AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Development and Evaluation of Floating Tablet of Salbutamol Sulphate and Theophylline

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ABSTRACT

The objective of this study was to formulate and evaluate gastroretentive effervescent floating matrix tablet of two anti-asthmatic drugs, Salbutamol sulphate and Theophylline which are often indicated for the management of asthma, their frequent dosing may reduce compliance, thus making a prolonged release formulation necessary. Tablets were prepared by wet granulation method using Hydroxy propyl methylcellulose (HPMC) as a release retardant agent and sodium bicarbonate and Citric acid as a gas-generating agents. The prepared granules showed satisfactory flow properties and compressibility. Formulations were evaluated for *in vitro* drug release profile and swelling characteristics. The similarity factor and dissolution kinetics were used as parameters for selection of the best batch. The result of formulation C7 batch showed the best result and was found to extend the release of Salbutamol Sulphate and Theophylline upto 12 hr. and was found to be comparable with marketed sustained released tablet Theoasthalin SR (Cipla). The *in- vitro* drug release followed Korsemeyer-Peppas kinetics and the drug release mechanism was found to be of anomalous type i.e, swelling and diffusion.

Keywords: Sustained release, floating matrix tablet, Formulation, Evaluation.

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Received 2 July 2012, Accepted 26 July 2012

Please cite this article in press as: Namewar SS *et al*., Development and Evaluation of Floating Tablet of Salbutamol Sulphate and Theophylline. American Journal of PharmTech Research 2012.

INTRODUCTION

Asthma is a common chronic inflammatory disease characterized by variable and recurring symptoms, airflow obstruction and bronchospasm with wheezing, coughing, chest tightness and shortness of breathing. These acute episodes may be triggered by such things as exposure to an environmental stimulant (or allergen), cold air, exercise or exertion, or emotional stress.[1] The treatment of asthma generally includes conventional oral dosage forms like tablets, capsules, oral liquids and inhalation therapy but oral administration is the most widely accepted route of delivery due to its ease of administration, convenience, compatibility and patient compliance.

Now a days, Salbutamol Sulphate & Theophylline are used in alone or in combination for the treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD) because of its bronchodilatory action.[2]

Salbutamol Sulphate is a directly acting sympathomimetic agent having predominantly beta-adrenergic activity and selectively acting on B_2 receptor.[3] Salbutamol Sulphate has a site specific absorption in the stomach or in the upper part small intestine showing the oral bioavailability upto 40%.[4] Theophylline (nonselective phosphodiesterase inhibitor) apart from its bronchodilatory action, presumably decreases the release of inflammatory mediators, improve mucillary clearance and stimulate the respiratory drive.[5] Theophylline has bioavailability 50% and half life of 6 hr.[6]

Relatively short half life (4 to 6 hr) with extensive first pass metabolism of Salbutamol and the propensity for interaction with other drugs and narrow therapeutic index of Theophylline makes it necessary to produce prolonged release formulation. [7,8] Theophylline produces an additive effect when used in combination with Salbutamol sulphate. [9] The combination appeared to be superior due to synergistic effects with no added side effect.[10] The combined effect of Salbutamol and Theophylline is always greater than the sum of their individual effects.[11]

GRDDS are designed to complement pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action.[12] GRDF are helpful to reduce the dosing frequency and side effects of the drugs and improve the patient convenience.[13] Floating matrix tablets of GRDF are relatively easy to fabricate by incorporating the drug molecule in a slowly disintegrating or inert porous materials.[14] Sustained release bilayer tablet is available in the market for the same combination, but the formulation of the bilayer tablet is time consuming and uneconomical.

Hence, an attempt was made to develop GRDF (effervescent floating matrix tablet) of Salbutamol

Sulphate & Theophylline Which will prolong the drug release leads to minimizing the incidence of asthma, exhibit the patient convenience, and provide the cost effective product and thus ensuring an effective treatment for prevention of COPD.

MATERIALS AND METHODS

Salbutamol sulphate was supplied by Litaka Pharmaceutical Ltd. (Pune, India). Theophylline was provided by Zim Lab. Kalmeshwar, Nagpur. HPMC K100M, Sodium Bicarbonate and citric acid were supplied by Research Lab Fine Chem Industries, Mumbai. All other chemicals and reagents used were obtained from commercial sources and were of analytical grades.

