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FORMULATION AND EVALUATION OF CONTROLLED POROSITY ORAL OSMOTIC PUMP TABLETS OF FUROSEMIDE

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Abstract

Oedema is an abnormal accumulation of fluid in the interstitium located beneath the skin and in the cavities of the body which can cause severe pain. Furosemide has been shown to be effective and safe in patients with hypertension and/ or coronary heart disease. Osmotic pump tablets deliver the drug in an optimized manner to maintain drug concentration within the therapeutic window and minimize toxic effects. The major objective of the study was to prepare and evaluate oral controlled porosity osmotic pump tablets of furosemide, to reduce the dosing frequency and thereby side effects, and to release the drug for a prolonged period in a controlled manner that is independent of pH and hydrodynamic activity. Pre-formulation studies and pre-compression parameters of tablet blends of osmotic pump tablets of furosemide were carried out. Oral-controlled porosity osmotic pump tablets of furosemide were prepared and subjected to different evaluation tests. Precompression parameters indicated that granules have a good flow property. All the formulations showed good mechanical strength. All the nine formulations showed a drug release of more than 60% in the 12th hour. Optimised formulation showed a drug release of 99.21% in 12th hr. Stability studies conducted indicate that the product is stable.

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Introduction

Furosemide is a loop diuretic used to treat oedema in people with hypertension, coronary artery disease and severe renal failure. The duration of action is short. The drug has short half-life and frequent dose is required for the desired therapeutic effect. This may result in risk of adverse effects. Controlled release osmotic drug delivery of furosemide delivers the drug dose in optimized manner to maintain drug concentration within therapeutic window and minimize the toxic effect.

Osmotic drug delivery system (ODDS) utilizes the principle of osmotic pressure and delivers drug dose in an optimized manner to maintain drug concentration within the therapeutic window and minimizes toxic effect. ODDS release drug at a controlled rate that is independent of the pH and thermodynamics of dissolution medium. The release of drug from osmotic system is independent of presence and absence of food, pH of gastrointestinal (GI) tract, Gl motility and hydrodynamic conditions of body due to rate controlling semi permeable membrane [4].

Controlled porosity osmotic pump (CPOP) is an osmotic tablet in which the membrane contains water soluble leachable pore-forming agents. The coating of semi permeable membrane is done by a suitable coating method.The membrane is permeable to water but impermeable to solute. Water soluble pore forming additives are dispersed throughout wall of the membrane. CPOP lacks aperture to release the drugs but drug release is achieved through the pores which are formed in the semi permeable wall in situ during the operation. When CPOP is exposed to low levels of water, soluble additives are leached from polymer materials that are permeable to water. The resulting sponge like structure is formed in the controlled porosity walls. In this system, the drug after dissolution inside the core is delivered from the osmotic pump tablet by hydrostatic pressure and diffusion through the pores incorporated in the microporous semi permeable membrane and controls the release of drug. The rate of drug delivery depends upon factors such as water permeability of the semi permeable membrane, osmotic pressure of core formulation, thickness and total surface area of coating [19].

Materials and Methods

Materials used are furosemide, mannitol, microcrystalline cellulose, polyvinyl propylene K30, talc, magnesium stearate, cellulose acetate, polyethylene glycol 400. Formulation and evaluation of controlled porosity osmotic pump tablets. Preparation of core tablet: The core tablets of furosemide were prepared by direct compression method with varying ratios of osmogen. All the ingredients were weighed and passed through

different mesh sieves accordingly. All ingredients except magnesium stearate are blended uniformly in a mortar. After the sufficient mixing of drug as well as other components, magnesium stearate and talc were added as lubricant and glidant and mixed.150 mg of powder blend was weighed and compressed into 8mm biconvex tablets by using rotary punch tablet machine. Nine different formulations were prepared by this method.

Preparation of coating solution

Selection of polymer: Cellulose acetate is insoluble in water (excellent solubility in organic solvent), independent of the pH and agitation (physiological condition). So, controlled release can be achieved by using this polymer. It is one of the most suitable membranes due to its mechanical strength, semi-permeable property and generally regarded as a safe polymer. The permeability can be adjusted by modifying pore former levels and/or altering membrane thickness,

Selection of pore former: PEG 400 was selected as pore former, because it is a hydrophilic material thereby forming pores in the coating film. It also has plasticizer properties. It is best suited with cellulose acetate as pore former. It was used on the basis of % w/w of coating polymer.

