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Formulation and Evaluation of Controlled Porosity Osmotic Drug Delivery System of Carvedilol Phosphate

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ABSTRACT:

Controlled porosity osmotic tablet of carvedilol phosphate prepared and evaluated in this study. Carvedilol phosphate is very low soluble drug. So it is difficult to formulate osmotic tablet of carvedilol phosphate which gives drug release up to 24 hr at zero order. To get desired dissolution profile various formulation parameters like osmogen concentration, level of weight gain and level of pore former concentration were studied. Polysorbate 80 was added as solubilizer to increase its dissolution rate and get drug release up to 24 hr at zero order. As concentration of solubilizer increases, dissolution rate increases. Final optimized formulation was studied for effect of pH of dissolution media, agitation intensity and osmotic pressure of dissolution media. There is no effect of pH of dissolution media and agitation intensity on dissolution. There is significant effect of osmotic pressure on dissolution confirms that prepared carvedilol phosphate tablet gives drug release with osmotic mechanism.

KEYWORDS: Carvedilol phosphate, Controlled porosity osmotic tablet, Zero order, Solubilizer

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Introduction:

Conventional drug delivery systems have little control over the drug release and so effective concentration at the target site can not be achieved. This kind of dosing pattern may result in unpredictable plasma concentrations. But oral controlled drug delivery dosage forms provide desired drug release pattern for longer period of time and so the rate and extent of drug absorption from oral controlled drug delivery formulations can be predicted. However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract¹. But drug release from osmotic drug delivery system is not affected by physiological factors.

Controlled porosity osmotic tablet contains core tablet coated with semipermeable membrane which allows active agent to come outside through pores formed in situ. The controlled-porosity osmotic pump has been developed via incorporation of leachable water-soluble small molecules, such as sodium chloride, potassium chloride, urea, and sucrose etc. into major component of film coating material²⁻⁴. These pore-forming agents are leached when contacted with an aqueous medium, and the pores are created on the surface to allow drug release. Plasticizer can also be used as pore forming agent. Plasticizer has been used to modify not only the mechanical properties but also the thermal property, water absorption behavior, and adhesive property of polymeric films⁵. All of these properties affect the strength of coating films and the integrity of final products, which further affect drug release performance. Many compounds can be acted as a function of plasticizer including poly(ethylene glycol)⁶, propylene glycol⁷, sorbitol⁸, urea⁹, oil¹⁰, citrate¹¹, adipate¹², and phthalate¹³, etc. The release of drug is dominated by thickness of coating films, the level of water-soluble components, the solubility of

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TABLE 1: Composition of Experimental Formulation

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9
Core Tablet Composition (mg/tab)									
Carvedilol phosphate	40	40	40	40	40	40	40	40	40
Lactose monohydrate	42.2	32.2	40.2	34.2	37.2	37.2	37.2	37.2	37.2
Sodium chloride	20	30	25	25	25	25	25	25	25
Povidone K 30	3	3	3	3	3	3	3	3	3
Polysorbate 80	18.8	18.8	15.8	21.8	18.8	18.8	18.8	18.8	18.8
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total (Core Tablet)	125.0	125.0	125.0	125.0	125.0	125.0	125.0	125.0	125.0
Coating Composition (mg/tab)									
Wt gain (%)	12	12	12	12	12	12	10	14	12
Sorbitol (% of CA)	60	60	60	60	50	70	60	60	60
Total (Coated Tablet)	140	140	140	140	140	140	137.5	142.5	140

drug, and the osmotic pressure difference. The advantage of blending of pore-forming agent avoids using high technical laser beam to drill an orifice for drug release, in addition, it is easily fabricated via traditional film coating technique¹⁴.

Candidate drugs for osmotic drug delivery have water solubilities of 50-300 mg/ml. High soluble drugs would show a high release rate that would be zero order release for very small percentage of initial drug load. Thus intrinsic water solubility of many drugs might preclude them from incorporation into osmotic drug delivery system. By modulating the solubility of drug within core, effective drug release can be obtained for even poor candidate drugs for osmotic drug delivery. This approach can be used for conversion of first order profile into zero order profile without altering the chemical structure¹⁵.

