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Preparation, Optimization and Evaluation of Oral Buoyant Effervescent Tablets, Containing Salbutamol Sulphate as a Model Drug for Gastric Retention

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ABSTRACT

The aim of the present research was to develop oral buoyant effervescent tablets to prolong residence in the stomach using salbutamol sulphate as a model drug. Sustained release (SR)-gastro retentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by narrow absorption windows. Thirteen Tablets formulations were designed by direct compression using HPMC K15M and Polyox WSR 1105 as release-retarding polymers and sodium bicarbonate as a gas former. Microcrystalline cellulose, talc (1%) and Magnesium stearate (1%) were used as diluent, glidant and lubricant respectively. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physicochemical characteristics. All the prepared formulations showed good *in vitro* buoyancy and exhibited sustained and prolonged drug release profiles while floating over the dissolution medium. The best formulation was selected based on in vitro characteristics and was subjected to in vivo radiographic studies. These studies revealed that the tablets remained in stomach for more than 5 hours. Thus, it has been revealed that floating type gastro retentive drug delivery system holds significant potential for better drug delivery of various therapeutics moieties and promising armour in fighting against several acute and chronic ailments.

INTRODUCTION

Salbutamol (Albuterol) sulphate, a moderately selected β_2 receptor agonist, is a racemic mixture of R- and S- isomers. It is widely used as a bronchodilator and is indicated for the management of asthma exacerbations or other chronic obstructive airway diseases. R isomer is primarily responsible for bronchodilation. The high cost involved in developing a new drug molecule has diverted the pharmaceutical industry to investigate various strategies in developing new drug delivery systems [1]. Several methods have been reported that can be used to retain the dosage form in the stomach, which then results in slowly spreading of the drug over the absorptive surface, these include bioadhesive systems [2], swelling and expanding systems [3, 4], floating systems [5, 6] and other delayed gastric emptying devise [7, 8]. A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT), thus enhancing the opportunity for absorption. Development of controlled release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled release preparations using alternative routes have been formulated but the oral route still remains preferable. Development of a successful oral sustained release dosage form requires an understanding of three aspects: (a) gastrointestinal physiology (b) physiochemical properties of the drug and (c) dosage form characteristics. Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent incomplete 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 [9]. The real issue in the development of oral controlled release dosage forms is to prolong the residence time of dosage forms in the stomach or upper gastrointestinal (GI) tract until the drug is completely released [10]. Salbutamol sulphate is one of the widely used drugs for the treatment of bronchial asthma, chronic bronchitis and emphysema [11]. The drug undergoes extensive first-pass metabolism and thus require frequent administrations by oral route. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. A strong need was recognised for the development of a dosage form to deliver salbutamol in the stomach and to increase the efficiency of the drug, providing sustained action. The present study focused on development of buoyant effervescent tablets of salbutamol sulphate, optimising the dosage form in the physical and technological sense, and proving the prolongation of the gastric residence time on albino rabbits.

MATERIALS AND METHODS

Salbutamol sulphate was supplied by Martin and Brown Pvt. Ltd., Hisar (India).

Polyox WSR 1105 was received as gift sample from Dow Chemicals, USA. HPMC KI5M was procured from Colocorn, Goa (India). Sodium bicarbonate, magnesium stearate and talc were generous gifts from S.D Fine-Chem Ltd., Mumbai.

Preparation of buoyant effervescent tablets

HPMC K15M, Polyox WSR 1105 and salbutamol sulphate were mixed to formulate oral buoyant effervescent tablets as depicted in table 1. Sodium bicarbonate was used as a gas generating agent and microcrystalline cellulose was used as diluent. Magnesium stearate (1%w/w) and talc (1%w/w) were used as a lubricant and glidant respectively. The amount of the drug in all of the formulations was kept constant i.e. 3.84% (9.6 mg in each tablet). All the ingredients except magnesium stearate were sifted from # 40 mesh and mixed in a lab scale blender for 15 minutes and then magnesium stearate was sifted from # 60 mesh and lubrication was done for 5 minutes. The lubricated blend was directly compressed in a tablet compressing machine fitted with concave punches and dies (9.0 mm diameter). The tablet weight was adjusted to 250 mg.

Table 1: Thirteen formulation's composition of oral buoyant effervescent tablets of salbutamol sulphate for central composite design.

Ingredients	**Formulation code**												
	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13
Salbutamol Sulphate (mg)	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
HPMC K15M (%)	30	30	30	40	40	40	50	50	50	40	40	40	40
Polyox WSR 1105 (%)	10	15	20	10	15	20	10	15	20	15	15	15	15
Sodium bicarbonate (%)	10	10	10	10	10	10	10	10	10	10	10	10	10

Avicel PH 102	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate (%)	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	250	250	250	250	250	250	250	250	250	250	250	250	250

Experimental Design

The amount of HPMC K15M (X_1) and Polyox WSR 1105 (X_2) were selected as the factors, studied at 3 levels each. The central point (0, 0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. Floating lag time, percentage drug release at 1st h, total floating time and percentage drug release after 12th h were taken as the response variables.

Table 2: Factor combination as per the chosen experimental design

Formulation Code	Coded Factor levels	
	X_1	X_2
B1	-1	-1
B2	-1	0
B3	-1	+1
B4	0	-1
B5	0	0
B6	0	+1
B7	+1	-1
B8	+1	0
B9	+1	+1
B10	0	0

B11	0	0	
B12	0	0	
B13	0	0	
Translation of coded levels in actual units			
Coded level	-1	0	+1
X_1 : HPMC K15M (%)	30	40	50
X_2 : polyox WSR 1105 (%)	10	15	20

Characterization of floating tablets

The prepared floating tablets were evaluated for hardness, uniformity of weight, thickness and length, friability (Roche type friability), drug content, in vitro buoyancy and in vitro dissolution studies. The results were expressed as Mean± S.D. The thickness and length of tablets were determined by the vernier calliper. The hardness of the floating tablets was determined by using a Monsanto hardness tester [12, 13].

