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# Formulating and development extended- release oral dosage forms

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**Abstract**
Developing a formulation to achieve the preferred target release to match the kinetics is expected to be the mainly important part of biopharmaceutics1. Innovators have a challenge to maintain the desired concentration of the drug plasma within the targeted therapeutic window to be effective as classified by the biopharmaceutical needs. Thus, the need for variety of delivery strategies and dosage forms has risen over the years. Models of pharmacodynamics and pharmacokinetics are defined to provide an understanding of the involved dynamics of time-course for the concentration of drug and planned target release which are adopted for finalizing the formulation development objectives. Out of several factors, few are closely related to the pharmacokinetics which were accomplishing the input flux of drug and reaching to the desired concentration time profile. A detailed consideration of these two parameters and studying the properties of drug is important to strategize the formulation development. Formulating a controlled release dosage form to achieve the desired input flux of drug is planned to be the biggest test. Also, developing pulsatile delivery formulations is considered as the still bigger challenge. For designing a successful controlled release delivery system the target is to achieve satisfactory input drug flux which is considered to be the greatest challenge. Some of the controlled release delivery dosage forms or systems even face a bigger design challenges, like the pulsatile drug delivery systems. The physiological processes ideally manage the drug disposition the body, but several pharmacokinetic parameters are still considered for evaluating drugs which could be considered as candidates for developing the controlled release delivery systems. Along with the drug potency, other pharmacokinetic parameters like systemic clearance, volume of distribution, and elimination rate constant or half-life can provide useful information in designing of the delivery systems. Half-life is considered to be an important link and hence could be considered in the design between systemic clearance and volume of distribution and controlled release delivery systems. Half-life is a good indicator how quickly systemic clearance can be intentionally modulated in either upward or downward direction.

**Keywords:** Furosemide, Povidone K30, HPMC K15M, Microcrystalline cellulose, Lactose monohydrate

## Introduction

### Drug Delivery Systems for Controlled Release

Developing a formulation to achieve the preferred target release to match the kinetics is expected to be the mainly important part of biopharmaceutics1. Innovators have a challenge to maintain the desired concentration of the drug plasma within the targeted therapeutic window to be effective as classified by the biopharmaceutical needs. Thus, the need for variety of delivery strategies and dosage forms has risen over the years. Models of pharmacodynamics and pharmacokinetics are defined to provide an understanding of the involved dynamics of time-course for the concentration of drug and planned target release which are adopted for finalizing the formulation development objectives. Out of several factors, few are closely related to the pharmacokinetics which were accomplishing the input flux of drug and reaching to the desired concentration time profile. A detailed consideration of these two parameters and studying the properties of drug is important to strategize the formulation development. Formulating a controlled release dosage form to achieve the desired input flux of drug is planned to be the biggest test. Also, developing pulsatile delivery formulations is considered as the still bigger challenge.

For designing a successful controlled release delivery system the target is to achieve satisfactory input drug flux which is considered to be the greatest challenge. Some of the controlled release delivery dosage forms or systems even face a bigger design challenges, like the pulsatile drug delivery systems. The physiological processes ideally manage the drug disposition the body, but several pharmacokinetic parameters are still considered for evaluating drugs which could be considered as candidates for developing the controlled release delivery systems. Along with the drug potency, other pharmacokinetic parameters like systemic clearance, volume of distribution, and elimination rate constant or half-life can provide useful information in designing of the delivery systems. Half-life is considered to be an important link and hence could be considered in the design between systemic clearance and volume of distribution and controlled release delivery systems. Half-life is a good indicator how quickly systemic clearance can be intentionally modulated in either upward or downward direction. It can also be said that shape of systemic clearance can be controlled by the half-life. In order to develop a good control release formulation the drug with shorter half-life are considered as a suitable candidate.

## MaterialS and methods

### Materials

**Drug:** Furosemide (API).

### Excipients

- HPMC K15M (matrix former)
- Microcrystalline cellulose (filler)
- Lactose monohydrate (diluent)
- Povidone K30 (binder)
- Magnesium stearate (lubricant)
- Talc (glidant)

### Chemicals/Solvents

Methanol, hydrochloric acid, phosphate buffers (pH 6.8), ethanol, sodium hydroxide - all of analytical grade.

