Research Article

Design and Evaluation of an Oral Floating Matrix Tablet of Salbutamol Sulphate

Suresh Kumar[1], Ram Kumar Sahu[2*], Shalini Sharma[1], Sukhbir Lal Khokra[1] and Rajendra Jangde[3]

[11]*Manav Bharti University, Laddo, Solan-173229 (H.P.),* [2]*Oriental College of Pharmacy, Raisen Road, Bhopal-462021 (M.P.),* [3]*Institute of Pharmacy, Pt. Ravi Shankar Shukla, University, Raipur (C.G.), India.*

Abstract

Purpose: To develop floating matrix tablets of salbutamol sulphate using ethyl cellulose and acrycoat S-100 as polymers, and sodium bicarbonate, citric acid and tartaric acid as gas generating agents.
Methods: Twenty four formulations were prepared and segregated into four major categories, A to D. The floating tablets were prepared by wet granulation technique, and the granules were compressed at a pressure of 50 kg/cm^2. The tablets contained drug, ethyl cellulose and Acrycoat S-100 (as release-retarding polymers), sodium bicarbonate, citric acid and tartaric acid (as gas formers) as well as various additives. The tablets were made by wet granulation technique. The formulations were evaluated for in vitro buoyancy, dissolution and in vitro drug release.
Results: All the formulations fulfilled the essential requirements for good floating systems. Formulation F8, containing citric acid and sodium bicarbonate, showed lower lag time and longer floating duration than the formulations containing only sodium bicarbonate. Formulation F8.2 (which contained citric and tartaric acid at a ratio of 1:1) showed longer floating duration (9 h) than F8. As the concentration of sodium bicarbonate increased in formulation F8.2, drug release decreased while floating duration increased.
Conclusion: Of all the 24 formulations, the one containing tartaric acid and citric acid in ratio 1:3 and 12 mg sodium bicarbonate showed the highest floating duration and least lag time.

Keywords: Salbutamol sulphate, Ethyl cellulose, Acrycoat S-100, Sodium bicarbonate, Citric acid, Tartaric acid

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Corresponding author: **Email:** *ramsahu79@yahoo.co.in;* **Tel:** *+91-9893577279*

INTRODUCTION

The high cost involved in the development of a new drug molecule has caused many pharmaceutical companies to divert greater attention to the development of new drug delivery systems. One of such delivery systems is gastroretentive drug delivery system (GDDS). Gastroretentive dosage formulations extend the duration of drug action by increasing time over which drug is released, thus increasing dosing intervals and patient compliance. Various gastroretentive techniques, including floating, swelling, high density, and bioadhesive systems, have been explored to increase gastroretention of dosage forms [1].

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting gastric emptying rate for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastric retentive time and reduced fluctuation in plasma drug concentration [2].

The drug selected for this study, salbutamol sulphate, is a sympathomimetic amine used as a bronchodilator in the treatment of reversible bronchospasm. This drug is given in a daily dose of 4 - 8 mg and has a short biological half-life (1.2 h). A GDDS formulation of the drug may be advantageous over the conventional oral dosage form and inhaler due to its ability to maintain prolonged therapeutic concentrations in systemic circulation [3,4]. Consequently, an attempt was made in the present work to develop a gastroretentive drug delivery system of salbutamol sulphate with a view to increasing the bioavailability of salbutamol sulphate.

EXPERIMENTAL

Materials

Salbutamol sulphate, ethyl cellulose and Acrycoat S-100 (Corel Pharma Chem,

Ahmedabad) were received as gifts from Cipla Laboratories, Himachal Pradesh, India. Sodium bicarbonate, citric acid (anhydrous) and tartaric acid were purchased from S.D. Fine-Chem Ltd, Ahmedabad, India. All other ingredients were of laboratory grade.

Preparation of floating tablets

All together, twenty four formulations, in four series (A to D), were prepared by wet granulation method.

Formulation A series

The composition of the formulations is mentioned in Table 1. The tablet incorporated the drug (salbutamol sulphate), ethyl cellulose and Acrycoat S-100 as matrix formers, and sodium bicarbonate and citric acid as gas generating agents. All the powder ingredients (talc and magnesium stearate) were passed through a 177 μm aperture sieve separately. Salbutamol sulphate, the polymers and diluents were mixed thoroughly in a glass mortar and sufficient quantity of the binding agent added slowly to obtain a dough. The mass was sieved through a 2.0 mm mesh screen and dried on trays in a hot air circulation oven at 60 °C for 30 min. The dried granules retained on a 500 μm mesh were mixed with talc and magnesium stearate and then compressed into tablets using an automated single punch tabletting machine, keeping tablet hardness at 4 – 5 kg/cm^2 and weight at 100 ± 5 mg.