Preparation of floating tablets of Salbutamol Sulphate and Theophylline

Different tablet formulations were prepared using wet granulation technique (Formulation C1-C9).Varying quantities of HPMC were added in the batches to form matrix. Sodium bicarbonate and citric acid with varying ratios were added to make the tablet float. Required quantity of drug, polymer and effervescence agent were mixed thoroughly. A sufficient quantity of granulating agent (8% solution of PVP K30 in Isopropyl Alcohol) was added slowly to get dough mass. The obtained mass was passed through sieve 16# and the granules thus obtained were air dried for 2-3 hrs and passed through sieve 16#. Dried granules were again passed through sieve 12#. Before compression, granules were mixed with 1% talc and 2% magnesium stearate. The mixed granules equivalent to 820 mg were compressed using 6.2 mm multi station rotary compression machine (Cemach Machineries Ltd.). Hardness of tablet was kept in between 5.0 to 7.0 kg/cm$^{2.}$

Table 1: Formulation of floating tablets

Formulations	SS	TH	HPMC K100M	$NaHCO_3$	Citric acid	MCC	Mg. stearate	Talc
C1	4	300	365	82	17	q.s	12	8
C2	4	300	365	82	33	q.s	12	8
C3	4	300	365	82	50	q.s	12	8
C4	4	300	380	82	17	q.s	12	8
C5	4	300	380	82	33	q.s	12	8
C6	4	300	380	82	50	q.s	12	8
C7	4	300	395	82	17	q.s	12	8
C8	4	300	395	82	33	q.s	12	8
C9	4	300	395	82	50	q.s	12	8

(**SS**-Salbutamol Sulphate, **TH**-Theophylline) Quantities in milligram per tablet. (Total weight-820 mg)

Compatibility study of Salbutamol Sulphate and Theophylline with polymers:

The compatibility study of Salbutamol Sulphate and Theophylline with polymers and excipients was done using Fourier Transform Infrared spectroscopy (FT-IR). FTIR spectra of pure drug, mixture of drug and polymers were obtained by FT-IR instrument using KBr disk method.

Evaluation of granules:

The flow properties of granules (before compression) were characterized in terms of bulk density, tapped density, Carr's index, Hausner ratio and Angle of repose.

Evaluation of floating tablets:

Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for hardness, uniformity of weight using 20 tablets, friability using 10 tablets and percent drug content.

Determination of % Swelling Index:

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 12 h. The swelling index (SI), expressed as a percentage was calculated from the following equation [15]

$$\%SI = \frac{\text{Weight of swollen tablet - Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

***In vitro* buoyancy studies:**

In vitro buoyancy studies were performed for all the nine formulations as per the method described by Rosa *et al* [16]. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1 N HCl (pH 1.2). The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time, the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

***In vitro* dissolution studies:**

The release rate of Salbutamol Sulphate and Theophylline from floating tablets was determined using USP Dissolution Test Apparatus II (paddle type). The dissolution test was performed using 900 ml of 0.1N HCl, pH 1.2 at 37°C ± 0.5°C and 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly upto 12 hour and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µm Whatmann filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at 276 nm and 270 nm wavelength (λmax) using a UV/Visible spectrophotometer (Shimadzu UV-1800). The % cumulative drug release was plotted against time to determine the release profile.

Kinetic treatment of dissolution profiles:

The drug diffusion through most types of polymeric systems is often best described by fickian diffusion but other processes in addition to diffusion are important. There is also a relaxation of the polymer chains, which influences the drug release mechanism. This process is described as

non-fickian or anomalous diffusion. Release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of the diffusion. A third class of the diffusion is Case II diffusion, which is a special case of non-fickian diffusion. A simple, semi-empirical equation given by Korsmeyer and Peppas[17] (Eq. 1) was used to analyze data of controlled release of drugs from polymer matrices.

$$\mathbf{Mt/M\infty = \mathit{k}t^{n}} \text{ ---------- (1)}$$

Where Mt is amount of drug release at time t, M∞ is total amount of drug present in formulation, *k* is release rate constant depend on geometry of dosage form and *n* is diffusion exponent indicating the mechanism of drug release.

Table: 2 Diffusion exponent and solute release mechanism for cylindrical Shape Diffusion exponent (n):

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non Fickian) diffusion
0.89	Case II transport
n > 0.89	Super case II transport

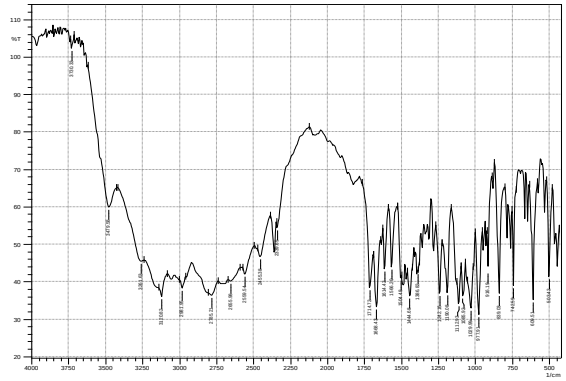
Comparison with marketed product:

The promising formulation was compared with marketed product Theoasthalin –SR (Cipla). The evaluation parameter were tested and compared for in-vitro dissolution profile.