### Drug Characterization

### Appearance & Solubility

The drug sample was observed for color and appearance. Solubility of the drug in methanol and water was determined. Furosemide (1 g) was added to a 100 mL conical flask containing 50 mL of individual mediums.

### Melting point

Drug in finely powdered and dried state was filled in a glass capillary tube, which was sealed at one end. Range of temperature from start of melting to the end was recorded. This range was compared with the reported value.

### Spectral specifications

#### A. UV Spectroscopy

Absorption of a 6.6 µg/mL methanolic solution was recorded on a UV spectrophotometer using a 1 cm path length quartz cuvette. The solution was scanned from 220 to 500nm and λ max was recorded.

#### B. Infrared Spectroscopy

IR spectrum of furosemide was recorded on Perkin Elmer IR spectrophotometer using the KBr disc method.

#### C. Differential Scanning Calorimetry

Thermogram of furosemide was recorded on Perkin Elmer DSC instrument. The sample was scanned at 5 °C/min with a 20 mL/min nitrogen purge using an identical empty pan as a reference.

### Formulation of Extended Release Tablet

#### Process selection

There are three main methods used for formulation of tablets.

- Wet granulation
- Dry granulation
- Direct Compression

#### A. Wet granulation

Wet granulation (WG) process is the most conventional technique in the manufacturing of tablets. This method involves large number of step viz. duration of blending, temperature of drying, sieve size, time, etc. Each of the parameters can significantly influence the drug dissolution profile.

#### B. Dry granulation (Slugging Method)

Dry granulation is also an important technique for the tablet formulation. This method is widely used when the drug degrades in presence of water.

#### C. Direct Compression

This process is widely used if the API has good compressibility, flowability and does not segregate during flow from the mixture.

### Study of granulation properties

#### Angle of Repose

Poured angle method was used to determine the angle of repose using Enar Reposograph. 10 g of powder was taken. The Powder funnel was fixed on a retort stand such that the bottom was 10 cm from orifice. The outlet was closed, funnel was filled to the brim with powder and the contents were allowed to pour out. The height (H) and radius (R) of the heap formed (average radius measured at three different ends) were measured. The angle of repose was calculated from the equation given below. The procedure was repeated thrice and average values recorded.

$$\text{Angle of Repose } (\Theta) = \tan^{-1}(H/R)$$

### Evaluation of Tablets

#### Appearance

Visual inspection was done for the tablets to observe for the surface characteristics and appearance of any dark spots.

#### Weight variation

Twenty tablets were randomly sampled and weighed. Average weight was calculated. Each tablet was then weighed individually followed by calculation of standard deviation from the average weight.

#### Thickness

Vernier Caliper was used to measure the thickness of six tablets.

#### Hardness

Hardness was tested using Monsanto hardness tester. Six tablets were used for hardness determination.

**Friability**
Tablets (20) was weighed accurately and placed on a sieve no. 60, loose dust was removed with the aid of a soft brush. Then the tablet sample was accurately weighed and placed in the Electrolab Friabilator drum. The drum was rotated 100 times and the tablets were removed. Any loose dust was removed from the tablets as before weighed. The tablets were weighed to the nearest milligram.
% Friability = (Loss in weight / initial weight) X100

**Acceptance Criteria**
A maximum loss of 1% of the mass of the tablets tested is acceptable.

**In-vitro dissolution study of furosemide tablet**
**Preparation of the standard solution**
Furosemide BPCRS (30 mg) was weighed accurately and transferred to a 100 mL volumetric flask and about 90 mL 0.1 M NaOH was added to the flask and solution was sonicated for 5 minutes to dissolve the content. Volume was made up to 100 mL with 0.1 M NaOH.

**Preparation of pH 6.8 phosphate buffer**
Potassium dihydrogen phosphate (6.8 gm) and sodium hydroxide pellets (0.9 gm) was added and dissolved in 1000 mL distilled water to give pH 6.8 phosphate buffer.

$$\% \text{ Furosemide dissolved} = \frac{At}{As} X \frac{10}{1} X \frac{Ws}{100} X \frac{1.1}{50} X \frac{900}{60} XP$$

Where,
At = Absorbance of test solution
As = Absorbance of standard solution
Ws = Weight of Furosemide standard taken for standard solution preparation in mg
P = Purity of Furosemide standard (on dried basis)

**Stability Studies**
The optimized formulation of furosemide extended-release tablets was subjected to accelerated stability studies as per ICH guidelines (Q1A R2).