Formulation B series

This formulations series (F8, F8.1 and F8.2) was prepared to improve the floating capability of the best formulation in A series, namely, F8, by incorporating an additional floating agent (tartaric acid) as well as its combination with citric acid. The method of preparation was the same as for A series; the composition of B series is shown in Table 2.

Formulation C series

Formulations C series (FCT1 to FCT9) was made to increase the floating time of the tablets while decreasing the disintegration rate. A full 3^2 factorial design applied on the best formulation of B series by taking reduced proportion of tartaric acid and citric acid to obtain the formulations. Tablet preparation was the same as described above; the composition of the series is shown in Table 3.

Formulation D series

Finally formulation design D (FCT8, FCT8.1 and FCT8.2) was optimized by incorporating mixtures of citric acid and tartaric acid in varying ratios while retaining the sodium bicarbonate content in F8 of formulation C series. The method of preparation was as described earlier for A series, and the composition is as shown in Table 5.

Full factorial design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations.

In vitro buoyancy studies

In vitro buoyancy was determined by floating lag time and total floating time. The tablets were placed in a 100 ml beaker containing 0.1M HCl. The time required for the tablet to rise to the surface of the liquid and the duration of the time it remained floating were noted as floating lag time and floating time, respectively.

In vitro dissolution studies

In vitro dissolution studies on the tablets were carried out in a USP XXIII type 2 dissolution test apparatus, employing a paddle stirrer at 100 rpm in 900 ml of dissolution medium maintained at 37 ± 0.5 °C. The first 2 h of dissolution was carried out in hydrochloric acid buffer (HCAB, pH 1.2), followed by 5 h in phosphate buffer (PB, pH 6.8). At predetermined time intervals, 5 ml samples were withdrawn by means of a syringe fitted with a filter (0.22 μm, Raylab NZ, Ltd). The volume withdrawn at each interval was replaced with the same quantity of fresh dissolution medium. The samples were analyzed for drug release by measuring the absorbance at 225 nm spectrophotometrically (UV-1800, Shimadzu, Japan) after suitable dilution. All determinations were performed in triplicate [5-8].

Analysis of kinetics of drug release

To analyze the *in vitro* release data, various kinetic models, including zero order (Eq 1), first order (Eq 2) [9], Higuchi (Eq 3) [10], and Hixson-Crowell cube root law (Eq 4) [11] were applied to the data.

$$C = k_0 t \qquad \text{………..…… (1)}$$
where, k_0 is the zero-order rate constant expressed in units of concentration, C is concentration of the drug and t is time.

$$\log C = \log C_0\, kt/2.303 \qquad \text{…………….. (2)}$$
where C_0 is the initial concentration of the drug and k is first order rate constant.

$$Q = k t_{1/2} \qquad \text{……..………….……… (3)}$$
where k is a constant reflecting the design variables of the system and Q is cumulative drug release.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \qquad \text{………..………… (4)}$$
where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the tablet and K_{HC} is rate constant for Hixson-Crowell rate equation.

Mechanism of drug release

Two relationships, Korsemeyer–Peppas and Weibull models [12,13], were applied to determine the mechanism of drug release as in Eqs 5 and 6, respectively.

$$M_t/M_\infty = kt^n \qquad \ldots\ldots\ldots\ldots.\ldots\ldots\ldots \text{(5)}$$

where M_t/M_∞ is the fraction of drug released at time t, K is the rate constant and n is the release exponent. The value of n was used to determine the drug release mechanism of the tablets.

$$log\,\{-\ln(1-M_t/M_\infty)\} = b\,log\,t + \log t_d \ldots\ldots\ldots \text{(6)}$$

where M_t/M_∞ is the fraction of drug released at the *log* of time, t, and b was used to determine the drug release mechanisms of the tablets.

Statistical analysis

Statistical evaluation was performed by analysis of variance (ANOVA) using Microsoft Office Excel 2003 and confidence limit was set at 95 %. Regression coefficient (R^2) was used to determine how well a regression model describes the release data. Mean ± standard deviation (SD) for floating lag time and floating time were calculated using Microsoft Office Excel 2003.