Drug Content

Five tablets were individually weighed and crushed. A quantity of powder equivalent to 9.6 mg was extracted in 100 mL of 0.1 N HCl. The solution was filtered through the Whatman filter paper. The drug content was determined using UV visible spectrophotometer at a wavelength of 276 nm after a suitable dilution with 0.1 N HCl [14].

Uniformity of weight

Twenty tablets were individually weighed and the average was calculated. From the average weight of the prepared tablets, the standard deviation was determined [15].

In vitro buoyancy test

Floatation lag time was determined by in vitro buoyancy test. In this test, the prepared tablets were placed in 100 mL beaker containing 100 mL 0.1 N HCl having pH of 1.2 and temp, 37± 0.5°C [16].

***In vitro* dissolution studies**

The release rate of salbutamol sulphate from floating tablets was determined using USP II apparatus. The dissolution test was performed using 900 mL of 0.1 N HCl (pH 1.2) for 12 hours at a constant temperature of 37± 0.5°C and 50 rpm. A sample (10 mL) of the solution was withdrawn at specified interval of time by auto sampler. After that the sample was filtered through Whatman filter paper and absorbance was measured at λ_{max} 276 nm by double beam UV visible Spectrophotometer. Then the concentration was determined from the standard curve in 0.1 N HCl (pH 1.2) [17-19].

Differential scanning calorimetry (DSC)

DSC allows rapid evaluation of possible interactions between the formulation components according to appearance, shift or disappearance of endothermic or exothermic peaks. Drug under investigation was analysed by heating at a scanning rate of 20°C over a temperature range 50-300°C under nitrogen environment [20].

Fourier transform infrared spectroscopy (FTIR study)

Drug polymer interactions were checked by comparing the IR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. FTIR analysis of the sample was carried out for qualitative compound identification.

In vivo ϒ-scintigraphy studies in rabbits

In vivo gastric residence (Gamma scintigraphic studies)

In vivo, gastric behaviour was evaluated by gamma scintigraphy using rabbits. Permission was obtained from the institutional Ethical Review Board.

Radiolabelling of salbutamol sulphate

Drug was labelled with ^{99m}Tc by the stannous reduction method. The ^{99m}Tc was chosen for radio labelling of tablets because of its short half-life (6 h) and allows very little electron emission. It can be administered in millicurie amounts, resulting in a very low radiation dose to the patient. Moreover, ^{99m}Tc is readily available in a sterile, pyrogen-free, and carrier-free state. For the radiolabelling of tablets, 2mCi of ^{99m}Tc was taken to reduce ^{99m}Tc to its valence state [21, 22].

Radiochemical purity

The radiochemical purity of ^{99m}Tc labelled drug was assessed by using ascending instant thin layer chromatographic plates using silica gel-coated sheets and dual solvent system (100% acetone and solvent mixture of pyridine: acetic acid: water) [5:3:1:5 v/v] [23,24].

Gamma imaging in rabbits

The scintigraphy was performed in healthy male New Zealand albino rabbits weighing 2.5 to 4 kg. The radiolabelled tablets were administered orally. Ten minutes before imaging, the animal was anaesthetized by 10 mg diazepam injection. The animal was fixed on a board in the posterior position, and imaging was performed using a gamma camera (Millenium^{TM} VG, GE Medical systems, USA). The scans were obtained at successive intervals.

Scanning electron microscopy (SEM) of tablets

The surface morphology of tablet membrane film of optimized formulation was examined before and after dissolution using scanning electron microscope. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were taken at excitation voltage of 20 KV.

RESULTS AND DISCUSSION

Physical properties of the compressed floating tablet systems

The floating tablets of salbutamol suphate were prepared by an effervescent technique using HPMC K15M, Polyox WSR 1105, sodium bicarbonate, microcrystalline cellulose, along with magnesium stearate and talc as anti adherent and glidant, respectively. Tablets were evaluated in terms of various parameters viz. Hardness, friability, weight variation, drug content uniformity, length and thickness, in vitro dissolution studies and analysis of dissolution data, in vitro buoyancy test, swelling index determination. The results are shown in the following table 2 which includes the values (Mean± S.D.) of hardness, friability, weight variation, drug content, length and thickness of all tablet formulation prepared.

Table 3: Values of physical parameters and drug content for all tablet formulations of salbutamol sulphate