Carvedilol phosphate is a beta blocker widely used for the treatment of hypertension. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a suitable candidate for controlled release and/or sustained release (CR/SR) preparations. Carvedilol phosphate is a low soluble drug and the release rate of carvedilol phosphate from oral osmotic pumps is usually low. Due to low solubility of carvedilol phosphate, it is difficult to formulate osmotic tablet. In present study, solubility of carvedilol phosphate was increased with addition of polysorbate 80 in the system. Polysorbate 80 increases its solubility and dissolution. Prepared osmotic tablet of carvedilol phosphate gives drug release for up to 24 hr. by osmotic mechanism.

MATERIALS AND METHODS:

Materials:

Carvedilol phosphate was obtained from Torrent Pharmaceuticals Ltd, Ahmedabad as a gift sample. Sodium chloride (s. d. fine chem., India) was used as osmogent and lactose monohydrate (DMV, India) was used as diluent.

Polysorbate 80(s. d. fine chem.) was used as solubilizer. Povidone (ISP Corporation, India) was used as binder and magnesium stearate (Ferro) was used as lubricant. Cellulose acetate with 39.8% acetyl content (Eastman chem., USA) was used as semipermeable membrane. Sorbitol and PEG 400(s. d. fine chem.) was used as pore former and plasticizer respectively. The other chemicals used were of analytical grade.

Evaluation of Developed Formulations

Dissolution of coated formulation (n=6) was carried out in 0.1 N HCl, 900 ml by using USP dissolution apparatus – II (Electrolab, India) at 100 rpm. Temperature of dissolution media was kept at 37±0.5 °C. The samples were withdrawn (10ml) at different time intervals and replaced with 10 ml of fresh media. Samples were withdrawn at 1, 2,4,8,12,18 and 24 hr for measurement of drug release. Samples were analyzed using UV spectrometer at 240nm.

A. Effect of pH

To study the effect of pH on drug release, dissolution study was carried in dissolution media having different pH. Dissolution was carried in 900 ml of 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Dissolution apparatus (USP-II) was used for drug release study at 100 rpm. The samples (10ml) were withdrawn at predetermined intervals and analyzed at 240nm using UV spectrometer.

B. Effect of Agitation Intensity

To study the effect of agitation intensity on drug release, optimized formulation was subjected to dissolution at various rotation speeds. Dissolution was carried out in USP-II (Paddle) at 50, 100 and 150 rpm. The samples (10ml) were withdrawn at predetermined intervals and analyzed at 240nm using UV spectrometer.

C. Effect of Osmotic Pressure

To confirm the mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride was added in dissolution media. Release studies were carried out in 900 ml of 0.1 N HCl using USP-II dissolution apparatus at 100 rpm. To increase the osmotic pressure of dissolution media, sodium chloride (2.5% & 5%) was added. Effect of osmotic pressure created by dissolution media was evaluated by drug release at different time intervals.

RESULTS AND DISCUSSIONS:

1. Formulation Development

Osmotic tablet consist of core tablet coated with a rate controlling membrane. Tablet core consists of drug along with release retardant, osmogen, and other conventional excipients to form the core compartment. The core tablet is surrounded by a membrane consisting of a semipermeable polymer and pore former cum plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane is permeable to aqueous fluids but substantially impermeable to the components of the core. During operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. The dissolved drug is released through the pores created after leaching of water soluble additive in the membrane. Cellulose acetate was used as water-insoluble polymer. PVP was used as water-soluble plasticizer and pore former. Carvedilol phosphate is having low solubility that precludes it from incorporation in osmotic dosage forms. Solubilizer was added in core to increase its dissolution.

A. Effect of Osmogen Concentration

To check the effect of osmogen concentration on drug release, formulations were prepared with different concentration of sodium chloride and all other parameters of tablet kept constant. Quantity of sodium chloride was varied in range of 20 mg/tab to 30 mg/tab.

By reducing the concentration of sodium chloride, dissolution rate of carvedilol phosphate decreases. (Figure-1)

Therefore it is concluded that drug release from prepared tablet was done through osmotic pressure. Concentration of sodium chloride is required to be optimized to get the required release profile.

