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Research Article

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Development and *In Vitro* Evaluation of Osmotically Controlled Oral Drug Delivery System of Carvedilol

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ABSTRACT
The aim of the current study was to design a controlled porosity osmotic pump capsule of carvedilol .The capsule contains pore-forming water-soluble additives, which after coming in contact with water, dissolve, resulting in an *in situ* formation of a micro porous structure. The effect of different formulation variables, namely, ratio of drug to osmogent, solubilizing agent and level of pore former, different environmental media and stirring rate on the *in vitro* release was studied. Cellulose acetate (CA) was used as the semi permeable membrane. It was found that drug release rate increased with the increase in amount of osmogent and solubilizing and independent of different environmental media and stirring rate. Carvedilol release was, directly proportional to the level of pore former, glycerin, in the membrane. This system was found to deliver carvedilol at a zero-order rate.

Keywords: Osmotic systems, Carvedilol, osmogent, cellulose acetate, pore former.

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INTRODUCTION

Carvedilol is extensively used in patients with hypertension and angina or congestive cardiac failure. The drug has a low solubility in gastrointestinal fluids and undergoes extensive first-pass metabolism in the liver, which leads to the low absolute oral bioavailability, which is about 20% in humans. [1] Thus, there is a therapeutic need to develop a delivery system that will release carvedilol in a controlled manner for a definite period of time. In order to achieve this goal asymmetric membrane capsule consisting of a drug and other excipients has been developed. One of the advantages of asymmetric membrane is the higher rate of water influx, allowing the release of drugs with a lower osmotic pressure or lower solubility. [2] Drugs can be delivered in a controlled manner over a long period of time by the process of osmosis. [3] Drug delivery from this system is not influenced by the different physiologic factors with in gut and lumen and the release from these system can be easily adjusted by the optimizing the parameters of the delivery system. [4-5] The aim of the work is to develop an asymmetric membrane capsules to deliver poorly water soluble drug carvedilol based on osmotic technology and to evaluate the influence of core formulation variables on the release characteristics.

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Materials and Methods

Materials

Carvedilol was obtained as a gift sample from Oscar Remedies Pvt. Ltd, Kala Amb, India. Mannitol, SLS and Cellulose acetate were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Glycerol was purchased from the Merck Limited, Mumbai. All other solvents and reagents used were of analytical grade.

Osmotic pump capsule preparation

Asymmetric membrane capsules were prepared by phase inversion process in which the membrane structure was precipitated on a stainless steel mould pin by dipping the mold pin in a coating solution followed by quenching in an aqueous solution. Then, the capsules were stripped off, trimmed to size and physically characterized. Typical formulations of the dip-coating solutions and solutions used for quenching and sealing the capsules are listed in table-1. Asymmetric membrane capsules were filled with a desired amount of drug-excipients mixture by hand (table 1). After filling the capsules were capped and sealed with a sealing solution. [6-9]

In Vitro Drug Release

In-vitro drug release from the formulation was studied by using USP basket type apparatus (rotating speed of 50 rpm at 37±1°C). The dissolution medium used was 900 ml

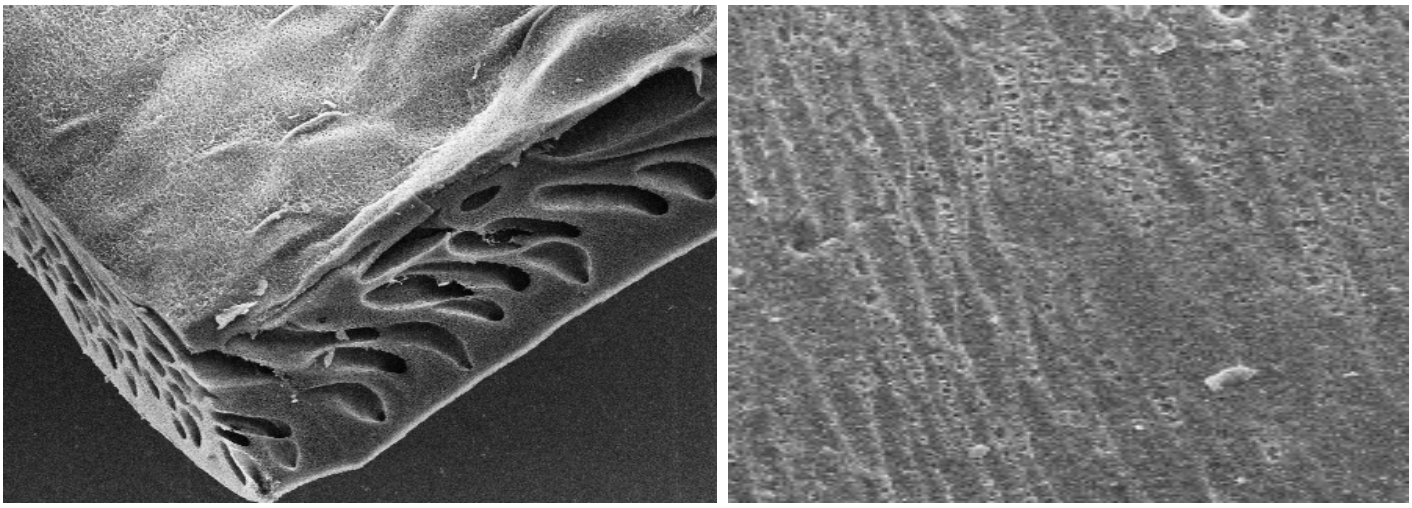

Fig.1: Scanning electron micrograph of the asymmetric membrane wall (A) cross section, at 60x magnification (A) dense region showing no pores, at 60x magnification.

