (EC) based coating system suitable for the application of swellable matrix cores loaded with highly soluble drugs. Venlafaxine HCl and Drug PH0168 were chosen as model drugs. The new coating system extends the utility of matrix system to the controlled delivery of highly soluble actives over extended periods of time and according to a variety of predetermined release rates. A controlled release coating suitable for application to swellable matrix cores that enables release duration of 15 to 24 hours for Venlafaxine HCl & Drug PH0168 without burst effect was developed.

**Tiwari Sandip B. et al**[21] studied the effect of concentration of hydrophilic (hy-droxypropyl methylcellulose [HPMC]) and hydropho-bic polymers (hydrogenated castor oil [HCO], ethylcel-lulose) on the release rate of tramadol. Hy-drophilic matrix tablets were prepared by wet granula-tion technique, while hydrophobic (wax) matrix tablets were prepared by melt granulation technique and in vitro dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. Hydro-phobic matrix tablets resulted in sustained in vitro drug release (>20 hours) as compared with hydrophilic ma-trix tablets (<14 hours). The presence of ethylcellulose in either of the matrix systems prolonged the release rate of the drug. Tablets prepared by combination of hydrophilic and hydrophobic polymers failed to pro-long the drug release beyond 12 hours. The effect of ethylcellulose coating (Surelease) and the presence of lactose and HPMC in the coating composition on the drug release was also investigated. Hydrophobic matrix tablets prepared using HCO were found to be best suited for modulating the delivery of the highly water-soluble drug, tramadol hydrochloride.

**Bodmeier Roland et al**[22] obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing/decreasing release rates with time) with hydroxypropyl methylcellulose (HPMC) compression-coated tablets. Drugs of varying solubility (carbamazepine, acetaminophen, propranolol HCl and chlorpheniramine maleate) were incorporated into the tablet core in order to evaluate the flexibility/ limitations of the compression-coated system. The HPMC-compression-coating resulted in release profiles with a distinct lag time followed by different release phases primarily determined by the drug solubility. Carbamazepine, a water-insoluble drug, was released in a pulsatile fashion after a lag time only after erosion of the HPMC compression-coat, while the more soluble drugs were released in a sigmoidal

fashion by diffusion through the gel prior to erosion. With carbamazepine, increasing the molecular weight of HPMC significantly increased the lag time because of the erosion-based release mechanism, while, in contrast, molecular weight did not affect the release of the more soluble drugs. The lag-time and the release rate could also be well controlled by varying the HPMC amount in and the thickness of the compression-coating. A pulsatile release could also be achieved for water-soluble drugs by introducing an enteric polymer coating between the drug core and the HPMC compression-coating. This novel concept of introducing an enteric subcoating eliminated drug diffusion through the gelled HPMC layer prior to its erosion. Incorporating drug in the compression-coating in addition to the tablet core in varying ratios resulted in release profiles with increasing, decreasing or constant release rates. In conclusion, a versatile single-unit delivery system for a wide range of drugs with great flexibility in release profiles was presented.

### 4.1. Material & Equipment information:

**Table6: Material information:**

| Material | Use |
|---|---|
| Drug PH0168 | Active Pharmaceutical Ingredient |
| Hypromellose(K100M premium CR) | Rate controlling polymer |
| Carmellose sodium(Blanose CMC 7H4XF Pharm) | Tablet binder |
| Microcrystalline cellulose(Avicel PH101) | Diluent |
| Ethyl cellulose (EC N22 Pharm) | Binder |
| Isopropyl alcohol | Solvent |
| Dichloromethane | Solvent |
| Colloidal anhydrous silica (Aerosil 200) | Lubricant |
| Magnesium Stearate | Anti adherent agent |
| Ethyl cellulose 10 CPS | Coating polymer |
| HPMC E3 LV | Coating polymer |
| PEG 4000 | Plasticizer |
| Isopropyl alcohol | Solvent |
| Dichloromethane | Solvent |

**Table7: Equipment information**

| Equipment | Company name | Model no. |
|---|---|---|
| Electronic weighing balance | Mettler Toledo | AB 204-5 |
| Fribilitor (USP) | Electrolab | EF-1W |
| Hardness tester | DR. Schleniger | 8M |
| Vernier calliper | Mitutoyo | CD-8 |
| Halogen moisture analyser | Mettler Toledo | HR 73 |
| Vibrating shifter | Ganson limted | - |
| Rapid mixer granulator | Saral | - |
| 16 station punching machine | Cadmach | CMD3-16/MT |
| Conventional coating machine | Erweka | AR-400 |
| Stirrer | Remi motor | RQ-123 |
| Sieve shaker | Cisa® | RP-09 |
| Mesh | Cisa® | - |

### 4.2.1. Drug profile

**Table8: Drug Profile**

| ATTRIBUTE | DESCRIPTION |
|---|---|
| Drug | Drug PH0168 |
| Category | Antidiabetic drug |
| BCS classification | Class-III drug |
| Solubility | Freely soluble as HCl salt, Freely soluble in water, Soluble in ethanol, Practically insoluble in ether, chloroform & acetone |
| Food effect | When 1000 mg Drug-PH0168 prolonged release tablet is administered in Fed condition the AUC is increased by 77% & no effect on $C_{max}$ & $T_{max.}$ |
| Absorption | Following single oral administration of 100 mg prolonged release tablet, a mean plasma conc. of 1195 ng/ml achieved within a median value of 5 hrs and range of 4-12 hrs. |
| Distribution | No plasma protein binding. Mean $V_d$ is ranged between 63-276 L |
| Metabolism | Excreted unchanged in urine |
| Elimination | Elimination half life of about 6.5 hours |
| Melting Range | 222˚ C to 224˚C |
| Bioavailability | 50 to 60 % |
| Particle size | 92% (Not less than 50% should pass through 230 mesh)<br>96% (Not less than 90% should pass through 100 mesh) |

### 4.2.2 Drug-excipient Compatibility Studies

Conventional pharmaceutical excipients at typical levels were selected for the manufacture of Drug PH0168 Extended Release Tablets USP 750 mg and 500 mg.