Selection of solvent: Solvent was selected based on the basis of solubility of both polymers (cellulose acetate and PEG 400). Both are soluble in acetone and hence this was selected as a solvent for making coating solution.[22]

Coating of tablets: In the present study, the spray coating method is used. The coating solution was sprayed on the weighed tablets at room temperature. The tablets were then dried at 60°C in an oven. During drying, the tablets were rotated occasionally. The tablets were subjected to a weight gain of 5 % w/w, 10% w/w, and 15 % w/w of the total weight of the tablet.

Determination of Precompression parameters

Angle of repose, Bulk density and tapped density, compressibility index and Hausner's ratio of the powder blend were determined

Evaluation of tablets

1. Weight variation: Twenty tablets were selected randomly from each formulation and weighed individually and the average weight is calculated.. Not more than two tablets deviate from the permissible percentage deviation as given in IP and none should deviate by more than twice that percentage.

2. Hardness: Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacturing, packing, and shipping. The Monsanto hardness tester was used which consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and zero reading is taken. The plunger is then forced against a spring by turning a threaded bolt until the tablet breaks. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of break is recorded and zero force reading is deducted from it.

3. Friability: The friability of tablet is determined by using Roche friabilator. It is expressed in percentage (%). 10 tablets are initially weighed and transferred into friabilator. The friabilator is operated at 25rpm and run up to 100 revolutions. The tablets are weighed again, the percentage friability is then calculated.

4. Drug content determination: Five tablets were taken and finely powdered, quantities of the powder equivalent to 20 mg of furosemide were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCl solution and mixed thoroughly. The solution was made up to volume and filtered and the absorbance of the resulting solution was measured at 271 mm using UV spectrophotometer.

5. In vitro dissolution studies: Dissolution of coated formulation was carried out using 0.1 N HCl for 2 hrs and pH 6.8 phosphate buffer for 10 hrs using USP dissolution apparatus-1 at 50 rpm. The temperature of dissolution media was kept at 37±0.5°C. 5 ml of samples were withdrawn, at 1, 2, 3, 4, 6, 8, 10, and 12 hrs for measurement of drug release. Each time samples were replaced with 5 ml of fresh media. Samples were analysed by using UV spectrophotometer at 271mm.

6. Effect of pH: To study the effect of pH and to assure a reliable performance of developed formulations independent of pH on drug release, studies of optimized formulations were carried out at pH 1.2 in simulated gastric fluid (SGF) and pH 6.8 in simulated intestinal fluid (SIF) using dissolution apparatus 1 at 50 rpm. The samples (5ml) were withdrawn at predetermined intervals and analysed at 271nm using UV spectrophotometer.

7. Effect of agitation intensity: To study the effect of hydrodynamic activity and to assure a reliable performance of developed formulations, release studies of optimized formulations were carried out using dissolution apparatus 2 at different rotational speed of 50, 100 and 150 rpm using 0.1 N HCI at first 2 hrs and then at 6.8 phosphate buffer. 5ml of samples were withdrawn at 1,2,3,4,6, 8, 10 and 12 hrs for measurement of drug release. Each time, samples were replaced with 5 ml of fresh media. Samples were analysed by using UV spectrophotometer at 271nm

8. Stability study: Optimized formulation was tightly sealed and kept at 40°C ±20° C / 75%±5% RH. Hardness , weight variation, drug content and in vitro dissolution study were conducted on 30th day and 90th day of storage.

Results and Discussion

In vitro dissolution study

In vitro drug release study was done with 0.1 N HCL in first 2 hr and then with pH 6.8 for 10hrs. Formulation F1 containing 20% osmogen with 55% weight gain showed a drug release of 60.34%. F3, which has 60% osmogen with 5% weight gain showed more drug release i.e. 62.33% than F2,which have 40% osmogen with 5% weight gain (69.41%). Formulation F4 (20 % osmogen with weight gain 10%) has drug release 75.89%. Formulation FS (40% osmogen with weight gain 10 %) and F6 (60 % osmogen with weight gain 10 %) showed drug release 75.21 and 77.93%, respectively. Formulation, F7(20% osmogen with 15 % weight gain) and F8(40% osmogen with weight gain 15%) showed drug release 80.01% and 91.45% respectively. Formulation F9 containing 60% osmogen with weight gain 15% showed drug release 99.21%. Hence formulation F9 showed better result when compared to all other formulations and therefore selected as the optimized formulation. This may be due to higher concentration of osmogen and pore former.

