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Floating Capsule for Delivery of Ketoprofen

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ABSTRACT

A floating capsule was prepared in the present study to effectively release ketoprofen, which is not highly soluble in water. By dipping stainless steel molds in a cellulose acetate solution with glycerol acting as a plasticizer, the capsule membrane was prepared using the phase inversion technique. Since ketoprofen, the medication chosen for this investigation, has a limited solubility in water, it cannot generate sufficient diffusion pressure to induce its own release. PEG 4000, a solubility enhancer, was used in this investigation to improve the drug's solubility and the core's diffusion pressure.

Key words: capsule, cellulose acetate, glycerol, ketoprofen , diffusion

INTRODUCTION

Wesselingh [1] thoroughly examined and described the use of diffusion pressure for regulated pharmacological agent administration. Based on the principles of diffusion or osmosis, these controlled drug delivery devices release the therapeutic substance at a predefined, usually zero-order, delivery rate. [2, 3]. Semipermeable membranes and osmotic excipients can be used to make the release rate from such a system independent of pH and agitation rate. [4]. An active core encircled by a semipermeable membrane—a barrier that is permeable to a solvent but impenetrable to ionic chemicals and heavier molecular weight compounds—makes up this type of diffusional drug delivery device. [5]. The semipermeable membrane for capsule can be prepared by phase inversion technique using a plasticizer. The plasticizer would leach out during the manufacturing process or dissolution. Hence the process of phase inversion will result into the formation of micro porous semipermeable membrane that will allow the system to float for a desired period of time [6, 7].

Floating capsule are designed to have an core surrounded by a semi-permeable membrane that allows water to move in at a rate determined by the fluid permeability of the membrane and diffusion pressure of the core but prevents salt and drug molecules from moving out. The drug molecules will now exit only through the membrane at a controlled rate due to the increase in diffusion pressure brought about by the volumetric increase inside the core [1]. The coating membrane allows the release of the drug by virtue of increased diffusion pressure inside the system. Numerous designs of such capsules have been reported [8, 9].

Moderately aqueous solubility of drug is a prerequisite for the drug to be released from such system. Hence increasing the solubility of the poorly water-soluble drugs in the core becomes the prime concern for their diffusional delivery. This can be done by incorporating solubilizing agents called like, mannitol [10], PEG 4000 [11] or using cyclodextrin derivatives [12].

Based upon these assumptions, floating capsules of cellulose acetate membrane were prepared by phase inversion technique for delivery of poorly water-soluble drug ketoprofen by using a solubilizing agent, PEG 4000. Ketoprofen is a potent non-steroidal anti-inflammatory agent, having short plasma half-life of 3-3.6 hrs, though it is the safest prfloatingionic acid derivative but is associated with gastro-intestinal hazards.

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Hence this drug was considered for develfloatingment of oral sustained/controlled release formulation.

MATERIALS AND METHODS

Cellulose acetate (CA) was obtained from Glaxo lab. Ltd., India, PEG 4000, was obtained from S.D. Fine Chemicals Ltd Delhi; the drug Ketoprofen was a gift sample from FDC Pharmaceutical, Ltd Bombay India.

Preparation of floating capsule

Cellulose acetate solution (15% w/v) was prepared in acetone/water (90/10) solvent system. Accurately weighed quantity of CA was added to acetone/water solvent system and the resulting mixture was stirred in a well-closed beaker to obtain a homogeneous solution. The required quantity of plasticizer, glycerol[13] (10% w/w of CA) was added to the solution while stirring. The stainless steel moulds fabricated in the dimension so as to form capsule body and cap were dipped in the coating solution for 2 minutes and then removed carefully so as to form a thin layer of solution on the mould, followed by brief air drying for 5 minutes. The pins were then immersed in aqueous solution (10% w/v glycerol), to effect phase inversion and formation of semipermeable membrane of CA. The resulting membrane was stripped off and trimmed to desired size and stored for future use. The thickness of the capsule wall and the area of capsule were determined by digital micrometer (Mitutoyo Japan).