Drug-excipient compatibility studies were performed using Drug PH0168 with individual excipients. The blends were stored at 40˚ C/75% RH sample after 1 month time period.

**Table9: Drug-excipietn compatibility study using drug PH0168 with individual excipient**

D- Drug pH0168 ND- Not Detected

AII- Any Individual Impurity TI- Total Impurity

| Sr. No. | DRUG + excipient | RATIO | RESULTS (%) | | | RESULTS (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | INITIAL | | | 4TH WEEK(40˚C±2˚C, 75±5% RH) | | |
| | | | AII | TI | Water | AII | TI | water |
| 1. | D | | 0.012 | 0.029 | 0.06 | 0.019 | 0.034 | 0.14 |
| 2. | D+ Hypromellose | 5 : 2 | ND | ND | 2.2 | 0.015 | 0.024 | 1.68 |
| 3. | D+ Carboxymethyl cellulose sodium | 25 : 1 | 0.013 | 0.013 | 0.45 | 0.017 | 0.024 | 1.68 |
| 4. | D+ Microcrystalline cellulose | 25 : 1 | ND | ND | 0.31 | 0.015 | 0.022 | 0.68 |
| 5. | D+Ethylcellulose | 10 : 1 | 0.012 | 0.012 | 0.41 | 0.019 | 0.030 | 0.33 |
| 6. | D+ Collidal Silicon Dioxide | 25 : 1 | ND | ND | 0.33 | 0.018 | 0.028 | 0.34 |
| 7. | D+ Magnesium stearate | 25 : 1 | ND | ND | 0.26 | 0.017 | 0.042 | 0.47 |
| 8. | D+ Placebo mixture | 1 : 1 | ND | ND | 3.87 | 0.014 | 0.024 | 4.58 |

**Observation:**

No significant changes were observed in physical, chemical properties and impurity profile of Drug-PH0168 with all excipients studied. There is increase in the water content compared to initial value at 40˚C±2˚C, 75±5% RH which indicates the hygroscopicity of material.

**Conclusion:**

Based on the data, it is concluded that DrugPH-0168 has no significant incompatibility with the excipients under study.

### 4.3 Innovator product characterization

#### 4.3.1 Table10: Physical characterization of innovator product

| Sr. No. | Strength→ | 500 mg | 750 mg | 1000 mg |
|---|---|---|---|---|
| 1. | Brand name | - | | |
| 2. | Generic name | Drug0168 prolonged release tablet | | |
| 3. | Label claim | Each tablet contain 500 mg of Drug 0168 | Each tablet contain 750 mg of Drug 0168 | Each tablet contain 1000 mg of Drug 0168 |
| 4. | Dosage form | Prolonged Release Tablet | | |
| 5. | Inactive ingredients | Mg. stearate, Carmellose sodium, Hypromellose, MCC | Mg. stearate, Hypromellose, Sodium CMC | Carmellose sodium, Hypromellose, Mg. stearate |
| 6. | Tablet description | White to off white, capsule shaped, biconvex tablet, debosed on one side with '500' | White capsule shaped biconvex tablet, debossed on one side with '750' and on the other side with 'Merck' | White to off white capsule shaped, biconvex tablet, debossed on one side with 'SR1000' |
| 7. | Tablet shape | Capsule shaped | | |
| 8. | Tablet dimensions | 19.15 × 9.35 mm | 19.15 × 9.35 mm | 22.2 × 10.6 mm |
| 9. | Embossing details | Debossed on one side with '500' | Debossed on one side with '750' and on the other side with 'Merck' | Debossed on one side with 'SR1000' |
| 10. | Avg. Weight (mg) | 1037.4 | 1095.7 | 1456.8 |

### 4.3.2 Dissolution profile of innovator product

**Table11: Dissoloution study of innovator is done under following condition:**

| | |
|---|---|
| Apparatus | USP type I |
| Volume of medium | 900 ml, pH 6.8 buffer |
| Temperature | 37±0.5˚C |
| Paddle speed | 100 RPM |

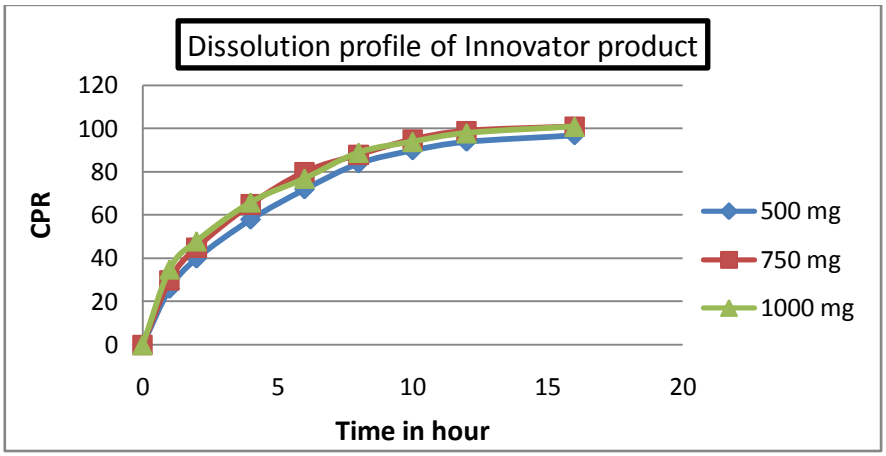



**Figure3: Dissolution profile of Innovator product**

### 4.3.3 Multimedia dissolution profile of innovator product

Dissolution profile of innovator product in different media performed on one strength like 0.1 N HCl, pH 4.5 acetate buffer, Water using USP type I paddle, 900 ml, at 100 RPM.A sample of solution was withdrawn from dissolution apparatus at different time periods and sample were replaced with fresh dissolution medium. Cumulative percentage drug release was calculated using an equation from a standard curve.