**Conditions:** 40±2 °C / 75 ± 5% RH (Accelerated stability chamber).

**Duration:** 0, 1, 2, and 3 months.

**Parameters Evaluated**
- Physical appearance (color, shape, surface)
- Hardness and friability
- Drug content (assay)
- In-vitro dissolution profile

At each interval, samples were withdrawn and evaluated for the above parameters to determine any significant changes in the formulation.

***In-vitro* dissolution conditions**
- **Apparatus:** ELECTOLAB TDT-08L
- **Dissolution medium:** pH 6.8 phosphate buffer at 37°C.
- **Volume:** 900mL
- **Apparatus:** USP Type II (paddle with sinker)
- **Speed (rpm):** 50
- **Temperature:** 37°C ±0.5°C
- **Sample withdrawal:** 10 ml
- **Time in hrs:** 1, 2, 4, 8, 12 and 16 hr.
- **Specification:** 1 hr: 20 % - 55 %
- **4 hrs:** 55 % - 85 %
- **8 hrs:** 75 % - 95 %
- **12 hrs:** NLT 80.0%

**Procedure**
Stated amount of the dissolution medium was placed in the vessel and apparatus was assembled. Speed of stirring element was adjusted to 50 rpm. Dissolution medium was equilibrated at 37 °C ± 0.5 °C. Paddles were immersed in the dissolution medium so that there was a distance of 25 mm ± 2 mm between the inside bottom of the vessel and the paddle.

**Calculations**

**Results and Discussion**
**Standardisation of Furosemide**
**Furosemide**
The drug was standardized to confirm the specifications as per those listed in British Pharmacopoeia. The following tests were done.
Description Furosemide exists as white to off-white, odorless, amorphous powder.

**Solubility**
Furosemide is freely soluble in methanol, practically insoluble in water (19.2 µg/mL).

**Melting point**
The melting point of drug was found to be 220-225°C (melts with degradation) [77].

**Spectral analysis**
**A. UV Spectroscopy**
Absorption spectrum was obtained for a range from 400-200 nm. As seen in the figure max was obtained at 274 nm.

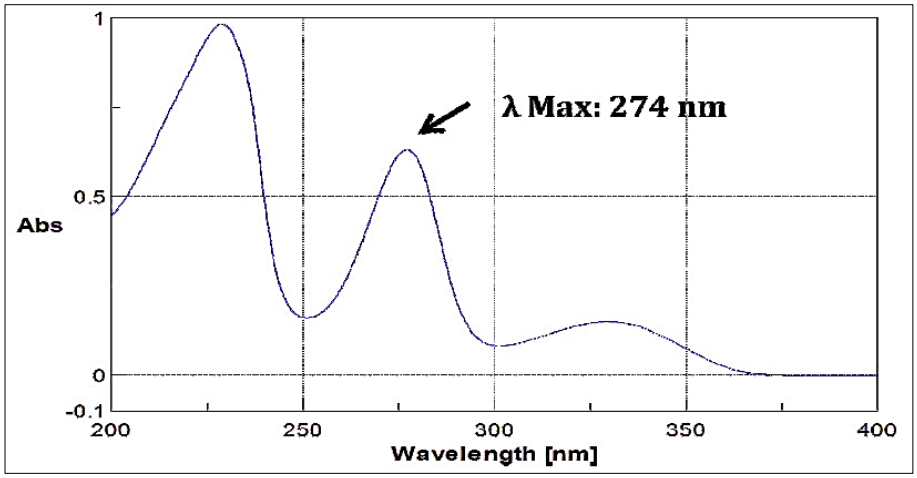


**Fig 4.1:** UV Spectrum of Furosemide

**B. Infra-red Spectroscopy**

The spectrum was found to be similar to the reference pattern. Major peaks at 3390 and corresponding to C-N stretching and carbonyl (COOH) stretching respectively were obtained. Peaks at 1591 and 1323 $cm^{-1}$ corresponding to N-H and S-O stretching were obtained.