RESULTS

Formulation A series

Bouyancy (floating time) data are shown in Table 1. Floating lag time ranged from 60 to 80 s while duration of floating was 5 h for formulations F1 to F3 which contained only sodium bicarbonate as gas-forming agent. However, when sodium bicarbonate was combined with citric acid, the release of CO_2 increased, thus lowering floating lag time to a range varying from 30 to 70 s for formulations F4 to F9 (Table 1). Formulation F8 exhibited the lowest lag time (30 ± 7 s) and longest floating duration (8±0.5 h*) compared. Consequently, F8 was used for optimization studies.

Formulation series A (F1 to F9) fitted most to zero order kinetics with coefficient of regression (R^2) ranging from 0.929 to 0.985 and 0.905 to 0.989 in HCAB and PB media, respectively, compared with 0.918 to 0.965 and 0.756 to 0.966 (for Higuchi) in HCAB and PB, respectively. Of all the formulations, F8 showed the best fit to zero order with R^2 of 0.985 and 0.989, HCAB and PB, respectively, and also showed the highest level of drug release. Hence, F8 was considered the most suitable for optimization study.

Formulation B series

Table 2 shows the results of further optimization of F8. It reveals that formulation F8.2 exhibited longer duration of floating (9 h) and lower lag time (20 ± 3 s) than F8.1 (6 h and 30 ± 5 s, respectively). Therefore F8.2

Table 1: Composition and floating properties of formulation A series

Composition (mg)									Floating behavior		Drug release	
FC	*Drug*	*EC*	*AS*	*SB*	*CA*	*LA*	*TC*	*MS*	*LT (s)*	*DF (h)*	HCAB (2 h)	PB (5 h)
F1	12	40	30	8	0	7	2	1	70±2	5±0.5	32.1%	42.9%
F2	12	40	30	10	0	5	2	1	80±2	5±0.5	31.3%	23.6%
F3	12	40	30	12	0	3	2	1	60±4	5±1.0	30.3%	45.9%
F4	12	40	30	8	0.5	6.5	2	1	65±3	6±0.25	27.4%	41.8%
F5	12	40	30	10	0.5	4.5	2	1	70±1	6±0.5	26.6%	41.3%
F6	12	40	30	12	0.5	2.5	2	1	40±7	7±0.5	26.0%	43.0%
F7	12	40	30	8	1	6	2	1	50±5	6±0.10	27.7%	42.1%
F8	12	40	30	10	1	4	2	1	30±7	8±0.5	27.1%	49.3%
F9	12	40	30	12	1	2	2	1	55±7	5±0.25	26.6%	41.5%

FC = Formulation code, EC = ethyl cellulose, AS = Acrycoat S-100, SB = sodium bicarbonate, CA = citric acid, LA = lactose, TC = talc, MS = magnesium stearate, LT = lag time, DF = duration of floating

Table 2: Composition and floating properties of Formulation B series

Composition (mg)										Floating property		Drug release	
FC	*Drug*	*EC*	*AS*	*SB*	*CA*	*TA*	*LA*	*TC*	*MS*	*LT (s)*	*DF (s)*	HCAB (2 h)	PB (5 h)
F8	12	40	30	10	1	-	4	2	1	30±7	8±0.50	27.1%	49.3%
F8.1	12	40	30	10	-	1	4	2	1	30±5	6±0.25	45.3%	48.1%
F8.2	12	40	30	10	0.5	0.5	4	2	1	20±3	9±0.75	24.8%	54.0%

Key: FC = Formulation code, EC = ethyl cellulose, AS = Acrycoat S-100, SB = sodium bicarbonate, CA = citric acid, TA = tartaric acid, LA = lactose, TC = talc, MS = magnesium stearate, LT = lag time, DF = duration of floating