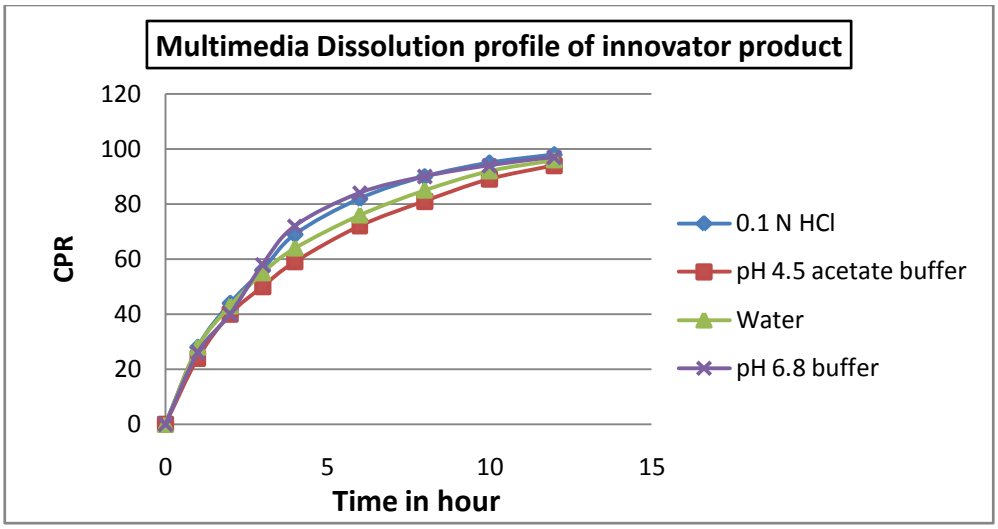



**Figure4: Multimedia Dissolution profile of Innovator product**

**Conclusion**: From the dissolution profile of innovator product in different media it can be concluded that dissolution profile is independent of pH of media. Thus dissolution study was done only in pH 6.8 buffer.

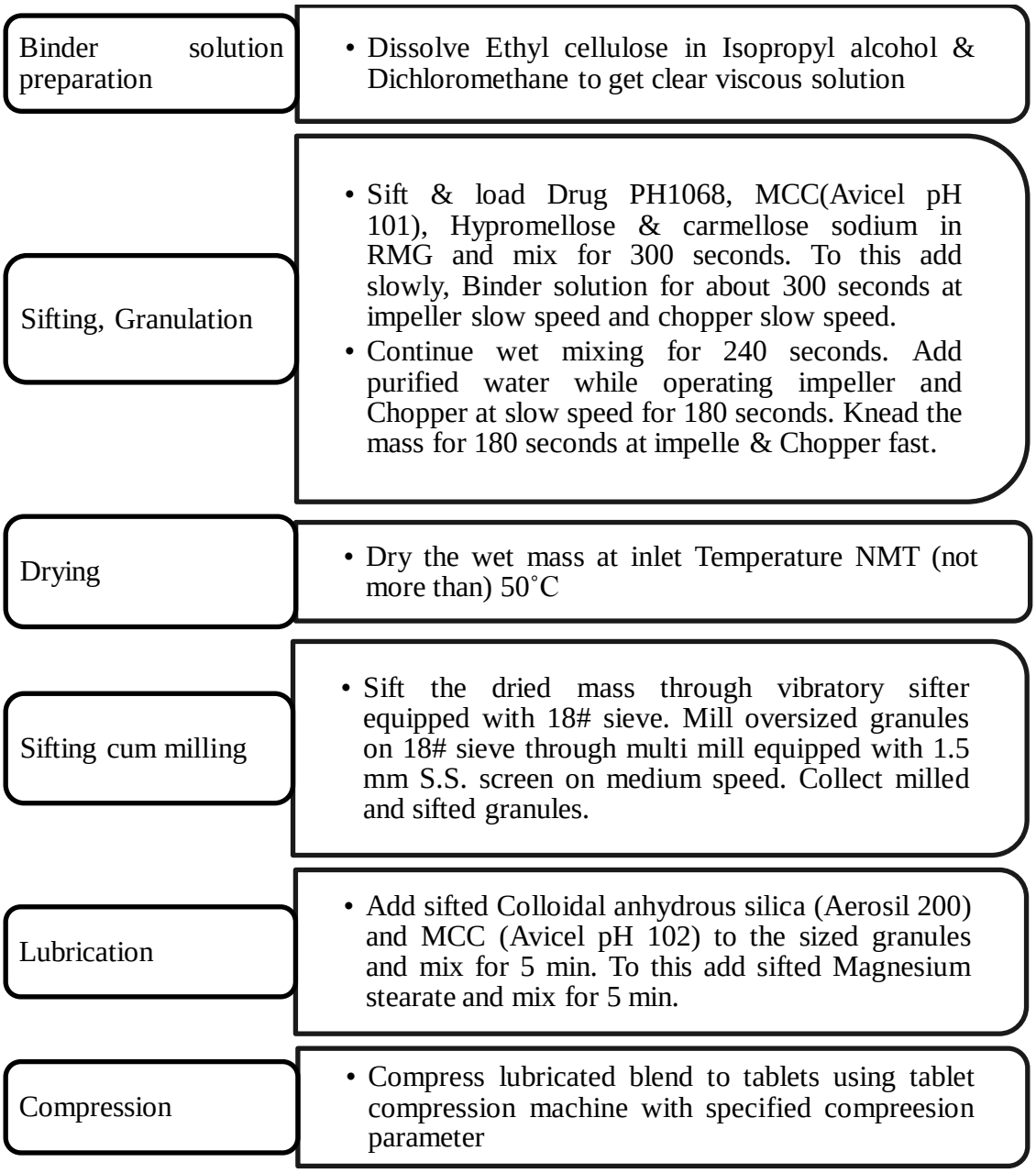
### 4.4. Method of preparation & evaluation of Control release tablet of Drug PH1068.