Formulation code	Hardness (Kg/cm^2) Mean ± S.D.	Friability (%)	Weight (mg) Mean ± S.D.	Uniformity of content (%)	Length (mm) Mean ± S.D.	Thickness (mm) Mean ± S.D.
B1	5.8 ± 0.18	0.27	250.42 ± 0.68	101.02	9.1±0.04	3.1 ± 0.12
B2	6.0 ± 0.19	0.50	250.40 ± 2.73	97.51	9.08±0.03	3.13 ± 0.07
B3	5.7 ± 0.36	0.29	246.09 ± 0.70	98.89	9.09±0.06	3.12 ± 0.17
B4	6.0 ± 0.50	0.50	250.38 ± 1.51	98.31	9.1±0.04	3.12 ± 0.07
B5	5.6 ± 0.34	0.52	251.60 ± 1.20	97.34	9.1±0.01	3.11 ± 0.04
B6	5.6 ± 0.13	0.30	253.13 ± 2.03	96.67	9.12±0.08	3.13 ± 0.07
B7	6.0 ± 0.31	0.26	251.10 ± 1.41	98.67	9.09±0.01	3.09 ± 0.07
B8	5.8 ± 0.35	0.28	252.19 ± 1.13	96.45	9.13±0.01	3.1 ± 0.04
B9	5.9 ± 0.27	0.26	248.93 ± 1.29	96.78	9.12±0.05	3.12 ± 0.12
B10	5.8 ± 0.28	0.29	251.82 ± 0.41	96.02	9.11±0.03	3.09 ± 0.05
B11	5.8 ± 0.41	0.27	247.05 ± 0.66	96.49	9.1±0.02	3.11 ± 0.13
B12	5.4 ± 0.24	0.32	248.26 ± 3.26	97.23	9.11±0.03	3.16 ± 0.21
B13	5.8 ± 0.34	0.28	252.10 ± 0.95	99.45	9.09±0.05	3.1 ± 0.12

In vitro buoyancy test

Floating lag time (FLT) is the time required for dissolution medium to penetrate the tablet matrix and develops the swollen layer for entrapment of CO_2 generated in situ. The tablet mass decreased progressively due to liberation of CO_2 and release the drug from the matrix. FLT of all tablet formulations was found to be less than 5 minutes and the total floating time were observed to be more than 12 hour as tabulated in table. As solvent front peneterated the glassy polymer layer, the swelling of HPMC K15M and Polyox WSR 1105 caused an increase in volume of the tablet. The combined effect is net reduction in density of the tablets, which prolongs the duration of floating beyond 12 hours. Floating lag time was found to be increased on increasing the concentration of polymers as shown in fig 4 and table 3. The floating lag time for formulation B1-B3 was found to be in the range of 132-138, in case of B4-B6 was 170-180 sec, with B7-B9 it was 243-270 sec and for B10-B13, it was 175-177 sec

as the concentration of HPMC K15M and Polyox WSR 1105 was increased as depicted in table. B1 formulation containing 30% of HPMC K15M and 10% of Polyox WSR 1105 was found to have minimum FLT and maximum 270 sec for B9 formulation containing 50% of HPMC K15M and 20% Polyox WSR 1105.

Table 4: Floating lag time and total floating time of all tablet formulations

Formulation code	Floating lag time (sec)	Total floating time (h)
B1	132	>12 h
B2	136	>12 h
B3	138	>12 h
B4	170	>12 h
B5	177	>12 h
B6	180	>12 h
B7	243	>12 h
B8	256	>12 h
B9	270	>12 h
B10	175	>12 h
B11	177	>12 h
B12	175	>12 h
B13	176	>12 h

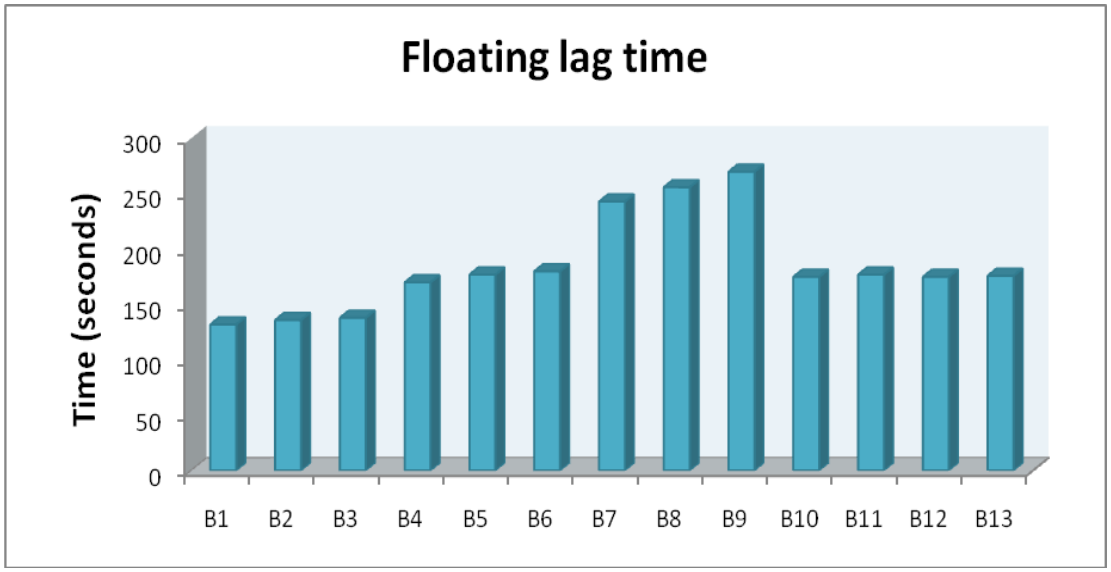

Fig. 1: Floating lag time of different formulations

In vitro dissolution test

In vitro dissolution was studied using USP dissolution apparatus II (Paddle type) in pH 1.2 buffers for 12 h. In vitro, drug release data for buoyant tablets were done in triplicate manner. Mean value of drug release of all tablet formulations is depicted in tables 4, 5.Drug release from formulations B1-B3 containing minimum polymer concentration was found to be 97.867%-99.487%. Drug release from formulations B7-B9 was found to be 81.593%-86.909% i.e. highly sustained due to presence of maximum polymer concentration. This pattern provides an idea about the effect of polymeric concentration on drug delivery. Percentage drug release was less due to presence of HPMC K15M with higher viscosity and this is due to increase in the resistance of gel layer to drug dissolution.