Table 3: Composition and floating properties of Formulation C series

Composition (mg)									Floating property		Drug release (7 h)
FC	Drug	EC	AS	SB	CA+TA	LA	TC	MS	LT (s)	DF (h)	
FCT1	12	40	30	8	0.5	6.5	2	1	51±7	6.0±0.20	61.4%
FCT2	12	40	30	8	1.0	6	2	1	40±7	7.5±0.025	65.5%
FCT3	12	40	30	8	1.5	5.5	2	1	44±7	6.5±0.50	64.2%
FCT4	12	40	30	10	0.5	4.5	2	1	38±4	7.5±1.00	60.5%
FCT5	12	40	30	10	1.0	4	2	1	21± 3	10.0±1.00	81.2%
FCT6	12	40	30	10	1.5	3.5	2	1	27± 5	8.5±0.025	82.9%
FCT7	12	40	30	12	0.5	2.5	2	1	25±6	16.0±0.50	63.0%
FCT8	12	40	30	12	1.0	2	2	1	22±9	18.0 ±0.50	57.9%
FCT9	12	40	30	12	1.5	1.5	2	1	24±8	15.5±0.20	54.8%

FC = Formulation code, EC = ethyl cellulose, AS = Acrycoat S-100, SB = sodium bicarbonate, CA = citric acid, TA = tartaric acid, LA = lactose, TC = talc, MS = magnesium stearate, LT = lag time, DF = duration of floating

was selected for further optimization.

All formulations in the series followed more closely zero order kinetics with R^2 in the range of 0.981 to 0.991 and 0.972 to 0.981 in HCAB and PB media, respectively, compared with 0.951 to 0.962 and 0.940 to 0.954 in HCAB and PB, respectively, for the Higuchi model. F8.2 with R^2 of 0.991 and 0.981 in HCAB and PB, respectively, showed higher values than the other formulations in the series and, therefore, was selected for further optimization.

Formulation C series

As Table 3 shows, when citric acid and tartaric acid were incorporated in 1:1 ratio while increasing the proportion of sodium

bicarbonate in the formulation in a full 3^2 factorial design, floating duration of the tablets increased from 6.0 ± 0.2 to 18.0 ± 0.5 h, while lag time decreased from 51 ± 7 to 22 ± 9 s; furthermore, the drug did not release rapidly from tablets not disintegrate rapidly. All tablets remained intact in HCAB. Formulation FCT8 was considered the best formulation on the basis of short lag time (22 ± 9 sec) and high duration of floating (18 ± 0.5 h).

When the release data for Formulations C series (FCT1 to FCT9) were subjected to five kinetic release models, the following R^2 values were obtained in HCAB media: zero order (0.912 to 0.998), Higuchi (0.803 to 0.953), first order (0.942 to 0.993), Hixson-Crowell (0.929 to 0.988) and Korsemeyer-

Peppas (0.961 to 0.993). The R^2 data fitted most closely to zero order kinetics, with FCT8 (R^2 = 0.998) fitting most closely of all the formulations in the series, hence was selected for further optimization.

The n data obtained Korsmeyer-Peppas relationship suggested that all the formulations in the series exhibited non-Fickian anamolous diffusion, except FCT5 and FCT6 which followed Case II transport and Super Case II transport, respectively (Table 4). Weibull data suggest that the formulations followed sigmoidal release which is indicative of a complex drug release mechanism where the rate of release increases up to the inflection point and

thereafter declines. Hence, FCT8 was selected for further optimization.

Formulation D series

Table 5 indicates that Formulation series D exhibited lag time ranging from 22 ± 9 to 18 ± 10 s and duration of floating ranging from 18.0 ± 0.5 to 48.0 ± 0.5 h. FCT8.2 with good lag time of 18±10 s and duration of floating of 48 h was the best in the series.

The Korsmeyer-Peppas n data suggest that FCT8 followed non-Fickian transport, i.e., anamolous transport while FCT8.1 and FCT8.2 followed Case II and super Case II transport, respectively. Weibull data suggest

Table 4: Model fitting analysis for formulation C and D

Formulation code	Korsmeyer-Peppas		Weibull
	n	Diffusion mechanism	b value
FCT1	0.746	Non Fickian Anamolous	1.803
FCT2	0.831	Non Fickian Anamolous	1.831
FCT3	0.781	Non Fickian Anamolous	1.736
FCT4	0.810	Non Fickian Anamolous	1.747
FCT5	0.917	Case II Transport	1.707
FCT6	1.052	Super Case II Transport	1.679
FCT7	0.879	Non Fickian Anamolous	1.830
FCT8	0.879	Non Fickian Anamolous	1.743
FCT9	0.800	Non Fickian Anamolous	1.771
FCT8	0.879	Non Fickian Anamolous	1.743
FCT8.1	0.940	Case II Transport	1.832
FCT8.2	1.028	Super Case II Transport	1.737