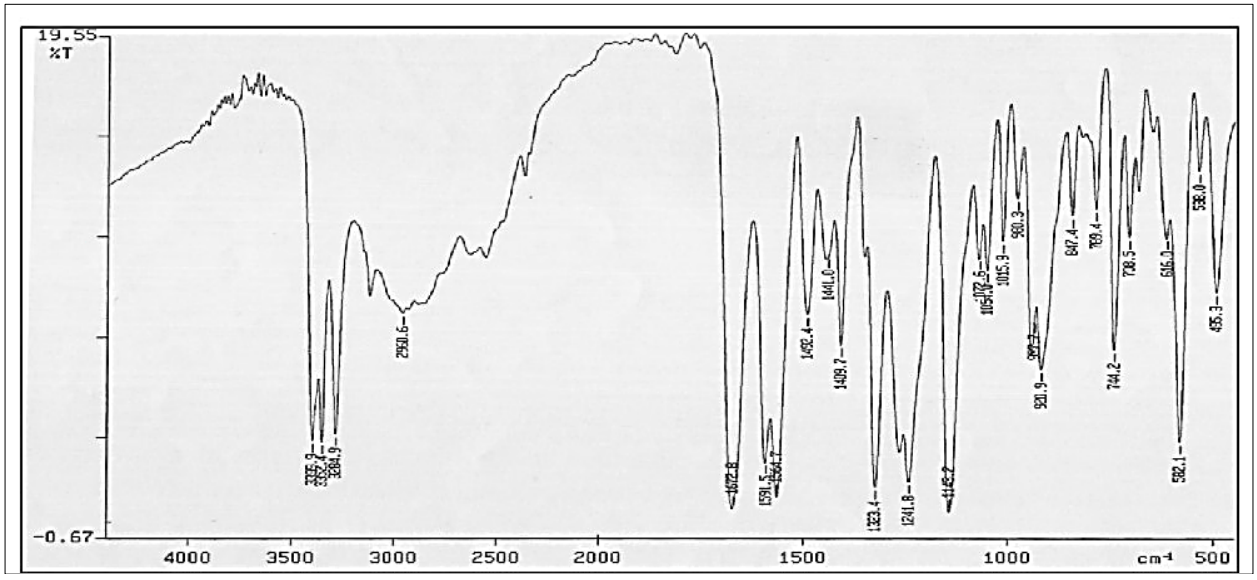


**Fig 4.2:** IR spectra of Furosemide

**C. Differential Scanning Calorimetry**

As seen in figure 4.3, an exotherm (at 222 °C) corresponding to the melting point of furosemide was obtained. Furosemide melts with degradation and thus this explains the appearance of exotherm instead of endotherm in the thermogram.

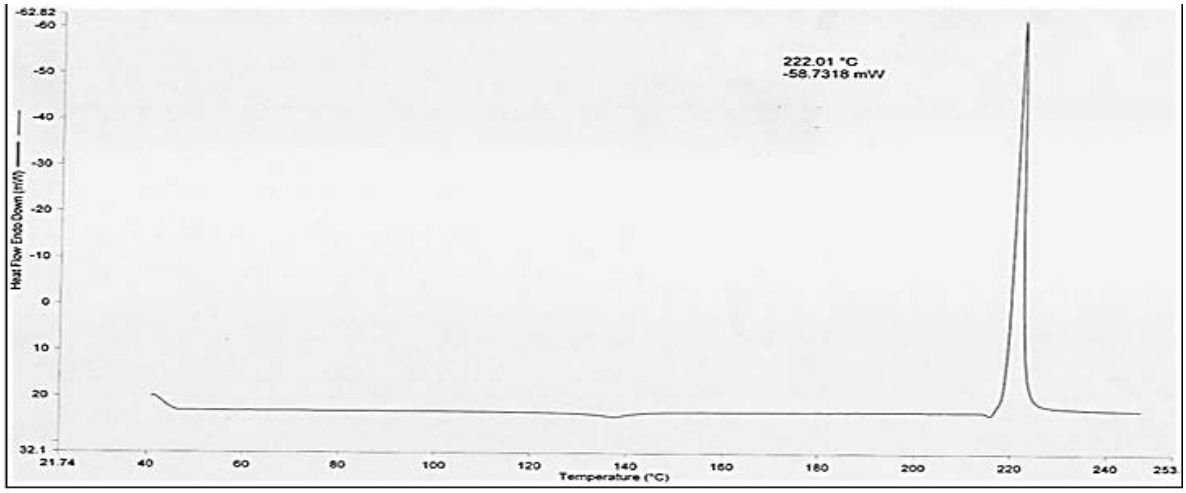


**Fig 4.3:** DSC thermogram of Furosemide

**Particle size analysis**

Given below (Figure 4.4) is the particle side distribution of furosemide sample. The average particle size obtained was 9.52µm.

