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ORIGINAL RESEARCH ARTICLE

Formulation of Floating Microspheres of Ritonavir by Crosslinking-Technique: Effect of $NaHCO_3$ as Gas Forming Agent

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ABSTRACT

Floating microspheres of Ritonavir was prepared by simple dripping method with an aim of increasing the gastric residence time and for controlled release. A polymeric mixture of Sodium alginate and hydroxy propyl methylcellulose was used. Sodium bicarbonate was used as the gas-forming gent. The solution was dropped to 1% calcium chloride solution containing 10 % acetic acid for carbon dioxide release and gel formation. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapped, morphology and in vitro release study. Effect of sodium bicarbonate on the above mentioned parameters were evaluated and it was found that the sodium bicarbonate had a pronounced effect on various parameters. The enhanced buoyancy and controlled release properties of sodium bicarbonate containing microspheres made them an excellent candidate for floating dosage form.

Keywords: Ritonavir, Floating microspheres, Sodium bicarbonate, controlled release.

INTRODUCTION

Oral controlled release dosage forms (OCRDFS) are being developed for the past three decades due to their advantages. The design of oral controlled drug delivery system is primarily aimed at achieving more predictable and increased bioavailability, thereby obtaining a maximum therapeutic effect. However some of these systems don't work as planned due to several physiological difficulties, such as an inability to restrain and localize the drug delivery system within desired region of GI tract and highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hours. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in stomach or upper part of small intestine[1].

Thus placement of drug delivery system in a specific region of the GI tract offers a numerous advantages especially to the drugs having narrow absorption window, stability problem in intestine, poor solubility in alkaline PH, local activity of in stomach and property to degrade in colon. Therefore the design of a sustained release preparation requires both prolongation of gastrointestinal transit of dosage form as well as controlled drug release. Recently one of such systems has been reported as floating drug dosage systems (FDDS)[2,3]. FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period of time. While the systems are floating, the drug is released slowly from the system at a desired rate.

Ritonavir is a antiretroviral agent used in treatment of HIV and viral diseases has been taken as a model drug in the present

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investigation because of its low biological half-life (3-5h) moreover It is primarily absorbed from stomach[4].

MATERIALS AND METHODS

Ritonavir was obtained as a gift sample from Aristo, Bhopal (MP). Sodium bicarbonate, calcium chloride, acetic acid, used was of analytical grade, purchased from Merck specialties Pvt Ltd, Chemistry-chem.Ltd, Loba chemie Pvt Ltd. Mumbai respectively.

Preparation of Floating alginate microspheres[5-8]:

Floating alginate microspheres were prepared by ionic gelation method method. The drug polymer ratio used to prepare different formulations were kept constant i.e. 1:1. A solution was prepared by dissolving 1000 mg of drug in 5 ml distilled water. The above solution was added to 30 ml alginate solution 3 % (W/V) containing HPMC (alginate: HPMC = 9:1 W/W). $NaHCO_3$ was added to the solution with levels from 50-500 mg as the gas-forming agent. The resulting solution was dropped through 24 G syringe needle into 1 % (W/V) calcium chloride solution containing 10 % acetic acid. The solution containing suspended microspheres were stirred with a magnetic stirrer for 10 minutes to improve mechanical strength and allowed to compete the reaction to produce gas. The fully formed microshperes were collected, washed with ethanol and then with distilled water, subsequently dried at low temperature (0-4^{0}C). Microspheres containing 50,100,250,500 mg of $NaHCO_3$ were given formulation code as F_1, F_2, F3 and respectivillyF_4 respectively and F_5 to formulation without $NaHCO_3$.

$$NaHCO_3 + CH_3COOH \rightarrow CH_3COONa + H_2O + CO_2$$

Measurement of Micromeritic properties[9]:

The flow properties of prepared microspheres were investigated by measuring the bulk density, tapped density, Carr's index and packing factor. The bulk and tapped densities were measured in a 10 ml graduated measuring cylinder. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which, their respective densities were calculated.

Particle size Analysis[9]:

Microspheres were separated into different size fractions by sieving for 10 minutes using a mechanical shaker (Labtech, Indore, Co. India) containing standard sieves # 16, # 24, # 30, # 44 and # 60 and mean particle sizes of microspheres were calculated.

Drug content and encapsulation efficacy of floating microspheres:

50 mg of formulations was dissolved in 50 ml of 0.1N HCl. The samples were assayed for drug content by UV- spectrophotometer (UV-1700) at 284 nm and the drug content was calculated.