The shape parameter, b, characterizes the curve as either exponential (b = 1, Case 1), sigmoid, S-shaped, with upward curvature followed by a turning point (b > 1, Case 2), or parabolic, with a higher initial slope and thereafter consistent with the exponential (b < 1, Case 3)

Table 5: Composition and floating properties of formulation D series

Composition (mg)										Floating property		Drug release (7 h)
FC	*Drug*	*EC*	*AS*	*SB*	*CA*	*TA*	*LA*	*TC*	*MS*	*LT (s)*	*DF (h)*	
FCT8	12	40	30	12	0.5	0.5	2	2	1	22±9	18±0.5	63.0%
FCT8.1	12	40	30	12	0.25	0.75	2	2	1	21±1	26±0.5	59.8%
FCT8.2	12	40	30	12	0.75	0.25	2	2	1	18±1	48±0.5	65.6%

FC = Formulation code, EC = ethyl cellulose, AS = Acrycoat S-100, SB = sodium bicarbonate, CA = citric acid, TA = tartaric acid, LA = lactose, TC = talc, MS = magnesium stearate, LT = lag time, DF = duration of floating

that the formulations showed sigmoidal release pattern which is indicative of a complex drug release mechanism where release rate increases up to the inflection point and thereafter declines. Therefore, FCT8.2 is selected as the best formulation for future *in vivo* studies.

DISCUSSION

In formulation A series, sodium bicarbonate induced CO_2 generation in the presence of gastric fluid. The gas generated is trapped within the gel formed by hydration of the polymer, thus decreasing the density of the tablet. As the density of the tablet falls below that of gastric fluid, the tablet became buoyant.

The formulations containing a mixture of citric acid and sodium bicarbonate decreased lag time but increased floating duration, compared with formulations containing only sodium bicarbonate. This could be explained by the fact that sodium bicarbonate present in the formulation as an insoluble dispersion becomes soluble in the acidic medium provided by citric acid, and released Na^+ which reacted with the polymer and produced a cross-linked three-dimensional gel network [14]. Thus the trapped gas increases the duration of floating time.

Moreover, strong gellation of polymer slowed down the rate of water diffusion into the tablet matrix, which resulted in the retardation of drug release. Additionally, citric acid produced a stabilizing effect on the formulations by forming cross-linked gel network in the tablets. Hence, drug release rate was always slower for formulations containing citric acid than for those without it (F8).

Drug release from these gels was characterized by an initial phase of rapid release (burst effect). However, as gelation proceeds, the remaining drug was released at a slower rate and this feature indicates matrix diffusion kinetics.

In formulation B series, the effect of an additional floating agent (tartaric acid) on the duration of floating and floating lag time of formulation A (F8) was studied. The result was that the duration of floating increased.

When sodium bicarbonate reacts with citric acid and tartaric acid, it produces three and two molecules of CO_2 gas, respectively [15]. The combination of citric acid and tartaric acid accelerated the changes of pH value inside the tablet gel compared to the formulation without tartaric acid, because tartaric acid is more soluble than citric acid. This favors increased production rate of CO_2 and lowers the lag time of floating but enhances the duration of floating time. Thus the floating ability of the formulation is greatly dependent on appropriate mixture of citric acid and tartaric acid.

In formulation C series, increase in the concentration of sodium bicarbonate along with the incorporation of citric acid and tartaric acid in 1:1 ratio led to a decrease in drug release. This probably may be related to the solubility of the drug. Salbutamol sulphate has good solubility in aqueous solution at pH 7 but is sparingly to slightly soluble in alkaline solution. Sodium bicarbonate being alkaline in nature creates an alkaline microenvironment around the tablet and the drug is less soluble in alkaline pH which would decrease drug release from the tablet matrix. Formulation FCT8 was the best formulation on the basis of short lag time and high duration of floating.

Interestingly, for formulation D series, the incorporation of citric acid and tartaric acid in ratio 3:1 increased floating duration to as high as 48 h but it also decreased drug release from the tablet. The mechanism underlying the increase in floating duration is not known yet.

CONCLUSION

All the formulations exhibited good floating properties. However, incorporation of

appropriate ratio of citric acid and tartaric acid to enhance buoyancy under elevated stomach pH conditions caused retardation in drug release. Thus, by selecting a suitable composition of citric acid and tartaric acid (3:1) and sodium bicarbonate concentration 12 mg, as in i.e. FCT8.2, the highest floating duration and least lag time were achieved.

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