Table 5: Dissolution data of formulations B1-B6

Time (h)	% Drug Release±S.D.					
	B1	B2	B3	B4	B5	B6
0	0.000	0.000	0.000	0.000	0.000	0.000
1	25.638±3.03	26.029±3.97	27.353±3.03	22.059±3.44	22.721±3.03	24.706±2.09
2	33.591±3.04	36.245±1.96	36.922±2.27	26.814±2.31	30.252±2.01	32.260±2.01
3	41.240±6.10	43.924±3.03	43.946±3.01	33.580±3.06	35.218±1.12	41.218±2.28
4	52.279±1.16	53.669±3.08	55.015±1.97	40.382±1.94	46.191±2.28	44.316±1.16
5	65.442±2.02	65.502±2.06	63.554±1.99	47.884±4.99	50.002±1.16	53.400±2.03
6	73.409±3.15	72.828±5.07	72.181±2.01	55.425±3.01	61.130±3.08	58.608±2.32
7	79.493±1.16	80.890±1.98	78.250±4.18	64.331±4.12	65.096±2.38	63.206±1.12
8	87.620±3.45	87.708±2.00	81.730±4.06	66.667±4.17	69.098±1.89	71.157±2.06
9	92.520±3.94	89.961±2.91	85.240±1.13	76.293±5.04	76.446±2.95	77.203±2.93
10	96.140±1.24	94.875±2.94	91.426±1.93	82.662±6.11	81.221±2.97	82.647±1.92
11	98.863±0.52	95.863±1.06	96.348±2.08	91.049±5.79	88.686±3.01	86.819±1.10
12	99.487±0.16	98.850±1.08	97.867±1.20	96.833±2.08	93.578±1.17	92.350±2.01

Table 6: dissolution data of formulations B7-B13

Time (h)	% Drug release±S.D.						
	B7	B8	B9	B10	B11	B12	B13
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	17.426±3.03	19.412±1.15	20.074±1.99	21.397±1.15	23.118±2.98	23.382±3.03	23.713±2.50
2	24.238±3.46	26.907±1.15	25.591±1.17	28.252±1.97	30.786±1.30	30.922±1.17	31.256±1.00
3	31.123±4.19	33.159±3.05	32.490±2.02	34.520±2.00	35.559±1.01	35.564±1.72	35.240±1.14
4	35.434±3.14	38.816±4.01	40.125±3.07	46.809±2.00	46.668±2.00	46.474±2.77	46.478±2.11
5	43.098±5.39	47.179±2.07	45.194±1.98	48.642±3.07	50.154±1.08	50.553±1.12	50.358±1.75
6	49.520±2.10	51.659±1.88	49.652±1.92	59.755±1.95	61.481±2.55	60.495±4.21	60.828±3.64
7	59.978±1.92	64.125±15.68	56.801±2.28	64.368±2.04	65.385±2.63	65.115±2.41	65.126±1.86
8	66.576±1.94	66.797±2.10	62.701±1.96	69.025±1.91	69.324±2.19	69.250±2.04	69.126±1.86
9	71.255±1.96	72.799±3.10	69.983±4.13	77.034±3.06	76.740±3.39	76.931±3.69	76.871±2.91
10	76.640±1.25	76.875±.16	74.029±3.52	80.496±3.93	81.716±3.75	81.644±2.47	81.716±2.91
11	82.738±.2.16	80.988±1.83	80.098±.1.13	87.951±3.05	89.055±3.48	89.048±2.44	88.922±2.67
12	86.909±1.37	84.475±1.17	81.593±1.86	92.836±1.22	93.884±0.72	93.878±1.40	93.883±0.69

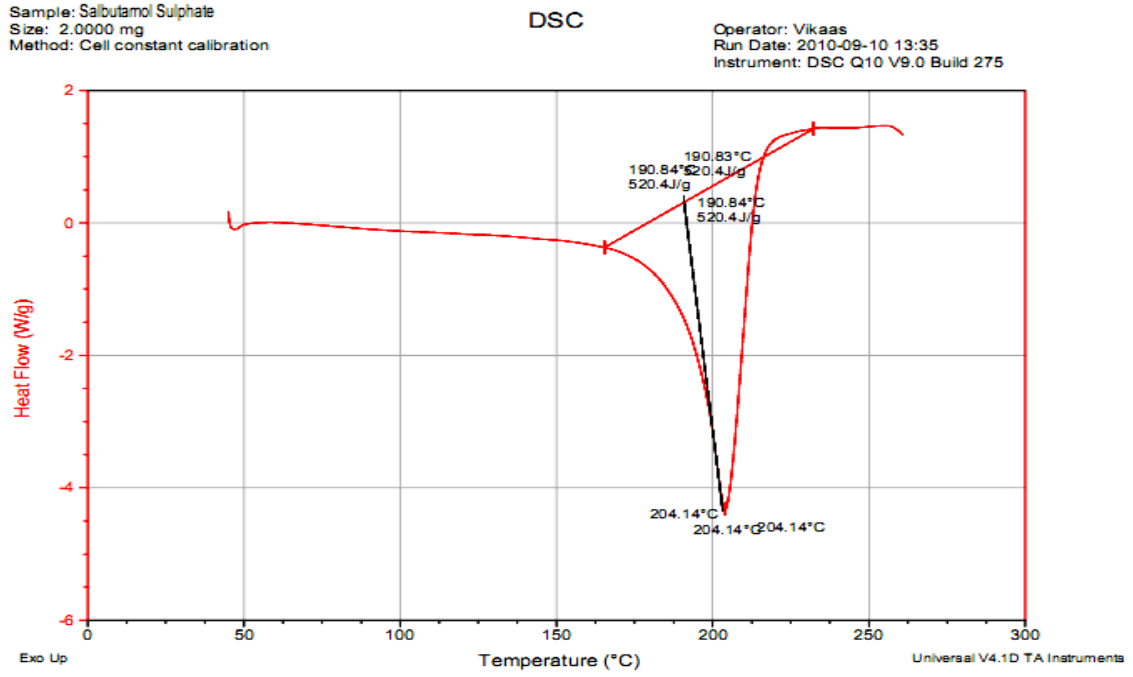

Fig. 2: DSC thermograph of salbutamol sulphate.