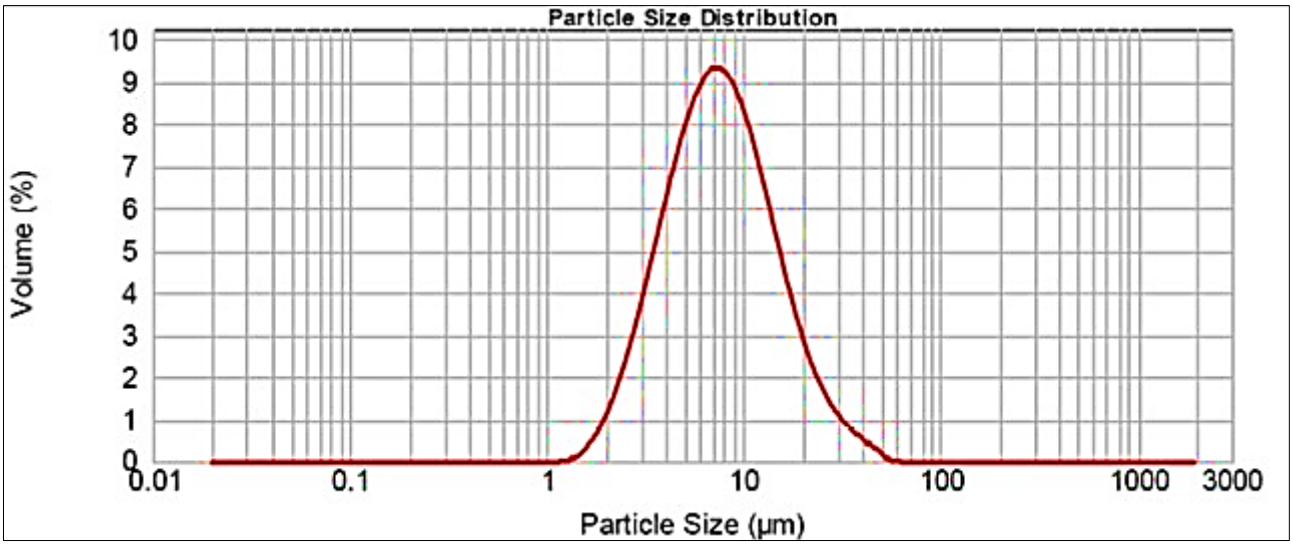


**Fig 4.4:** Particle size distribution curve of Furosemide

**Calibration curve of Furosemide in pH 6.8 phosphate buffer**

An absorption maximum of Furosemide in pH 6.8 buffer was 274nm. Absorption is directly proportional to concentration for the range 2-12µg/mL. Coefficient of regression value was 0.9995. The line showing linear relationship between absorption and concentration has a slope of y = 0.064x - 0.003.