Filling of floating capsule

The floating capsules were filled with different proportions of ketoprofen and solubilizing agent (PEG 4000), to study the effect of solubilizing agent on the diffusion of drug from the capsule. The amount of the drug in the mixture was kept constant (100 mg) and the proportions of PEG 4000 were varied as; 25 mg, 50 mg, 75 mg and 100 mg respectively. The physical mixtures of ketoprofen and PEG 4000 were prepared by mixing them thoroughly in laboratory blender for 10 minutes and subsequently passing the mixture through sieve No. 80. Each of the mixtures was filled in the body of the capsule and the micro drilled cap was snuggly fitted to the body and finally sealed with a 16% w/v solution of CA only so as to ensure that no release takes place through the seal of the capsule.

In vitro drug release test

The *in vitro* release studies were performed according to USP dissolution apparatus II (50 rpm, 37° ± 5 ° C); and distilled water was used as a dissolution medium. The samples were withdrawn hourly for nine hours and analyzed by using UV spectrophotometer at 257nm λmax. To investigate the effect of diffusion pressure on the drug release behavior, release of the drug was studied in aqueous solutions of different osmotic pressure. Linear regression was carried out for the linear part of the dissolution curve for each capsule.

RESULT AND DISCUSSION

The capsules were subjected to floating test to prove that the prepared system floats for a prolonged time and thus releasing its encapsulated content. For this purpose the capsules were gently floated in the simulated gastrointestinal fluid. It was observed that the system floated for 18 hrs. The capsule was then filled with a amaranth dye and allowed to float in gastrointestinal fluid. In this case the release of dye was observed after a time lag of 13 mins. The lag time observed is due to the time required for hydration and subsequent permeation of water through the wall of capsule, which results in solubilization and formation of saturated solution of dye resulting in increase of hydrostatic pressure inside the system and causing its release [10, 15].

In vitro release rate study showed that as the amount of PEG 4000 was increased in the core of floating capsule the amount of drug released also increased as shown in fig.1. This may primarily be due to the solubilization effect of PEG 4000, resulting in increased solubility of drug and subsequent increase of diffusion pressure inside the system causing increased amount of drug being released from the system. As PEG 4000 is also released along with the drug, hence its solubility effect inside the core would be terminated more promptly at when it is present at low level (25 mg) as compared to its higher in the core (100 mg). This leads to the released amount of drug being the function of the added amount of PEG 4000. When the maximum drug released from the Capsule with different proportion of PEG 4000 was plotted against the amount of PEG 4000 in the core a linear relationship ($r^2 = 0.9734$). Based on this

the amount of PEG 4000 required for 100% release was calculated to be 178.62 mg.

Dissolution data of all the formulations was fitted to various mathematical models (zero order, first order and Higuchi) to describe the kinetics of drug release Drug release from the formulation fitted well into first order model (Table 1), suggesting that the release of the drug depends upon the concentration of the components incorporated in the core of the formulation.

Table 1: Kinetics of *in-vitro* release and dissolution parameters of different floating capsule.

Drug: PEG 4000	Zero-order		First Order		Higuchi		Lag-time (hr)	Max drug released (%)
	K_0 (%/h)	r^2	K_1 (h^{-1})	r^2	K_H (%/$h^{1/2}$)	r^2		
1:0.25	5.469	0.9857	-0.0284	0.9857	23.944	0.9832	2.04	32.14±0.95
1:0.5	7.966	0.9852	-0.0455	0.9941	35.082	0.9839	1.99	48.29±0.86
1:0.75	9.025	0.9871	-0.0551	0.9961	39.729	0.9951	1.84	54.26±0.88
1:1	10.383	0.9881	-0.0706	0.9981	45.712	0.9969	1.58	67.85±1.06