DSC (Differential Scanning Calorimetry)

The DSC thermogram of an obtained sample of drug showed a sharp melting endotherm at 204.14°C with a normalised energy of 520.4 J/g, as shown in fig. 5. The obtained endothermic peak was found to be similar to the reported thermogram value of salbutamol sulphate.

FTIR study

FTIR spectra of pure drug salbutamol sulphate, and that of polymers were obtained, which are shown in fig. No. 6 and 7. All the characteristic peaks of salbutamol sulphate were present in spectra thus revealing compatibility between drug samples and polymers.

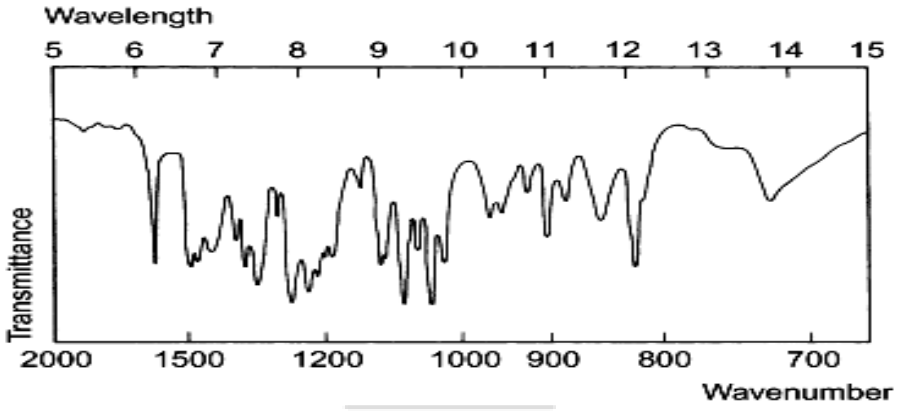

Fig. 3: Standard FTIR spectra of salbutamol sulphate.

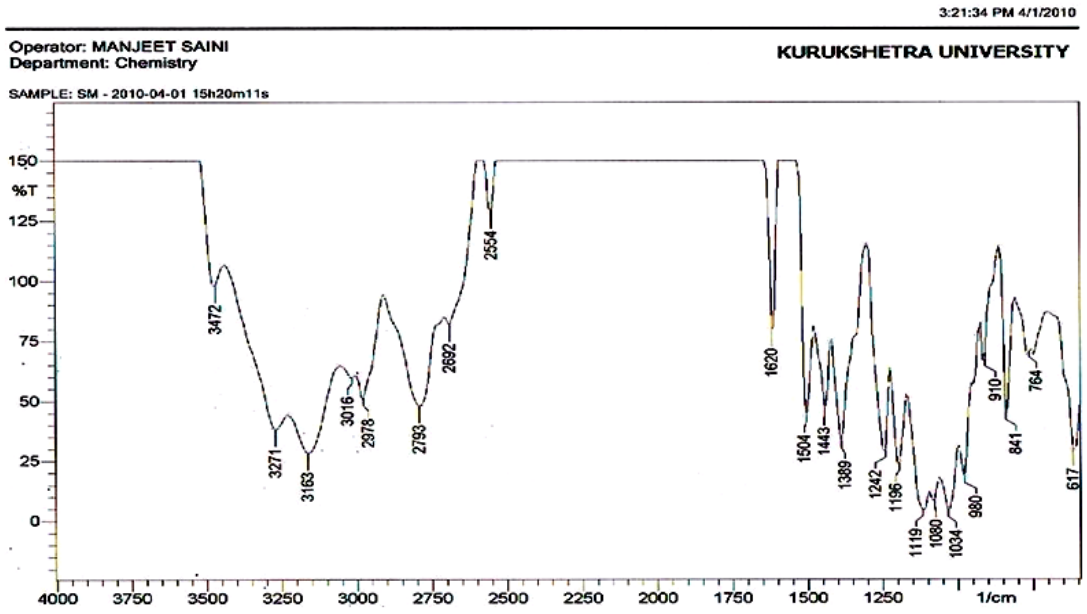

Fig. 4 FTIR spectra of obtained sample (salbutamol sulphate)

In vitro drug release kinetics

The different kinetics models which was used to analyse the data obtained from dissolution studies were zero order, first order, matrix model, Hixon-crowell model, Korsmeyer-Peppas model and the final results are reproduced in table 6.