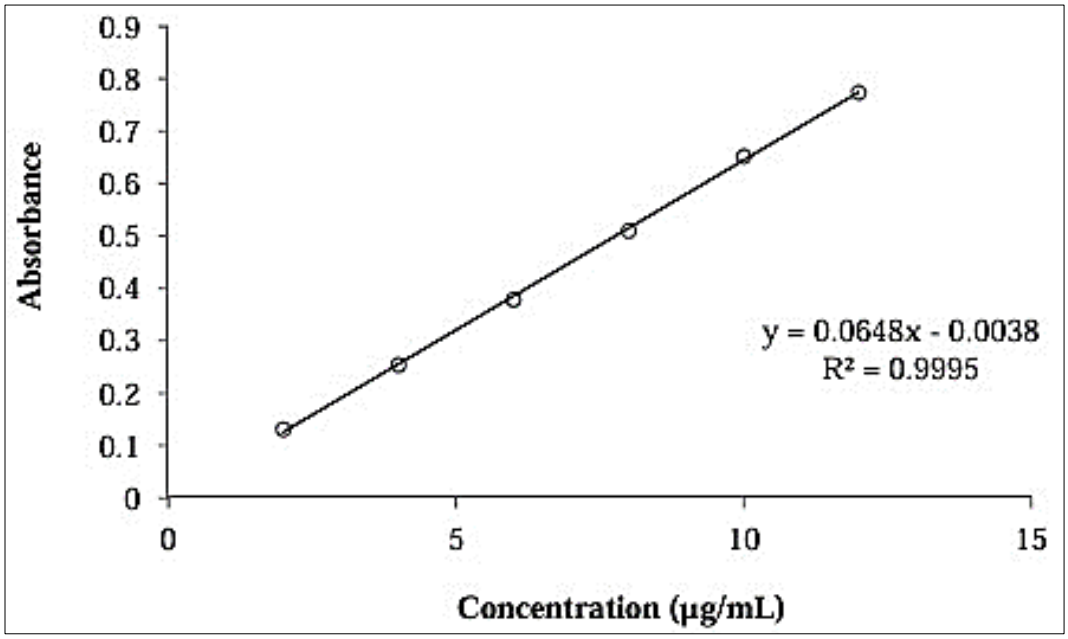


**Fig 4.5:** Calibration curve of Furosemide in pH 6.8 phosphate buffer

**Formulation Development**

**Reference product characterization:** Lasix Retard® 60mg (Sanofi Aventis, Netherlands) was identified as reference product for furosemide extended release tablets 60mg. The reference product was procured from the European market. It consists of pellets filled in hard gelatin capsules having average weight of 352 mg. The in-vitro release characteristic of the reference product was studied in pH 1.2 SGF (without enzymes), acetate buffer pH 4.5, phosphate buffer pH 5.8 and phosphate buffer pH 6.8. The dissolution profile of Lasix Reatrd® studied in different medium of different pH is depicted in the figure 4.5 below.

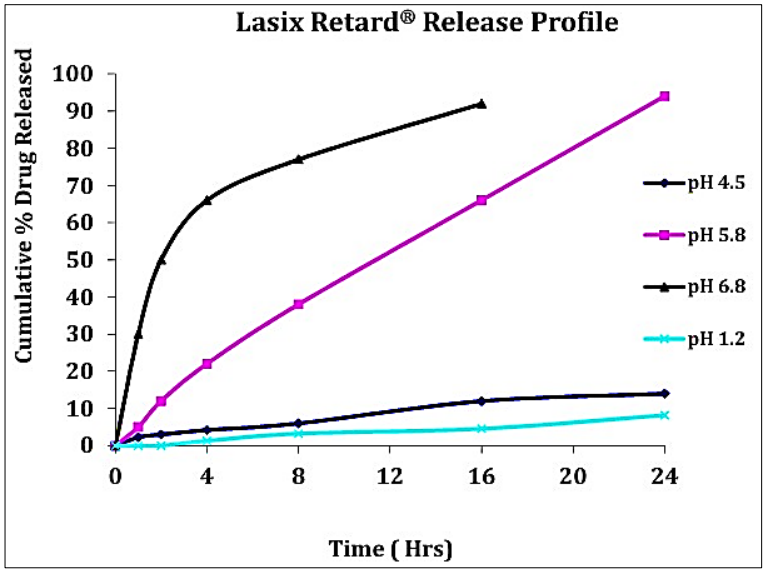


**Fig 4.6:** Dissolution profile of Lasix Retard® in different medium of different pH

**Formulation Strategy**

After performing the dissolution studies on the reference product, it was thought to formulate a bilayered tablet containing involving two layers; one immediate release layer releasing almost 50% drug in the initial 2 hrs and other layer comprised of release retardant polymer termed as extended release layer releasing the drug over extended period of time.

**Materials used for the Manufacture of Furosemide ER Bilayered tablets**

**Furosemide**

It was purchased from Ipca Laboratories, Po. Sejavta, Dist. Ratlam, (M.P) India limited (Hyderabad, India).