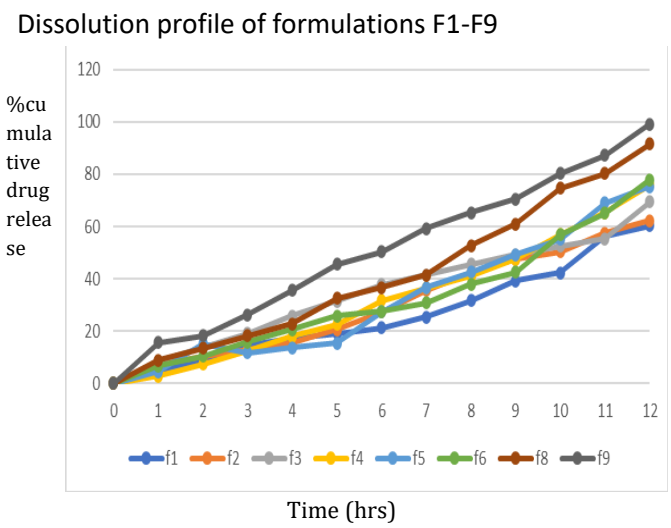

Figure 1: In vitro drug release plot of furosemide controlled osmotic pump tablet.

Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations, release studies of optimized formulations were carried out at different pH.

Dissolution profile at pH 1.2 and pH6.8

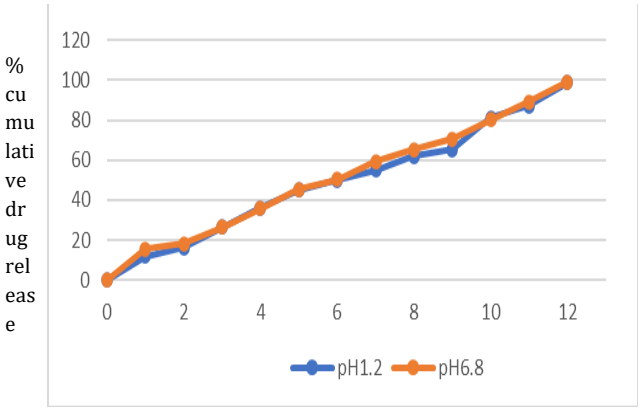

Figure 2: In vitro dissolution profile in pH1.2 and 6.8.

It can be seen that drug release profile at pH 1.2 and 6.8. were superimposing. From this it is clearly evident that the drug release is independent of pH.

Effect of agitational intensity on drug release

The dissolution study was carried out in different agitational intensity such as 50, 100 and 150 rpm.

Dissolution profile at 50,100,150rpm

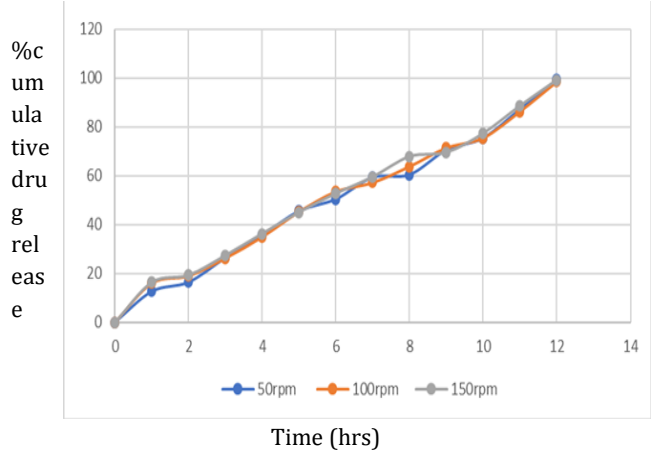

Figure 3: In vitro dissolution profile in different rpm.

From the above dissolution profile, it is clear that the drug release from optimized formulation is independent of agitational intensity.

Conclusion

Controlled porosity osmotic pump tablets of furosemide were prepared in an attempt to release the drug in optimised manner for maintaining drug concentration within therapeutic window. This reduces the dosing frequency, improves patient compliance and minimizes the side effects. All the nine formulations showed a drug release of more than 60% in 12 hr. Optimized formulation F9 showed a drug release of 99.21% in 12 hr which may be due to higher content of osmogen and pore former. Studies such as effect of pH and agitational intensity were conducted and showed that the drug release from the optimized formulation is independent of pH and hydrodynamic activity. Optimised formulation was found to be stable after 3 months of storage.

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