Table 7: Modeling of dissolution data of all tablet formulations

Formulation Code	Zero order		First order		Matrix model		Peppas model		Hixson Crowell model	
	R	K_0	R	K_F	R	K_M	R	K_P	R	K_{HC}
B1	0.9200	10.0396	0.9171	-0.3358	0.9868	29.3232	0.9883	23.4924	0.9879	-0.0657
B2	0.8929	9.9268	0.9751	-0.2719	0.9899	29.1154	0.9894	25.1177	0.9912	-0.0602
B3	0.8945	9.7397	0.9229	-0.2743	0.9951	28.5770	0.9917	26.0822	0.9855	-0.0589
B4	0.9706	8.5698	0.8831	-0.2018	0.9671	24.7205	0.9786	18.4410	0.9573	-0.0472
B5	0.9465	8.6117	0.9544	-0.1814	0.9850	25.0331	0.9895	20.5293	0.9846	-0.0453
B6	0.9278	8.6231	0.9653	-0.1776	0.9907	25.1619	0.9914	22.7355	0.9861	-0.0449
B7	0.9754	7.8874	0.9754	-0.1467	0.9683	22.7273	0.9903	15.5009	0.9916	-0.0388
B8	0.9457	7.9778	0.9690	-0.1466	0.9730	23.1524	0.9847	17.7419	0.9769	-0.0390
B9	0.9531	7.6656	0.9843	-0.1346	0.9822	22.2493	0.9903	17.8830	0.9896	-0.0365
B10	0.9530	8.5430	0.9601	-0.1773	0.9831	24.7995	0.9908	19.3604	0.9870	-0.0446
B11	0.9441	8.6523	0.9519	-0.1840	0.9855	25.1617	0.9899	20.9149	0.9834	-0.0457
B12	0.9438	8.6434	0.9525	-0.1836	0.9853	25.1352	0.9892	21.0582	0.9836	-0.0456
B13	0.9435	8.6447	0.9529	-0.1833	0.9856	25.1434	0.9882	21.2456	0.9839	-0.0456

K_0 = Zero order rate constant; K_F = First order rate constant; K_M = Matrix rate constant; K_P = Korsmeyer Peppas rate constant; K_{HC} = Hixson Crowel rate constant; R = Regression coefficient

Evaluation of tablet of optimized batch

Evaluation parameters of tablets of optimized formulation are shown in the following table 7.

Table 8: Evaluation parameters of tablet of OF-B

Final Batch	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Thickness of tablets (mm)	FLT (sec)	Length (mm)	Drug Content (%)
OF-B	5.2 ± 0.2	0.39	251.2 ± 2.3	3.11 ± 0.100	134.18	9.1±0.02	98.49

Validation of results

For the final formulation, the results of the physical evaluation were found to be within limits. Table 8 lists the composition of the final batch, its predicted and experimental values of all the response variables, and the percentage error.

Table 9: Composition of the optimized formulation, the predicted and experimental values of response variables, and percentage prediction error

Composition HPMC K15M: Polyox WSR 1105 (%)	Response Variable	Experimental Value	Predicted Value	Percentage Error (%)
30:20	FLT	134.18	132.388	-1.335
	% Drug release at 1^{st} hour	26.691	27.4705	-2.9204
	% Drug release at 12^{th} hour	98.003	98.633	-0.642

Swelling indices

The hydration ability of the formula is important because it influences: (1) tablet buoyancy, (2) the adhesion ability of swellable polymers as HPMC K15M in contact with the test fluid and (3) drug release kinetics. The hydrodynamic volume occupied by the hydrated polymer chains is larger in high viscosity grade polymer.

Gamma scintigraphic studies

For the optimization of radiolabeling method, the best results were obtained with 100 µL of stannous chloride as maximum radiolabeling was achieved. Gamma scintigraphic studies revealed the location of tablets in healthy albino rabbits. Posterior whole-body images at various time intervals (1, 2, 3, 4, 5 and 6 h) (fig. 8) showed the retention of tablet in stomach for more than 5 hours [26].