**Methocel® K100M, Methocel® K15M, Methocel® K4M**

Methocel® (Colorcon Ltd, Mumbai, India) is the propriety name for the methylcellulose derivative that is also known as hypromellose or hydroxypropyl methylcellulose (HPMC). It has the chemical name cellulose, 2-hydroxypropyl methyl ether and a CAS registry number 90004-65-3. HPMC is an odourless, tasteless white or creamy-white fibrous or granular powder that is widely used in solid oral products and is primarily used as a tablet binder, as a film coating or as the release-controlling matrix of extended release dosage forms.

**Lactose monohydrate**

It is used as diluent in tablet manufacturing and as channelling agent.

**Microcrystalline cellulose**

Microcrystalline cellulose is a standard diluent used in the internal phase during tablet manufacture.

**Aluminium hydroxide powder**

Aluminium hydroxide powder was procured from S. D. Fine Chemicals, India. It is generally used as buffering agent or as alkalizer in the internal phase of the tablet.

**Kollidon® 30 (PVP K30)**

Kollidon 30 was procured from Evonik, India. Kollidon 30 is a new and excellent pharmaceutical excipient most commonly used as binder for tablets.

**Talc**

Talc was obtained from (Signet, Mumbai, India) and has a CAS registry number of 14807-96-6. Talc is an odourless fine white to greyish white impalpable crystalline powder.

**Magnesium Stearate**

Magnesium stearate was obtained from (Signet, Mumbai, India) and is the non-propriety name for the chemical compound octadecanoic acid magnesium salt that has a CAS registry number of 557-04-0. Magnesium stearate is a fine, impalpable white powder with a faint odour of stearic acid and a characteristic metallic taste.

**Aerosil® 200 (Colloidal anhydrous silica)**

Aerosil® 200 was procured from Evonik, India. Colloidal anhydrous silica can absorb a large amount of water whilst retaining its powdery consistency. Thanks to its hydrophilic nature, it maintains the flow ability of the final mixture, even in the presence of moisture.

**Red oxide of iron**

Red oxide of iron (Pink colour) was added in the formulation to differentiate the two layers of tablets [84].

**Eudragit® L 100 (Methacrylic acid copolymer Type a NF)**

This polymer is enteric coating polymer which dissolves at the pH of 6.0±0.2. This is used as release modifier in the formulation.

**Eudragit® S 100 (Methacrylic acid copolymer Type B NF)**

This polymer is enteric coating polymer which dissolves at the pH of 7.0±0.2. This is used as release modifier in the formulation.

**Triethyl citrate**

Triethyl citrate is low molecular weight hydrophilic liquid used as plasticizer for the coating. Triethyl citrate decreases the glass transition temperature and modifies the film property.

**Titanium dioxide:** Titanium dioxide acts as opacifier in the coating composition. When added in the coating composition, imparts elegant, opaque film.

**Optimization of Extended Release (ER) Layer Optimized Formula**

**Table 1:** Optimized formula for Extended Release Layer of the tablets

| | Ingredients | Weight/Tablet (mg) |
|---|---|---|
| Internal Phase | Furosemide | 30 |
| | Pharmatose 200M | 47.5 |
| | Aluminium hydroxide powder | 7.5 |
| | Methocel K4M CR premium | 60 |
| | Kollidon 30 | 4.5 |
| | 2-Propanol | q.s |
| External Phase | Aerosil 200 | 1.5 |
| | Magnesium Stearate | 1.5 |
| Total Weight (mg) | | 152.5 |

**Evaluation of the Optimized Formulation**

***In-vitro* Dissolution**

***In-Vitro* Release Study**

- **Dissolution medium:** Phosphate buffer pH 6.8
- **Volume:** 900mL
- **Apparatus:** USP II (Sinker)
- **Speed (rpm):** 50
- **Temperature:** 37°C ±0.5 °C

**Data Analysis**

The dissolution release data analyzed using various release kinetics models in order to study the mechanism of drug release. Optimized formulation as well as reference product had a split- release profile having mixed type of release kinetics. In order to study the kinetics and mechanism of drug release through the extended release layer, the initial 2 hrs drug release data was excluded.