#### 4.4.1Method of preparation is divided in to two steps.

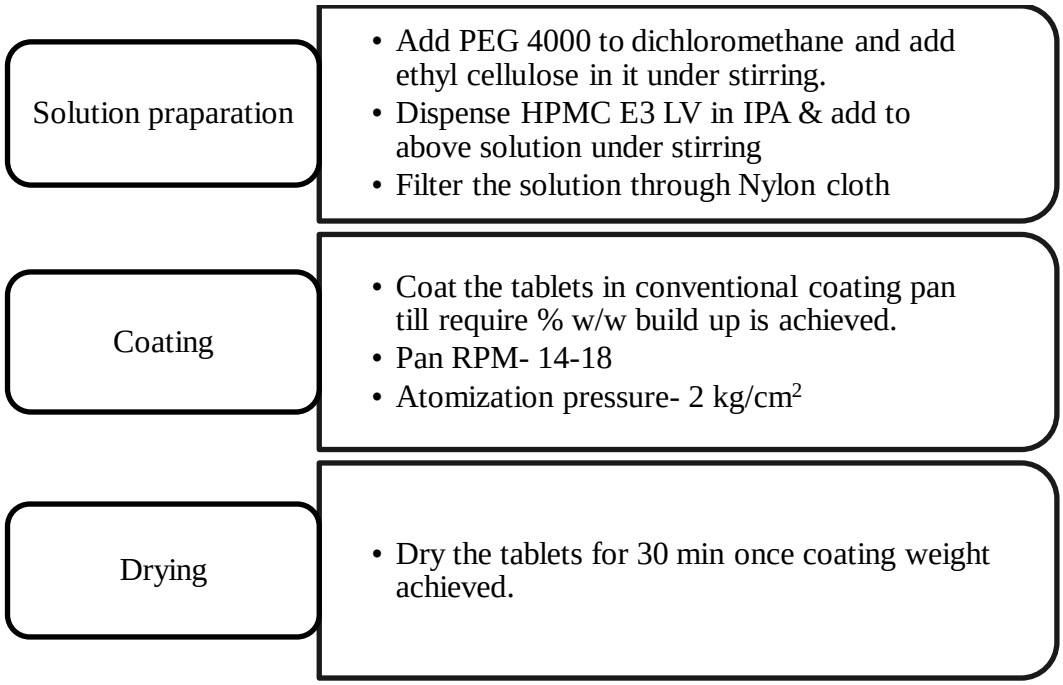
4.4.1.1 Preparation of matrix tablet of Drug pH0168

4.4.1.2 Functional coating on matrix tablet.

**4.4.1.1 Process flow Diagram for preparation of matrix tablet of drug PH0168**



**4.4.1.2 Process flow Diagram for functional coating on matrix tablet of drug PH0168**



### 4.4.2 Evaluation parameter:

- For uncoated Tablets.
  - **Uniformity of weight**

    The weight variation of the tablets was carried out by taking the Average weight of 20 tablets. As per USP, weight individually 20 whole tablets, and calculate the average weight. The requirement were met if the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed in the accompanying table and no tablet differs in weight by more than double that percentage.

| Average weight of tablet(mg) | Percentage difference |
|---|---|
| 130 or less | 10 |
| From 130 through 324 | 7.5 |
| More than 324 | 5 |

  - **Thickness**

    The thickness of the tablet was measured by using digital vernier scale. Thickness was expressed in mm.

  - **Hardness (tablet breaking force)**

    Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users. Manufacturing processes such as coating, packaging and printing can involve considerable stresses, which the tablet must be able to withstand. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured.

    Hardness was measured by using SCHLENGER hardness tester.

  - **Friability**

    For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 gm. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets.

    The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weighed.

If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

- For coated tablet
  - **Drug content**

    Drug content was measured by specific analytical method.

  - **In-vitro dissolution studies**

    In-vitro dissolution studies were carried out by USP type-I apparatus at 100RPM using pH 6.8 buffer, 900ml, as Dissolution media. A sample of solution was withdrawn from dissolution apparatus at different time periods and sample were replaced with fresh dissolution medium. Cumulative percentage drug release was calculated using an equation from a standard curve.

| | |
|---|---|
| Apparatus | USP type I |
| Volume of medium | 900 ml, pH 6.8 buffer |
| Temperature | 37±0.5˚C |
| Paddle speed | 100 RPM |

## 4.5 Experimental Trials

### 4.5.1 Optimization of core matrix tablet

**In this trial only matrix tablet was prepared by using common blend for three of the strength as following**

**Table14: Formula for matrix tablet for batch A1, B1 & C1**

| Sr. No. | Ingredients | Strength | | | % w/w |
|---|---|---|---|---|---|
| | | Batch A1 | Batch B1 | Batch C1 | |
| | | 500 mg | 750 mg | 1000 mg | |
| 1. | Drug PH0168 | 500 | 750 | 1000 | 62.50 |
| 2. | Hypromellose(K100M premium CR) | 211.33 | 317 | 422.66 | 26.42 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 10 | 15 | 20 | 1.25 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 20 | 30 | 40 | 2.50 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 50.67 | 76.00 | 101.34 | 6.33 |
| 6. | Anhydrous Ethanol | q.s. | q.s. | q.s. | - |
| 7. | Purified Water | q.s. | q.s. | q.s. | - |
| 8. | Colloidal anhydrous silica (Aerosil 200) | 3 | 4.5 | 6 | 0.50 |
| 9. | Mg. Stearate | 3 | 4.5 | 6 | 0.50 |
| | CORE TABLET WEIGHT | 800 mg | 1200 mg | 1600 mg | 100% |