B. Effect of Solubilizer Concentration

Due to low solubility of carvedilol phosphate, it is difficult to formulate osmotic tablet of carvedilol phosphate. However, it is possible to modulate the solubility of drugs within the core and thus extend this technology for delivery of drugs, which otherwise may be poor candidates for osmotic delivery¹⁶⁻¹⁹.

Carvedilol phosphate is low soluble in water. Polysorbate 80

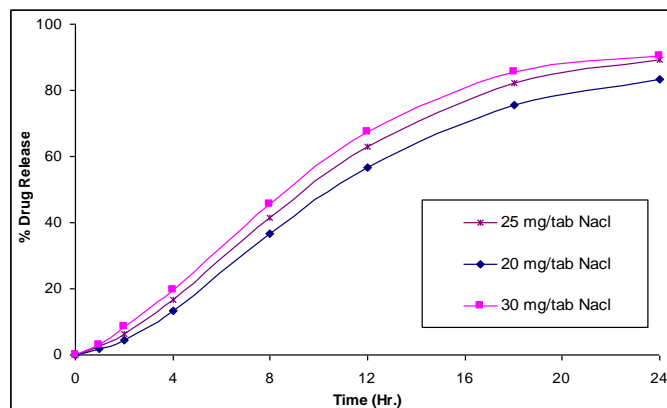


FIGURE 1: Effect of Osmogen Concentration

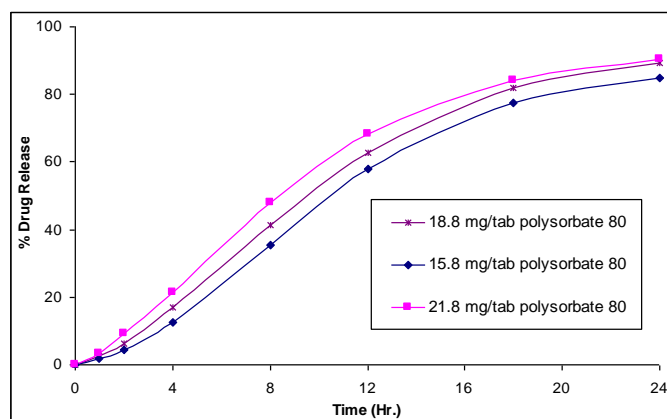


FIGURE 2: Effect of Solubilizer Concentration

was added in the formulation to increase the dissolution rate of carvedilol phosphate. Different concentration of polysorbate 80 was tried and it was very clearly indicate that drug release rate is dependent on concentration of polysorbate 80. As the concentration of polysorbate 80 increases, the dissolution rate increases. Prolonged time drug release can be obtained with formulation containing polysorbate 80. (Figure -2) Different concentration of polysorbate 80 was tried for desired dissolution profile.

C. Effect of Pore Former Concentration

In controlled porosity osmotic pump, core tablet was coated with semipermeable membrane having pore former. After coming in contact with aqueous media, pore former dissolves and leaches out from the coating which creates microporous membrane around tablet. Drug release was done through these pores. So concentration of pore former in controlled porosity osmotic pump is important parameter in controlling the release rate. Tablets were coated with different ratios of cellulose acetate/sorbitol and subject to dissolution after sufficient weight gain achieved. Different concentration of sorbitol (% of cellulose acetate) like 50%, 60% and 70% were tried. (Figure -3)

By decreasing the concentration of pore former, drug release was decreased linearly. There is significant effect of pore former concentration on drug release observed.