Buoyancy test[10]:

In vitro evaluation of floating behavior studies were performed by placing 50 particles into 50 ml glass flask and subsequent addition of 50 ml 0.1 N HCl containing 0.02% w/v. Tween 20 was added to exclude floating due to non wetted surfaces followed by horizontal shaking (37 ^{0}, 75 rpm). At pre determined time intervals (2, 4, 6, 8 hrs) the flasks were allowed to stand to 5 mins without agitation and numbers of floating particles were counted. The % of floating microspheres was calculated by following equation.

$$\% \text{ floating microsphere} = \frac{no.of\ floating\ microspheres}{initial\ no.of\ floating\ microspheres} x100$$

Fourier Transform Infrared Spectroscopy [FTIR] Study:

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug, pure polymer and drug-loaded microspheres using FTIR. Samples were prepared in KBr desks [2mg sample in 200mg KBr]. The scanning range was 400-4000cm^{-1} and the resolution was 2cm^{-1}.

In vitro drug release study:

The drug release rates from floating microspheres were carried out using Tablet dissolution test apparatus. A weight of floating microspheres corresponding to 100 mg of drug was filled into a capsule and placed in basket. Dissolution media was 500 ml 0.1N HCl maintained at 37 ± 1^0 and stirred at 100 rpm. Samples (5 ml) were withdrawn at suitable interval of time and volume was adjusted. It was then assayed spectrophotometrically at 284 nm.

RESULTS AND DISCUSSION

Most of floating microspheres were obtained in the size range of 1000-1700 μm **(Table 1).** The highest and lowest mean particle size was found to be 444.5 μm and 374 μm respectively. The variation in mean particle size could be due to

weight variation of $NaHCO_3$. $NaHCO_3$ significantly increase the pore size and hence the bead size. The effect of $NaHCO_3$ on drug content and drug encapsulation was also calculated, it was found that with increase in amount of $NaHCO_3$ the drug content and encapsulation decreases **(Table 2).** This might be attributed to the increase in porosity of formulation with higher proportion of $NaHCO_3$. These pores might act as a channeling agent for bleaching out of drug during formulation. More than 60 % of particles kept floating for 8 hours except formulation without gas forming agent, F5 **(Table 2 & Fig 1)** .The $NaHCO_3$ containing floating microspheres had a highly porous internal and external structure, which entraps air within the system. Upon exposure to aqueous medium the entrapped air was slowly removed from system leading to extended floating time. Spherical microspheres could not be formed because released CO_2 gas burst the spheres before it was sufficiently hardened making the surface rough. From the *in vitro* release study it was observed that the drug release rate increased with increase in proportion of $NaHCO_3$ and in absence of $NaHCO_3$ (F5) the release rate was very slow. This may be due to the fact that in absence of $NaHCO_3$ the alginate forms a highly dense internal structure which retains the drug more promptly but in presence of $NaHCO_3$ the formulations becomes porous and the porosity increases with increase amount of $NaHCO_3$ and drug is released at faster manner **(Fig 2)**

FDD of Ritonavir was successfully prepared by cross-linking technique using alginate and HPMC. The physical properties of the resulting microspheres, drug entrapment, drug content and drug release pattern varied according to amount of gas forming agent that is $NaHCO_3$.So it could be concluded that by delineation of the formulation factors and further research a more therapeutically effective floating drug delivery system of Ritonavir can be developed.

Table 1: Micromeritic Properties Of Ritonavir Floating Microspheres

Formulations	Mean particle size (µm)	Flow properties	
		% Compressibility	Packing factor
F1	374 ± 5.56	17.86 ± 0.33	1.21 ± 0.06
F2	423 ± 5.70	12.49± 0.25	1.14± 0.025
F3	444.5 ± 4.86	9.7 ± 0.52	1.10 ± 0.014
F4	444.0 ± 3.68	5.1 ± 0.26	1.05 ± 0.035
F5	401.7 ± 5.13	13.1 ± 0.48	1.15 ± 0.04
Pure drug	---	30.55 ± 0.11	44 ± 0.021

Each observation is the mean ± S.D. of three determinations

Table 2: Characteristic Of Ritonavir Floating Microspheres

Formulation	% Yield	% Drug content	% Drug entrapped	% Particles floated at 8h
F1	77.1± 0.503	34.99 ± 0.093	69.98 ± 0.185	40.22 ± 1.52
F2	86.26 ± 0.569	32.27 ± 0.246	64.55 ± 0.491	47.27 ± 1.14
F3	89.6 ± 0.864	29.84 ± 0.221	59.69 ± 0.443	53.65 ± 1.43
F4	83.8± 0.449	29.18 ± 0.113	58.37 ± 0.226	67.85 ± 0.57
F5	90.2 ± .614	35.5 ± 0.177	71.0 ± 0.350	---

Each observation is the mean ± S.D.of three determinations.