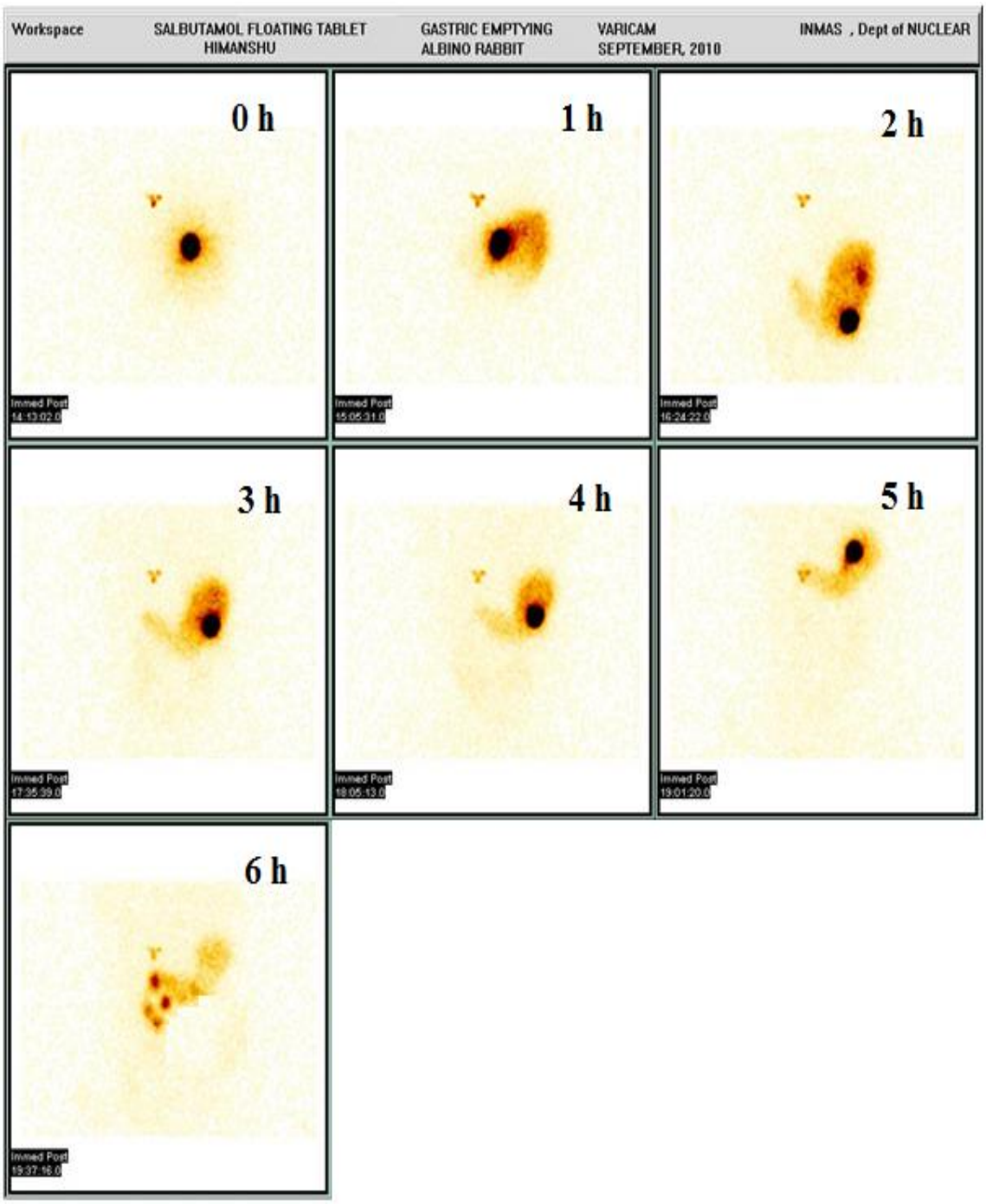

Fig. 5: In vivo gamma scintigraphy of buoyant tablet (OF-B) in albino rabbit

Scanning Electron Microscopy (SEM)

SEM of the optimized formulation showed a well-uniformed gel structure which might be due to polymer relaxation upon absorption of water. SEM study further confirmed both diffusion and erosion mechanisms to be operative during release from the optimized batch of matrix buoyant tablet. SEM images of the buoyant tablet were taken before and after dissolution studies. (Fig. 9, 10). Showed an intact surface without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the centre of tablet (fig). Drug diffuses out of the matrix after it comes in contact with dissolution medium [27].

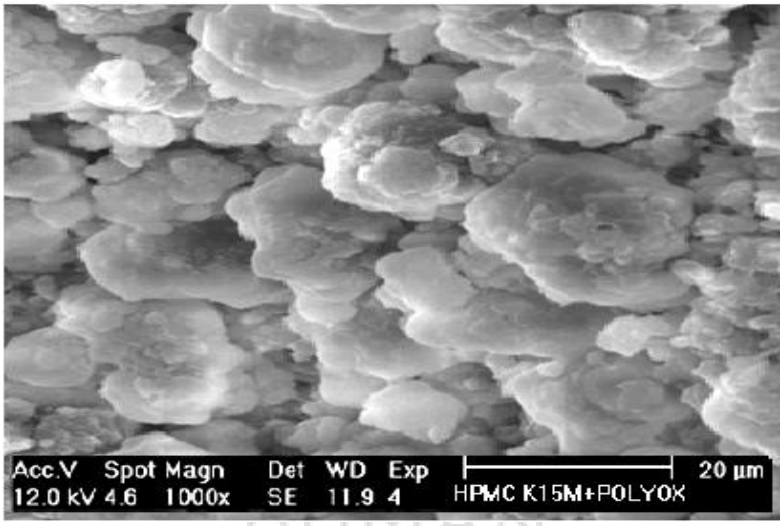

Fig. 6: SEM photomicrograph of OF-B before dissolution

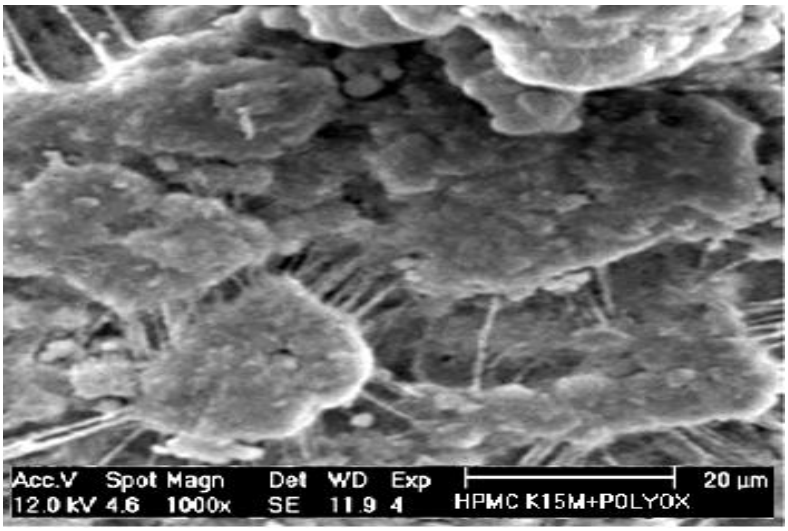

Fig. 7: SEM photomicrograph of OF-B after 8 hours of dissolution

CONCLUSION

In the present study floating tablets of salbutamol sulphate showed encouraging results. The methodology adopted for preparation of Gastroretentive tablet was very simple and cost-effective. It was observed that for the development of controlled-release dosage form of salbutamol sulphate, polymers like HPMC K15M and Polyox WSR 1105 which imparts hydrophillic environment leads to more uniform drug release. Optimization technique was carried out and it was observed to be a useful tool in the evaluation of several response variables. SEM of tablets showed that drug release was due to diffusion and surface erosion of polymeric gel. Gamma scintigraphic studies depicted retention of optimized buoyant tablet in stomach of albino rabbits for more than 5 hours. It can be concluded that formulating salbutamol sulphate as buoyant effervescent tablets can improve the low bioavailability by extended drug release in the upper part of the stomach.