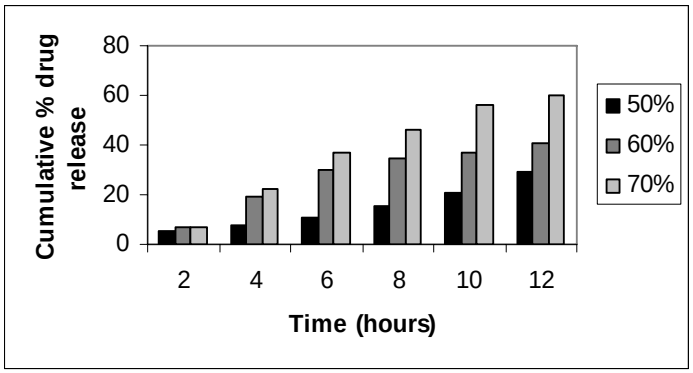

Fig. 2: Effect of concentration of pore former on drug release from developed formulation.

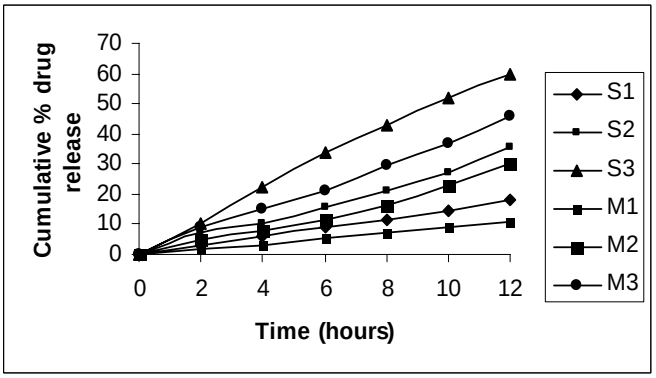

Fig. 3: Dissolution of carvedilol from asymmetric membrane capsules - nominally one-component systems.

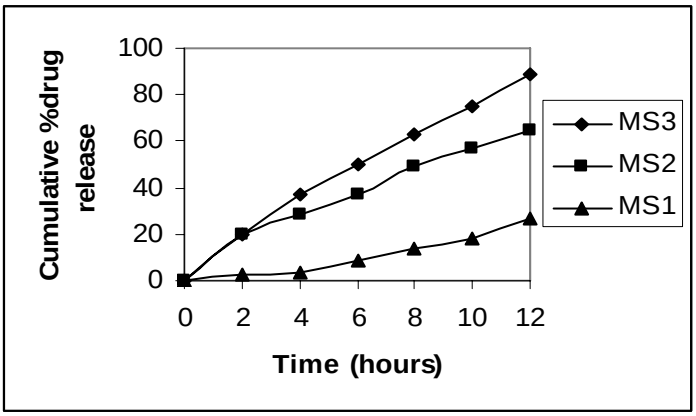

Fig. 4: Dissolution of carvedilol from asymmetric membrane capsules — nominally two-component systems.

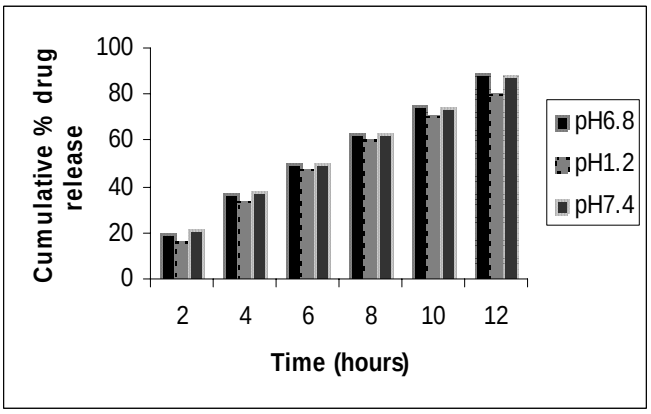

Fig. 5: Effect of pH on drug release from optimized formulation.