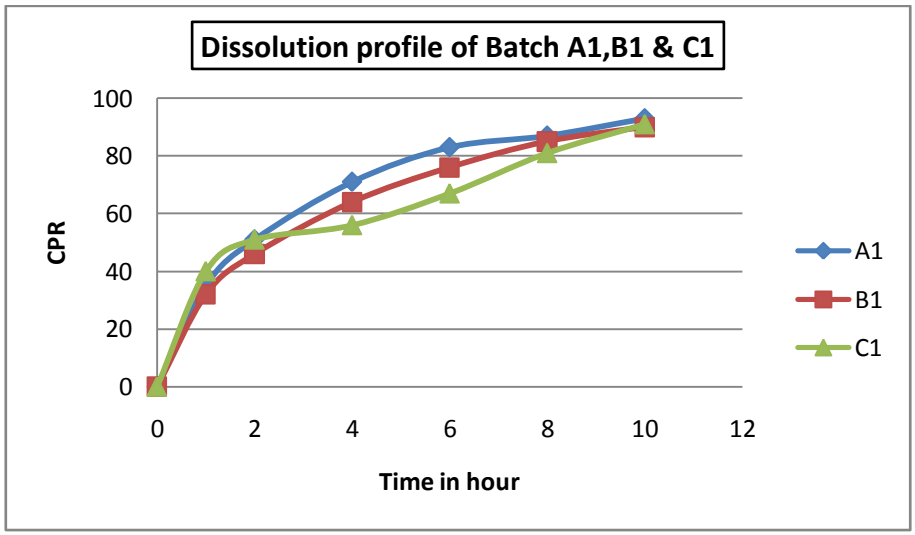



**Figure5: Dissolution profile of Batch A1,B1 and C1**

**Conclusion**: By preparing the matrix tablet for all strength total weight of tablet for the 1000 mg strength is 1600 mg. It is difficult to swallow this tablet hence it was found necessary to reduce tablet weight & for getting desired dissolution release profile, functional coating was carried out on core tablets i.e. with core-coat technology.

**Table16: Optimized formula for core tablet (500 mg)**

| Sr. No. | Ingredients | Batch A2 (500 mg) | % w/w |
|---|---|---|---|
| 1. | Drug PH0168 | 500 | 78.37 |
| 2. | Hypromellose(K100M premium CR) | 60 | 9.40 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 12 | 1.88 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 35 | 5.48 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 15 | 2.35 |
| 6. | IPA | q.s. | - |
| 7. | Dichloromethane | q.s. | - |
| 8. | Microcrystalline cellulose(Avicel PH102) | 10 | 1.57 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 3 | 0.47 |
| 10. | Mg. Stearate | 3 | 0.47 |
| | CORE TABLET WEIGHT | 638 mg | 100% |

**Table17: Optimized formula for core tablet (750 mg)**

| Sr. No. | Ingredients | Batch B2 (750 mg) | % w/w |
|---|---|---|---|
| 1. | Drug PH0168 | 750 | 78.37 |
| 2. | Hypromellose(K100M premium CR) | 90 | 9.40 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 18 | 1.88 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 52.5 | 5.48 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 22.5 | 2.35 |
| 6. | IPA | q.s. | - |
| 7. | Dichloromethane | q.s. | - |
| 8. | Microcrystalline cellulose(Avicel PH102) | 15 | 1.57 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 4.5 | 0.47 |
| 10. | Mg. Stearate | 4.5 | 0.47 |
| | CORE TABLET WEIGHT | 957 mg | 100% |

**Table18: Optimized formula for core tablet (1000 mg)**

| Sr. No. | Ingredients | Batch C2 (1000 mg) | % w/w |
|---|---|---|---|
| 1. | Drug PH0168 | 1000 | 78.37 |
| 2. | Hypromellose(K100M premium CR) | 120 | 9.40 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 24 | 1.88 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 70 | 5.48 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 30 | 2.35 |
| 6. | IPA | q.s. | - |
| 7. | Dichloromethane | q.s. | - |
| 8. | Microcrystalline cellulose(Avicel PH102) | 20 | 1.57 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 6 | 0.47 |
| 10. | Mg. Stearate | 6 | 0.47 |
| | CORE TABLET WEIGHT | 1276 mg | 100% |

### 4.5.2 Optimization of functional coating

Now coating on matrix tablet is done by using polymer blend of Ethyl cellulose (EC) and Hydroxypropyl methyl cellulose (HPMC) and optimization of ratio of Ethyl cellulose and HPMC was carried out in further experimental trials.

#### 4.5.2.1 Optimization ratio of EC: HPMC in functional coating

Optimization of the ratio of EC: HPMC for 500 mg strength and ratio of EC: HPMC is varying to 50:50, 55:45 and 60:40. Coating is done 4%w/w on all batches.

**Table19:Optimization ratio of EC: HPMC in functional coating**

| Sr. No. | Ingredients | Batch(Quantity per tablet) | | |
|---|---|---|---|---|
| | | A3 | B3 | C3 |
| | | 500 mg (50:50) | 500 mg (55:45) | 500 mg (60:40) |
| 1. | Drug PH0168 | 500 | 500 | 500 |
| 2. | Hypromellose(K100M premium CR) | 60 | 60 | 60 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 12 | 12 | 12 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 35 | 35 | 35 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 15 | 15 | 15 |
| 6. | IPA | q.s. | q.s. | q.s. |
| 7. | Dichloromethane | q.s. | q.s. | q.s. |
| 8. | Microcrystalline cellulose(Avicel PH102) | 10 | 10 | 10 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 3 | 3 | 3 |
| 10. | Mg. Stearate | 3 | 3 | 3 |
| | CORE TABLET WEIGHT | 638 | 638 | 638 |
| Coating (4%) | | | | |
| 11. | Ethyl cellulose 10 CPS | 12.26 | 13.49 | 14.71 |
| 12. | HPMC E3 LV | 12.26 | 11.03 | 9.81 |
| 13. | PEG 4000 | 1 | 1 | 1 |
| 14. | Isopropyl alcohol | q.s. | q.s. | q.s. |
| 15. | Dichloromethane | q.s. | q.s. | q.s. |
| | TOTAL WEIGHT | 663.52 | 663.52 | 663.52 |