Fig 1: Effect of $NaHCO_3$ on floating behaviour of alginate formulations at various time intervals. (□) Formulation F1, (▨) formulation F2, (▩) formulation F3, (▨) formulation F4

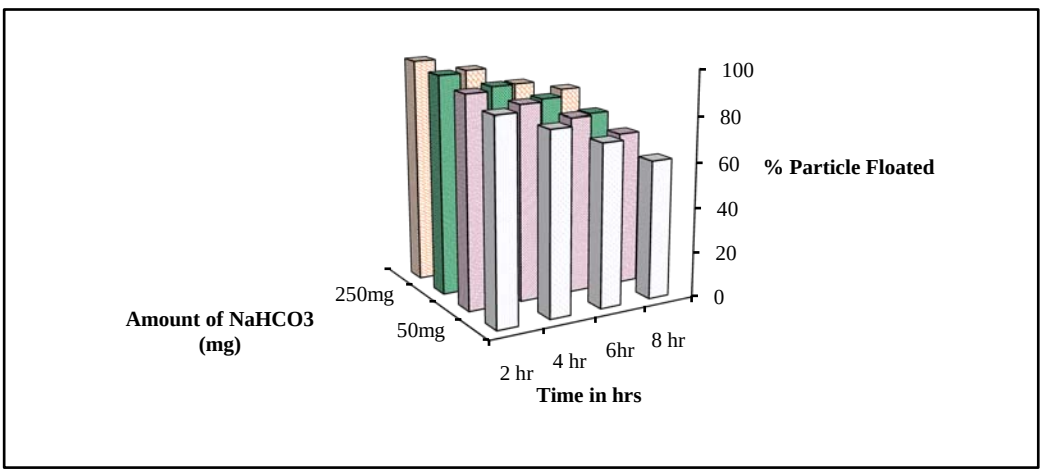
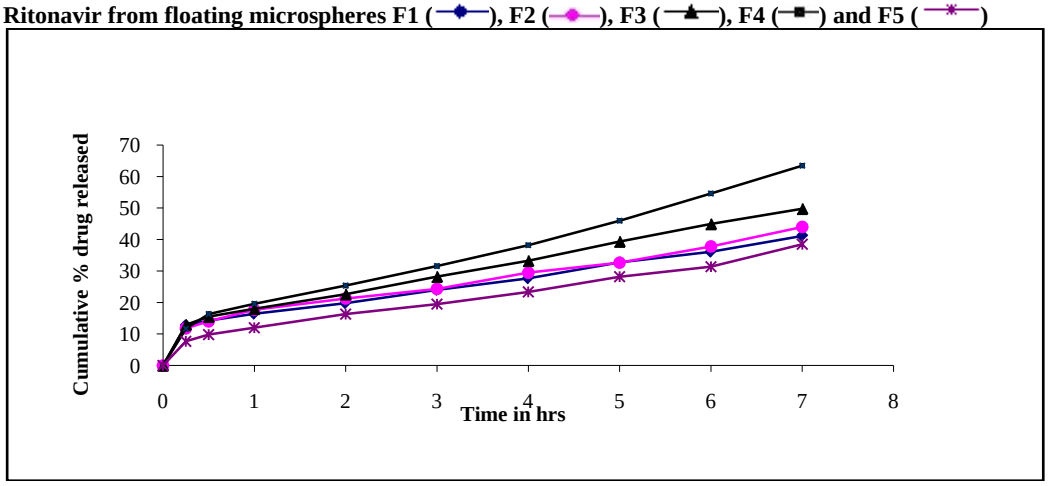


Fig 2: Comparative *In vitro* dissolution profile of Ritonavir from various alginate floating microspheres

Release rate of Ritonavir from floating microspheres F1 (—◆—), F2 (—●—), F3 (—▲—), F4 (—■—) and F5 (—✳—)



CONCLUSION

The floating microspheres of ritonavir was prepared by cross-linking technique and effect of $NaHCO_3$ was studied and concluded that the increase in amount of $NaHCO_3$ the drug content and encapsulation decreases. This might be attributed to the increase in porosity of formulation with higher proportion of $NaHCO_3$ and leading to extended floating time.

SUMMARY

The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapped, morphology and in vitro release study. Effect of sodium bicarbonate on the above mentioned parameters were evaluated and it was found that the sodium bicarbonate had a pronounced effect on various parameters. The enhanced buoyancy and controlled release properties of sodium bicarbonate containing microspheres made them an excellent candidate for floating dosage form.

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