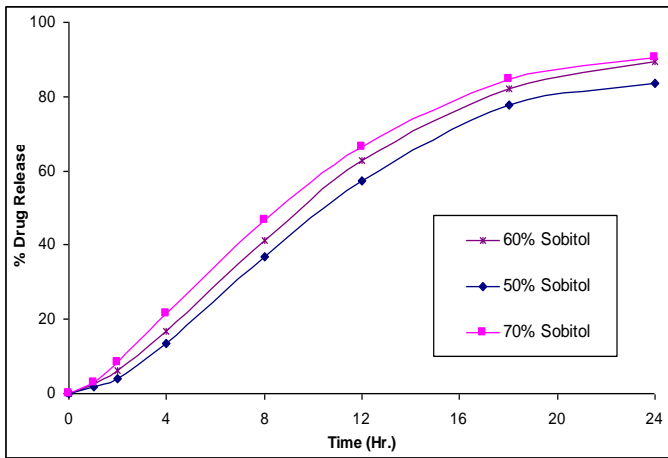


FIGURE 3: Effect of Pore Former Concentration

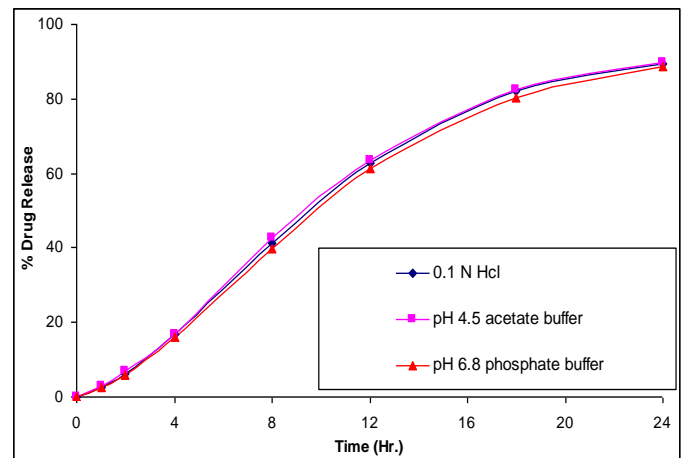


FIGURE 5: Effect of Ph

D. Effect of Coating Weight Gain

Core tablets were coated with semipermeable membrane of cellulose acetate with different weight gain to identify the effect of coating gain on drug release. Core tablets were coated with 10%, 12% and 14% weight gain and subject to dissolution. (Figure 4)

There is difference in dissolution observed with different weight gain tablets. With increase in coating weight gain, drug release rate decreased.

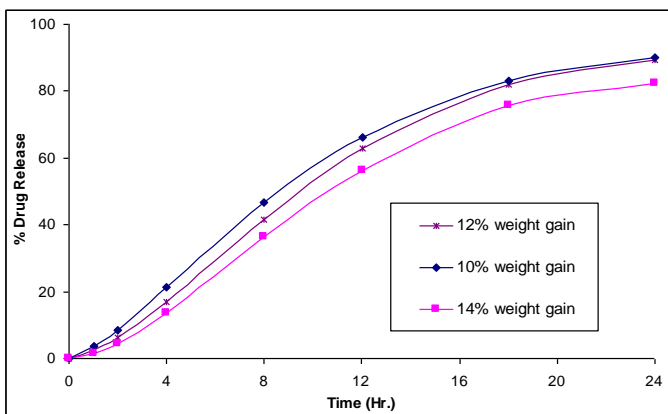


FIGURE 4: effect of coating weight gain

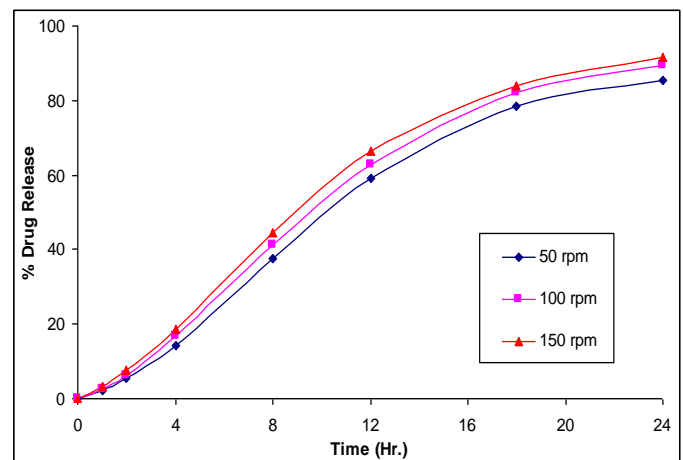


FIGURE 6: Effect of RPM

To study the effect of agitational intensity of the release media, release studies of the optimized formulation was carried out in USP dissolution apparatus type II at varying rotational speed (50, 100, and 150 rpm) in 900 ml of 0.1 N HCl. It is clearly evident from figure 6 that the release of carvedilol phosphate is independent of the agitation intensity.