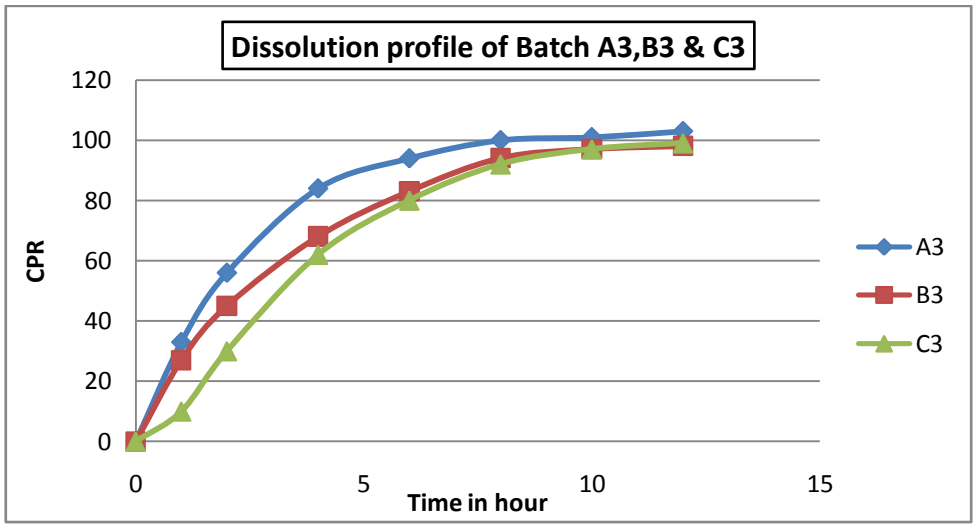



**Figure6: Dissolution profile of Batch A3,B3 & C3**

**Conclusion**: For functional coating, Ethyl cellulose: HPMC ration choosen was 55:45 (B3) based on scientific understanding and suppliers recommendations to get desired release profile. Next trials were planned to compare release data at different coating percentage.

### 4.5.2.2 Optimization of percentage of coating on batch A2 (500 mg)

Optimization of percentage of coating on tablet of batch A2 was done by 3%, 4% and 5% coating and dissolution profile was obtained. Ratio of EC: HPMC used was 55:45.

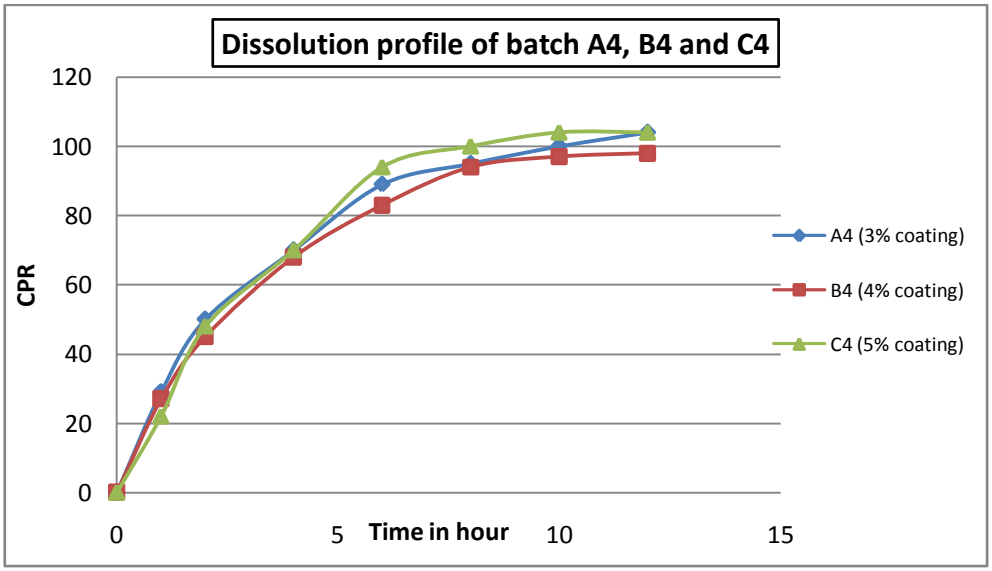



**Figure7: Dissolution profile of batch A4, B4 and C4**

**Conclusion:** Based on the dissolution profile and similarity factor (F2) comparison from batch A4, B4 and C4, Batch B4 (4% coating) was optimized.

### 4.5.2.3 Optimization of percentage of coating on batch B2 (750 mg)

Optimization of percentage of coating on tablet of batch B2 was done by coating 3%, 4% and 5% and dissolution profile was obtained. Ratio of EC: HPMC used was 55:45.