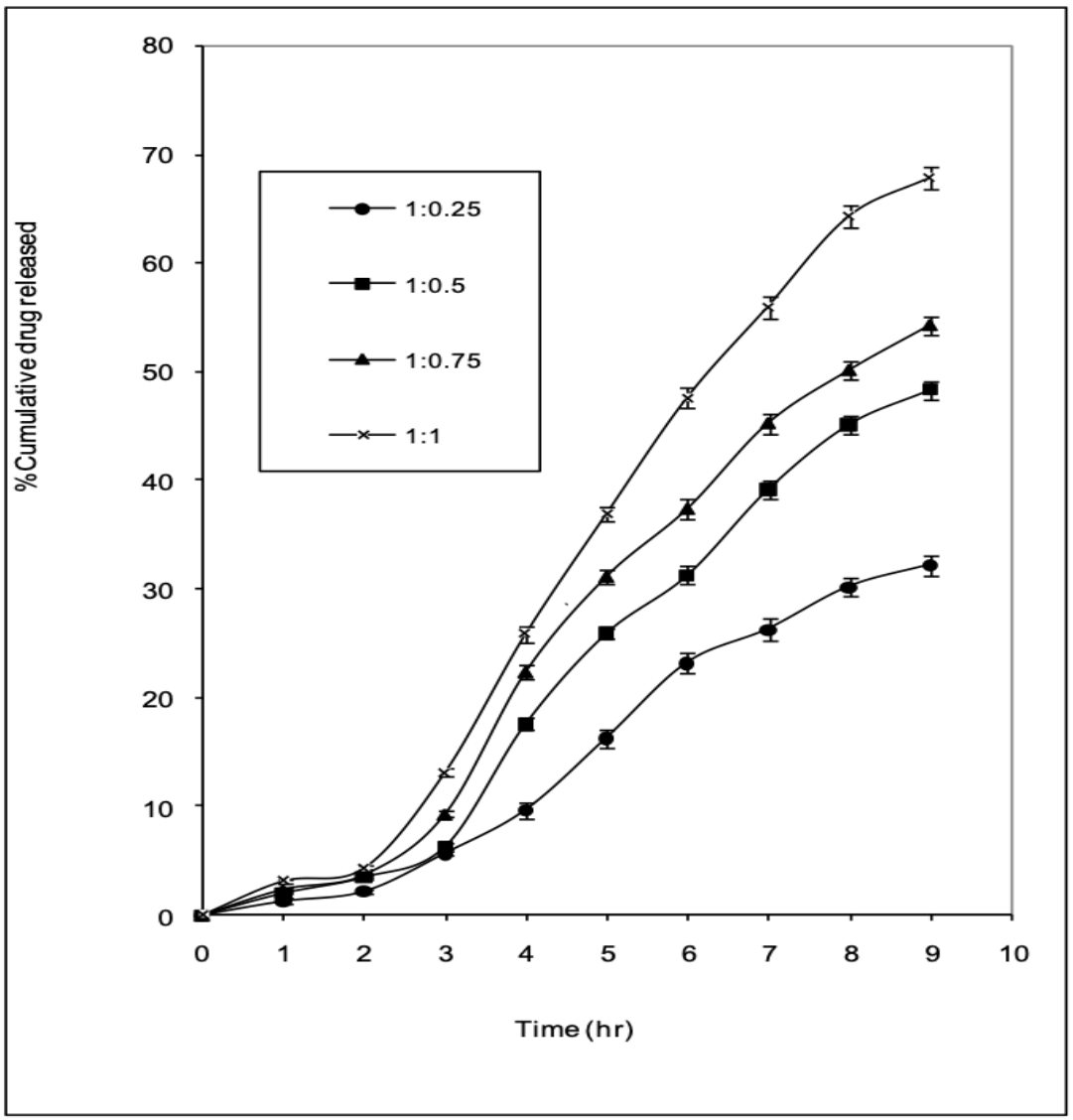

Figure 1: Release profile of ketoprofen from floating capsule filled with different ratio of drug: PEG 4000 (●) 1:0.25, (■) 1:0.5, (▲) 1:0.75 & (×) 1:1.

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