Drug release in all three conditions found similar. The f_1 and f_2 values were found to be 6.7 and 74.9 (between 50 and 100 rpm), 11.9 and 63.7 (between 50 and 150 rpm), and 4.9 and 80.0 (between 100 and 150 rpm), respectively.

To study the effect of osmotic pressure, release studies of the optimized formulation were conducted in media of different osmotic pressure. The results of release studies in media of different concentration of sodium chloride (2.5% and 5%) showed that the drug release is highly dependent on the osmotic pressure of the release media. Carvedilol phosphate release from the formulations decreased as the osmotic pressure of the media increased (Figure 7). The f_1 and f_2 values were found to be 20.9 and 47.5 (between without Nacl and 2.5% Nacl), 46.3 and 30.8 (between without Nacl and 5% Nacl), and 32.1 and 44.0 (between 2.5% Nacl and 5% Nacl), respectively.

2. Performance Evaluation of Optimized Formulation

Final formulation was evaluated for various dissolution studies to check effect of pH, agitation intensity and osmotic pressure.

In order to study the effect of pH on drug release, dissolution was carried out in media of different pH. Dissolution was carried in 900 ml of 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer in USP-II apparatus (Paddle) at 100 rpm. Drug release for optimized formulation was found similar in all three media. Optimized formulation shows pH independent drug release as per figure 5. The f_1 and f_2 values were found to be 1.3 and 96.0 (between 0.1 N HCl and pH 4.5 acetate buffer), 2.3 and 90.7 (between 0.1 N HCl and pH 6.8 phosphate buffer), and 3.5 and 84.7 (between pH 4.5 acetate buffer and pH 6.8 phosphate buffer), respectively.

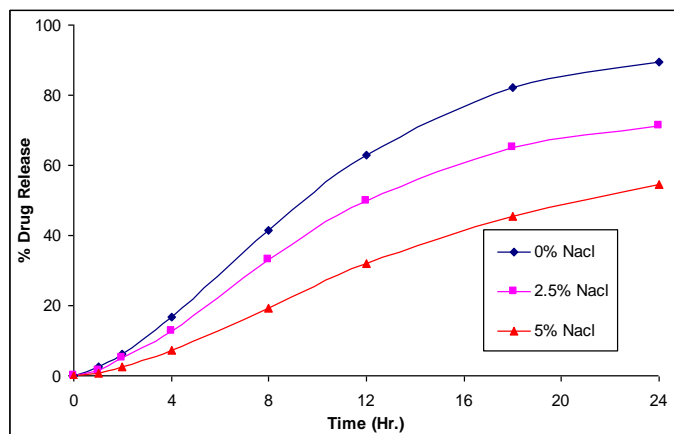


FIGURE 7: Effect of Osmotic Pressure

It was concluded that osmotic pumping is the major mechanism governing drug release from developed formulations²⁰⁻²³.

CONCLUSION:

Extended release formulations of carvedilol phosphate were developed based on osmotic technology. The effect of different formulation variables was studied to optimize release profile. Solubility of active pharmaceutical ingredient is the key factor in development of osmotic dosage form. It is difficult to formulate the osmotic tablet of drugs having low solubility. Solubility of drug is required to increase to get desired profile. Level of solubilizer affected the release from the developed formulations. As the concentration of polysorbate 80 increased, release rate was increased. Effect of sodium chloride concentration, pore former concentration and weight gain of tablets on dissolution was also checked. Concentration of sodium chloride, pore former increases, dissolution rate of carvedilol phosphate also increases. But increase in the tablet weight gain is inversely proportional to the dissolution release rate.

The release from the optimized formulations was independent of pH and agitation intensity of the release media, assuring the release from the tablet was independent of pH and hydrodynamic conditions of the body. Carvedilol phosphate release from the developed formulation was inversely proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release.

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