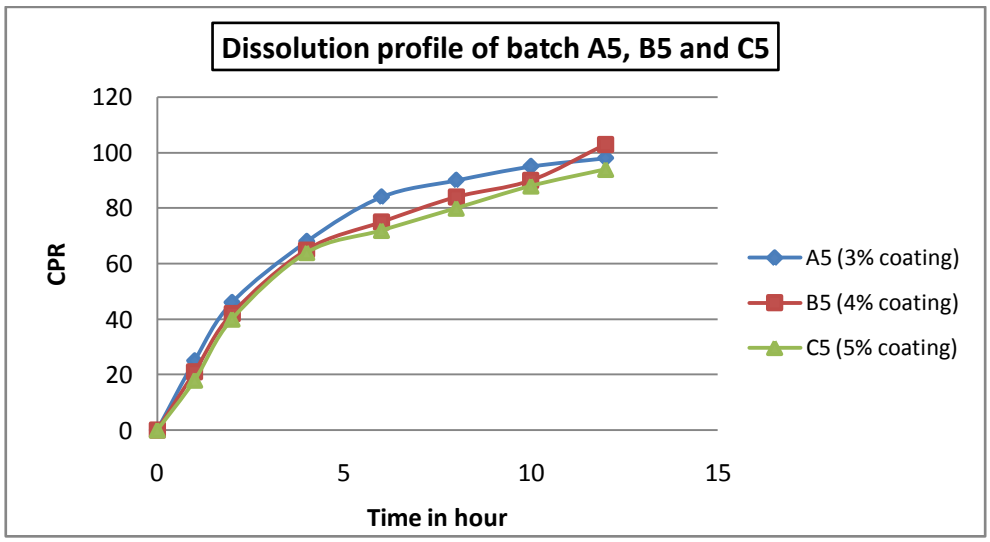



**Figure8: Dissolution profile of batch A5, B5 and C5**

**Conclusion:** Based on the dissolution profile and similarity factor (F2) comparison between batch A5, B5 and C5, Batch A5 (3% coating) was optimized.

### 4.5.2.3 Optimization of percentage of coating on batch C2 (1000 mg)

Optimization of percentage of coating on tablet of batch C2 is done by 3%, 4% and 5% coating and dissolution profile was obtained. Ratio of EC: HPMC used was 55:45.

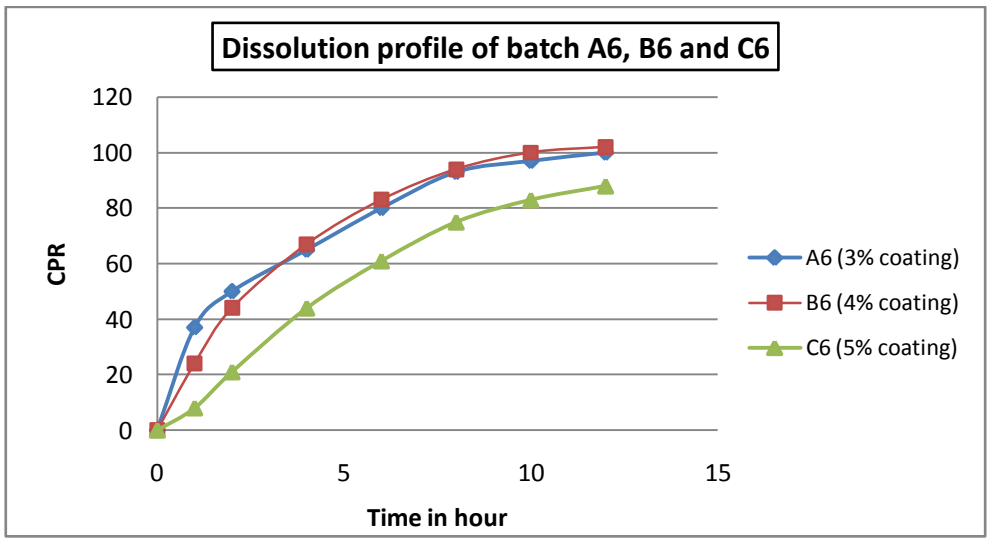



**Figure9: Dissolution profile of batch A6, B6 and C6**

**Conclusion:** Based on the dissolution profile and similarity factor (F2) comparison between batch A6, B6 and C6, Batch A6 (3% coating) was optimized.

## Final Formula for optimized batches

**Table24: Optimized batch of 500 mg strength**

| Sr. No. | Ingredients | (500 mg) | % w/w |
|---|---|---|---|
| 1. | Drug PH0168 | 500 | 75.35 |
| 2. | Hypromellose(K100M premium CR) | 60 | 9.04 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 12 | 1.81 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 35 | 5.27 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 15 | 2.26 |
| 6. | Isopropyl Alcohol | q.s. | - |
| 7. | Dichloromethane | q.s. | - |
| 8. | Microcrystalline cellulose(Avicel PH102) | 10 | 1.51 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 3 | 0.45 |
| 10. | Magnesium Stearate | 3 | 0.45 |
| | CORE TABLET WEIGHT | 638 | - |
| COATING (Ratio of EC to HPMC 55:45) | | 4% coating | |
| 11. | Ethyl cellulose 10 CPS | 14.04 | 2.03 |
| 12. | HPMC E3 LV | 11.48 | 1.66 |
| 13. | PEG 4000 | 1 | 0.15 |
| 14. | Isopropyl alcohol | q.s. | - |
| 15. | Dichloromethane | q.s. | - |
| | TOTAL WEIGHT | 664.52 | 100% |

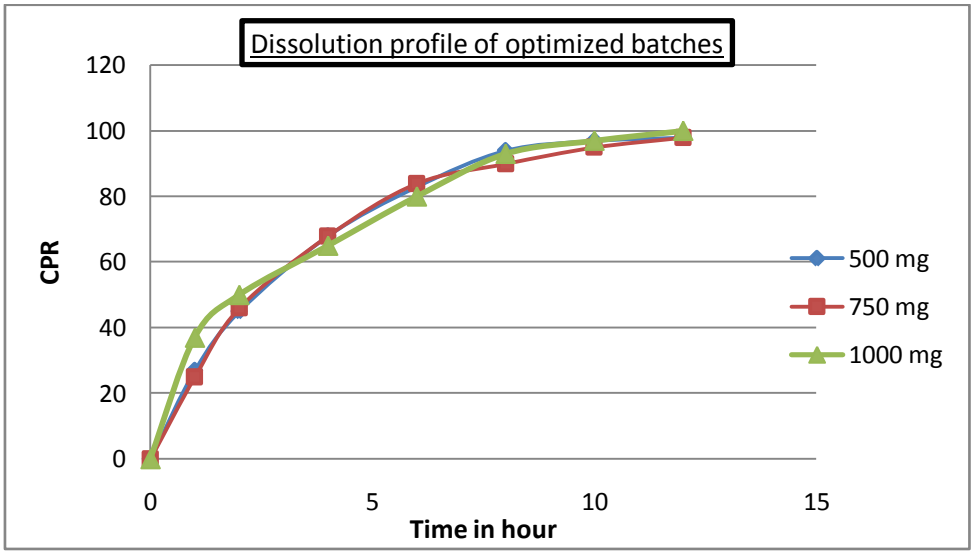
**Table25: Optimized batch of 750 mg strength**