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REFERENCES

1. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: gel layer behaviour, mechanism and optimal performance. Pharm Sci Technol Today. 2000; 3: 198-204. Doi: 10. 1016/S 1461-5347 (00)00269-8
2. Santus G, Lazzarini G, Bottoni G. An in vitro-in vivo investigation of oral bioadhesive controlled release furosemidde formulations. Eur J Pharm. 1997 ;44: 39-52. Doi: 10.1016/S0939-6411 (97)001008
3. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm. 1996; 22: 531-540. Doi: 10.3109/03639049609108355.
4. Deshpande AA, Shah NH, Rhodes CT, Malick AW. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997; 14: 815-819. Doi: 10.1023/A: 10121711010492.
5. Nenon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994; 83: 239-245. Doi: 10.1002/jps.26008300225.
6. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J Control Rel. 1998; 55: 3-12. Doi: 10.1016/SO168-3659(97)00266-6.
7. Singh B, Kim K. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel. 2000; 63: 235-259. Doi: 10.1046/SO168-3659(99)00204-7.
8. Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. Pharm Technol. 2003; 27: 50-68.

9. Choi, B.Y., Fark, H.J., Hwang, S.J. and Park, J.B. (2008). Floating in situ gelling system of acetohydroxamic acid for clearance of H. Pylori. Drug Dev. Ind. Pharm. Sci. 85: 732-740.
10. Baumgartner S, Kristi J, Vrecer F, Vodopivec P, Zorko b. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000; 195: 125-135. Doi: 10.1016/SO378-5173(99)00378-6.
11. Kelly HW, Murphy S, Beta-adrenergic agonists for acute, severe asthma. Ann. Pharmacother, 26, 1992, 81-91.
12. BP Rao, NA Kottan, VS Snehith, C Ramesh, 2009. Development of gastro retentive drug delivery system of cephalexin by using factorial design. ARS Pharm. 50(1), 8-24.
13. R Kumar, MB Patil, SR Patil, MS Paschapur, 2009. Formulation and evaluation of effervescent floating tablet of famotidine. Int J pharm Tech Res. 1(3), 754-763.
14. MRP Rao, GS Sonar, RR Mandusaurwale, SD Vanshive, 2009. Evaluation of effervescent floating matrix tablet formulation of salbutamol sulphate using full factorial design. Asian J Pharm. 3, 43-49.
15. MRJ Castellanos, H Zia, CT Rhodes, 1994. Design and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. Int J Pharm. 105, 65-70.
16. S Baumgartner, A Tivador, F Vrecer, JO Kristl, 2001. Development of floating tablets as a new approach to the treatment of *Helicobacter pylori* infections. Acta Pharm. 51, 21-33.
17. SS Patel, S Ray, RS Thakur, 2006. Formulation and evaluation of floating drug delivery systems containing clarithromycin for *H. Pylori*. Pol Pham Sco. 63(1), 53-61.
18. KA Khan, CT Rhodes, 1975. The concept of dissolution efficiency. J Pharm Pharmacol. 27, 48-49.
19. A Kuksal, AK Tiwary, Jain NK, Jain S, 2006. Formulation and in vitro, in vivo evaluation of extended-release matrix tablet of zidovudine: influence of combination of hydrophilic and hydrophobic matrix formers. APPS PharmSciTech. 7(1), Article 1. Doi: 10.1208/pt070101
20. SA Botha, AP Lotter, 1990. Compatibility study between naproxen and tablet excipients using differential scanning calorimetry. Drug Dev Ind Pharm. 16, 673-83.
21. J Ali, S Arora, A Ahuja, AK Babbar, RK Sharma, RK khar, S Baboota, 2007. Formulation and development of hydrodynamic balanced system for metformin: In vitro and in vivo evaluation. Eur J Pharm Biopharm. 67, 196-201.
22. J Ali, S Arora, A Ahuja, AK Babbar, RK Sharma, RK khar, S Baboota, 2007. Formulation and development of floating capsule of celecoxib: In vitro and in vivo evaluation. APPS PharmSci Tech. 8(40, E1-E8.
23. AK Babbar, AK Singh, HC Goel, UPS Chauhan, RK Sharma, 2000. Evaluation of ^{99m}Tc-labeled photosan-3, as a hematoporphyrin, as a potential radiopharmaceutical for tumor scintigraphy. Nucl Med Biol. 27, 419-426.
24. AK Babbar, AK singh, HC Goel, UPS Chauhan, 1996. A critical evaluation of radiolabeling of glucaric acid with ^{99m}Tc as a potantial myocardial infarct imaging radiopharmaceutical. Ind J Nuclear Med. 11, 98-103.
25. V Kumar, SH Kothari, 1999. Effect of compressional force on the crystallinity of directly compressible cellulose excipients. Int J Pharm. 177, 173-182.
26. GS Sonar, DK Jain, DM More, 2007. Preparation and in vitro evaluation of bilayer and floating bioadhesive tablets of rosiglitazone maleate. Asian J Pharm Sci. 2(4), 161-169.
27. P Vijayalakshmi, VK Devi, C Narendra, 2008. Development of extended zero order release gliclazide tablets by central composite design. Drug Dev Ind Pharm. 34(1), 33-35.