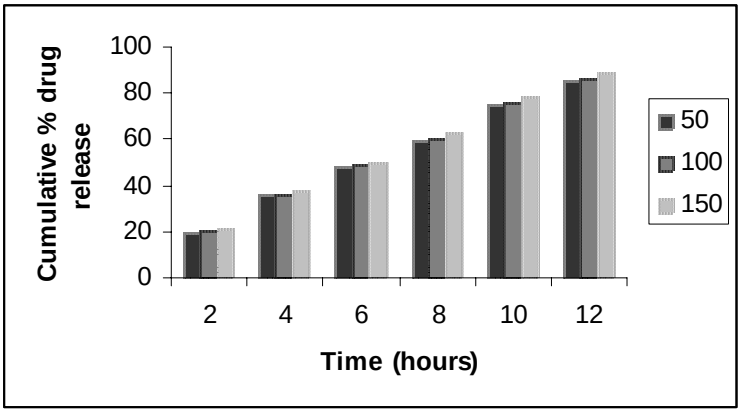

Fig. 6: Effect of agitational intensity on drug release from optimized formulation.

Table 1: Formulation of Carvedilol CPOP

Formulation	A	B	C
Polymeric Shell Content			
Cellulose Acetate (g)	15	15	15
Acetone (mL)	62	62	62
Alcohol (mL)	34.5	34.5	34.5
Glycerol (g)	10	10	10
Quenching Solution Content			
Water (mL)	100	100	100
Glycerol (mL)	10	10	10
Filling Content in formulation C			
Formulation Code	M1	M2	M3
Pure Carvedilol (mg)	12.5	12.5	12.5
Mannitol	12.5	62.50	125
Formulation Code	S1	S2	S3
Sodium Lauryl Sulphate (mg)	12.5	62.50	125
Formulation Code	MS1	MS2	MS3
Pure Carvedilol (mg)	12.5	12.5	12.5
Mannitol	12.5	62.50	125
Sodium Lauryl Sulphate (mg)	12.5	125	62.50
Sealing Solution Content			
Cellulose Acetate (g)	10	10	10
Acetone (mL)	50	50	50

phosphate buffer pH 6.8. One milliliter samples were withdrawn at specified time intervals (replaced with fresh dissolution medium), centrifuged, suitably diluted and supernatant was analyzed immediately by UV spectrophotometrically (wavelength 285 nm).

Results and Discussion

The controlled porosity osmotic pump capsule (CPOP) capsules prepared by dipping technology appeared to be white, opaque, and glossy with no visible imperfection. Weight variations, membrane thickness and surface area in the asymmetric membrane capsules were consistent. Scanning electron micrographs (Fig. 1A) indicates the presence of a porous region at 60x magnification. No pore structures were shown in the dense region (Fig. 1 B).

***In vitro* drug release study**

Influences of capsule membrane variable on drug release

The release of carvedilol from the capsule was determined. It was cleared from the results that as the concentration of glycerin increased in the capsule formulation rate of drug release also increases, this is because as the concentration of pore forming agent increased the number of pores in the porous region also increased, hence influx of dissolution medium increased (Fig 2).

One component system

Fig. 3 shows the in vitro release from asymmetric membrane capsules containing carvedilol and different ratio of osmotic agent and solubilizing agent. The excipients were chosen to span a wide range of solubility or osmotic pressures. Higher release rates were observed from the systems with the solubilizing agent, SLS, compared to systems filled with osmogent, mannitol. This may be due to the solubilization effect of SLS causing increased solubility of the drug, increasing the osmotic pressure of the drug itself, resulting in an increased amount of drug being released from the system. It appears that SLS, besides imparting, solubilization effect, also acts as an osmogent in dissolved form.

Two component system

It is clear from the dissolution data that in order to deliver carvedilol over useful delivery duration, such as 12 h, the formulations must include a suitable osmotic agent, i.e. one that has a high aqueous solubility and one solubilizing agent. Fig. 3 shows the in vitro release from asymmetric membrane capsules containing carvedilol and different ratio of physically mixed mannitol and SLS. SLS is known for being a solubilizing agent which also induces osmotic pressures proportional to its amounts which will synergize with the osmotic effect of mannitol.

Evaluation of optimal CPOP capsule

Based on the results obtained, the optimal formulation was selected as following: the weight ratio of carvedilol to Mannitol (1:5) and SLS (1:10); percent of Glycerol in CA membrane was 70%. To investigate the influence of release media on drug release, release tests of the optimal formulation were conducted in hydrochloric acid solution pH 1.2, phosphate buffer pH 7.4 and phosphate buffer pH 6.8. Fig 4 shows the release profiles in these release media. One way analysis of variance was used to assess the difference in release rate. Comparing the data of drug release in different media and at different agitation speed the p value were obtained to be 0.93 and 0.98 respectively, which was larger than 0.05, indicated that no significant differences existed in drug release in different release media and at different agitation speed.

The osmotic release rate of a drug from an asymmetric membrane capsule is dependent on its solubility and concentration of glycerin in capsule formulation. Thus, drug substances with a poor aqueous solubility are released at very low rates. This limitation can be overcome for a drug such as carvedilol by including a solubility enhancing excipient in the capsule core.

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