| Sr. No. | Ingredients | (750 mg) | % w/w |
|---|---|---|---|
| 1. | Drug PH0168 | 750 | 76.08 |
| 2. | Hypromellose(K100M premium CR) | 90 | 9.13 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 18 | 1.82 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 52.5 | 5.32 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 22.5 | 2.28 |
| 6. | Isopropyl Alcohol | q.s. | - |
| 7. | Dichloromethane | q.s. | - |
| 8. | Microcrystalline cellulose(Avicel PH102) | 15 | 1.52 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 4.5 | 0.45 |
| 10. | Magnesium Stearate | 4.5 | 0.45 |
| | CORE TABLET WEIGHT | 957 | - |
| COATING (Ratio of EC to HPMC 55:45) | | 3% coating | |
| 11. | Ethyl cellulose 10 CPS | 14.97 | 1.51 |
| 12. | HPMC E3 LV | 12.24 | 1.24 |
| 13. | PEG 4000 | 1.5 | 0.15 |
| 14. | Isopropyl alcohol | q.s. | - |
| 15. | Dichloromethane | q.s. | - |
| | TOTAL WEIGHT | 985.71 | 100% |

**Table26: Optimized batch of 1000 mg strength**

| Sr. No. | Ingredients | (1000 mg) | % w/w |
|---|---|---|---|
| 1. | Drug PH0168 | 1000 | 76.09 |
| 2. | Hypromellose(K100M premium CR) | 120 | 9.13 |
| 3. | Carmellose sodium(Blanose CMC 7H4XF Pharm) | 24 | 1.83 |
| 4. | Microcrystalline cellulose(Avicel PH101) | 70 | 5.33 |
| 5. | Ethyl cellulose (EC N22 Pharm) | 30 | 2.28 |
| 6. | Isopropyl Alcohol | q.s. | - |
| 7. | Dichloromethane | q.s. | - |
| 8. | Microcrystalline cellulose(Avicel PH102) | 20 | 1.49 |
| 9. | Colloidal anhydrous silica (Aerosil 200) | 6 | 0.46 |
| 10. | Magnesium Stearate | 6 | 0.46 |
| | CORE TABLET WEIGHT | 1276 | - |
| COATING (Ratio of EC to HPMC 55:45) | | 3% coating | |
| 11. | Ethyl cellulose 10 CPS | 19.95 | 1.51 |
| 12. | HPMC E3 LV | 16.33 | 1.24 |
| 13. | PEG 4000 | 2 | 0.15 |
| 14. | Isopropyl alcohol | q.s. | - |
| 15. | Dichloromethane | q.s. | - |
| | TOTAL WEIGHT | 1314.28 | 100% |

**Figure10: Dissolution profile of optimized batches**



The aim of present investigation was to develop controlled release coating system (Core-coat technology) for highly soluble drug matrix tablets of Drug PH0168.

The following strategy was adopted in present investigation

- To develop a controlled release coating system for highly soluble drug matrix tablets of an anti-diabetic category.
- Optimization of dissolution profile in-line with UK innovator's formulation.

The innovator's formulation was present in 500, 750, and 1000 mg strengths. To develop generic product, it is essential to match dissolution profile with respect to similarity factor (f2 values). By core-coat technology, the attempts was carried out to get desired release profile of all strengths with similarity factor greater than 50.

**Preformulation Studies:**

All physical and chemical parameters of Drug PH0168 were similar to the reported parameters.

Excipients used in formulations are compatible with the Drug PH0168.

**Optimization of core matrix tablet formulation:**

Hypromellose(K100M premium CR) were selected as release retarding polymers. In this trial only matrix tablet was prepared by using common blend for three different strength (500 mg, 750 mg, 1000 mg).

It is necessary to reduce the tablet weight & for getting desired dissolution release profile, functional coating was carried out on core tablets i.e. with core-coat technology.

**Optimization of Functional coating:**

Now coating on matrix tablet was done by using polymer blend of Ethyl cellulose (EC) and Hydroxypropyl methyl cellulose (HPMC) and optimization of ratio of Ethyl cellulose and HPMC was carried out in further experimental trials.

Optimization ratio of EC: HPMC in functional coating was found as follows:

Optimization of the ratio of EC: HPMC for 500 mg strength and ratio of EC: HPMC is varying to 50:50, 55:45 and 60:40. Coating was done by 4%w/w.

Optimization of percentage of coating:

Optimization of percentage of coating is done by varying the percentage coating 3%, 4% and 5% and dissolution profile was obtained.

**Calculation of similarity and dissimilarity factors:**

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

**Discussion and Conclusion**: The innovator's formulation was present in 500, 750, and 1000 mg strengths. To develop generic product, it is essential to match dissolution profile with respect to similarity factor (f2 values). By present core-coat technology the attempts were made successfully to get desired release profile of all strengths with similarity factor greater than 50. The optimised ration was Ethyl cellulose: HPMC was 55:45 and % functional coating levels were 3% for 750 and 1000 mg and 4% for 500 mg strength. The formulation developed was cost effective generic product and have good patient compliance with respect to high dose and tablet weight so ease for patient to swallow the tablet.

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