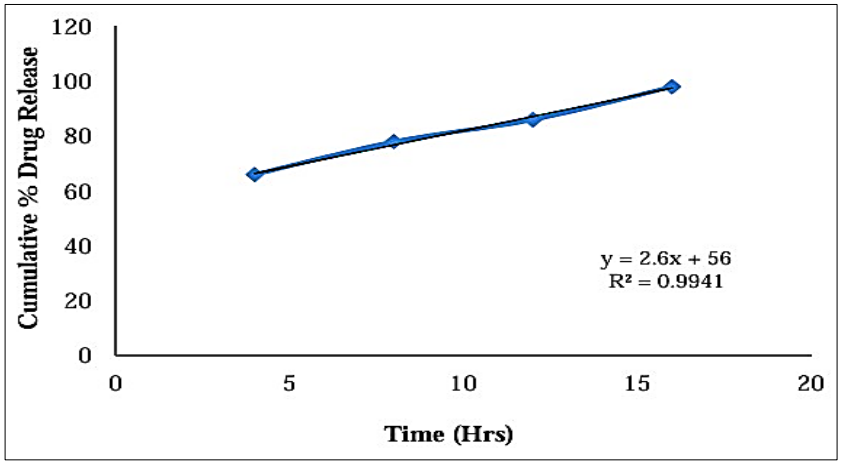


**Fig 4.7:** Zero order release model of furosemide bilayered tablets

**Stability Studies**

The optimized formulation of furosemide extended-release tablets was subjected to accelerated stability testing at 40±2 °C / 75±5% RH for 3 months.

**Discussion**

Furosemide was successfully standardized as per British Pharmacopoeia guidelines. It was confirmed to be a white to off-white amorphous powder, freely soluble in methanol but poorly soluble in water, which explains its limited bioavailability. Spectral analyses using UV, IR, and DSC confirmed the identity and purity of the drug, with characteristic absorption peaks and a melting point in agreement with reported values. The particle size analysis further supported its suitability for formulation. To overcome its poor absorption, particularly in the upper small intestine, a bilayer tablet was developed with an immediate release layer and an extended release layer using HPMC K4M and Eudragit polymers. The optimized formulation demonstrated a sustained release of Furosemide over 16 hours in phosphate buffer (pH 6.8), with dissolution data fitting best to zero-order kinetics, indicating a steady drug release. Accelerated stability studies conducted over 3 months showed that the tablets remained physically and chemically stable, with no significant changes in hardness, friability, drug content, or release profile. These findings suggest that the developed formulation can improve the therapeutic performance of Furosemide by enhancing its bioavailability and ensuring consistent drug release while maintaining stability under accelerated conditions.

**Conclusion**

**Formulation Development and Evaluation of Novel Extended Release Matrix Bilayer Tablet of Furosemide**

The objective of the present work was to formulate extended release formulation of furosemide which releases the drug at predetermined time to improve the bio-efficacy of the formulation and to reduce the dieresis peak. Another objective of the present work was to match in-house extended release formulation to reference product Lasix Retard® (manufactured and marketed by Sanofi Aventis, Netherlands) with respect to in-vitro release profile in different medium of different pH (DPDM).

UV Spectroscopic method for the routine analysis of the drug was developed and validated. High Performance Liquid Chromatography (HPLC) for assay and for related substances was developed and validated. There was no interference of placebo or the degradations products at the retention time of the drug peak. The method was thus validated and found to be specific, linear, precise, accurate and robust.

Saturation solubility of furosemide was determined in different pH medium and it was found that furosemide has pH dependent solubility, freely soluble in alkaline pH and insoluble in acidic pH. Drug excipients compatibility study was performed at the accelerated temperature and humidity to observe any physical change with respect to the controlled samples. Based on the study, suitable excipients were selected for the formulation trials.

The innovator formulation Lasix Retard® 60 mg was procured from the Netherlands and was studied for its *in-vitro* release profile in different dissolution medium, drug assay, related substances, content uniformity and for its physical properties. The development of in-house formulation was directed as per the *in-vitro* release profile of innovator product. Innovator product was comprised of loading dose and maintenance dose. In addition, innovator product showed pH dependent release profile. It showed no release in simulated gastric acidpH1.2 (SGF) and10-15%drug release after 24hrs in pH4. 5 acetate buffer. InpH6. 8 phosphate buffer, it showed immediate drug release in the first hour (Loading dose) followed by extended drug release over next 12 hrs (Maintenancedose).Thus, in-order to match the innovator, it was decided to formulate.

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