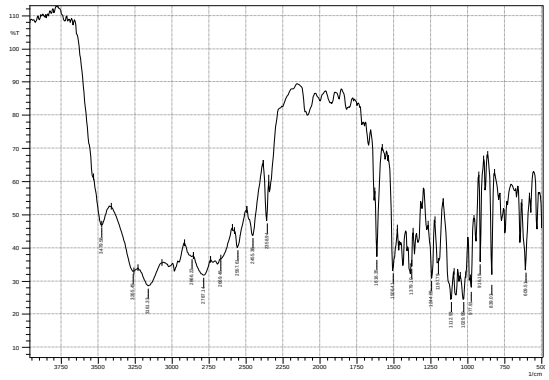
RESULTS AND DISCUSSION

Compatibility study of Salbutamol Sulphate and Theophylline with polymer:

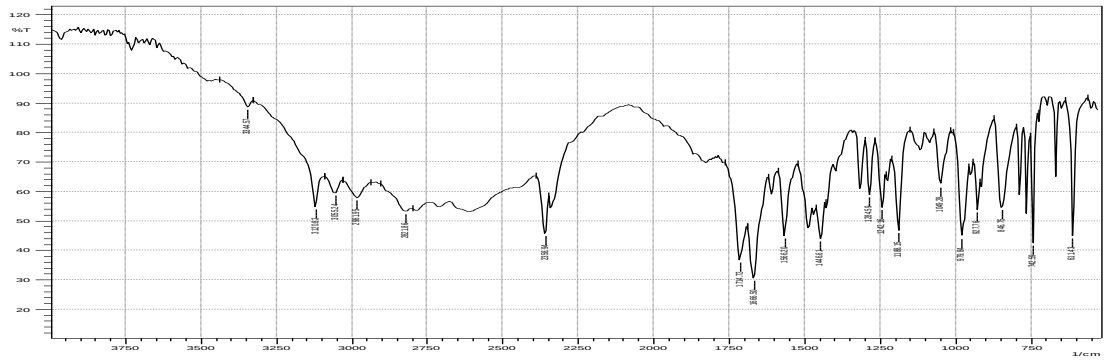
The interaction of Salbutamol Sulphate and Theophylline with the polymers used was studied using FT-IR spectroscopy and it was found that drug had no interaction with the polymer. Therefore, the drug was found to be compatible with the polymers (figure 1).



A: Salbutamol Sulphate (SS)



B: Theophylline (TH)



C: SS+TH+HPMC K100M

Figure 1: Infrared spectra spectra of A: Salbutamol Sulphate (SS), B: Theophylline (TH), C: SS+TH+HPMCK100

Pre compression parameters of granules:

The formulations showed good flow property and Carr's index (Table 3). The bulk density and tapped density of the prepared granules ranged from 0.319 to 0.452 and 0.336 to 0.498 respectively. Carr's index and Hausner's ratio was below 15% and 1.14 respectively, indicating good flow properties for all the batches. Angle of repose ranged from 25.80 to 30.50. The results of angle of repose indicated good flow property of the granules and the value of Carr's index further showed further support for the flow properties.

Table 3: Result of evaluation of granules for various parameters.

Formulations	Parameters				
	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
C1	0.323	0.359	10.02	1.11	27.84
C2	0.448	0.487	8.15	1.08	29.57
C3	0.452	0.498	9.23	1.10	28.13
C4	0.338	0.362	6.62	1.07	27.62
C5	0.347	0.391	11.32	1.12	24.12
C6	0.405	0.449	9.83	1.10	23.08
C7	0.439	0.492	10.85	1.12	25.77
C8	0.345	0.372	7.36	1.07	28.12
C9	0.319	0.336	5.05	1.05	30.32

Post compression parameters of floating tablets:

The thickness and diameter of tablets were measured by vernier calipers and was ranged between 3.60±0.17 mm to 3.85±0.04mm and 9.13 mm to 9.77 mm respectively. The hardness of the tablets was measured by Monsanto tester and was in between 5.84 to 8.11 kg/cm2. The friability was measured by Friabilator and was found to be 0.28% to 0.63%, which is an indication of satisfactory mechanical resistance of the tablets. The results are shown in Table 4. The values

obtained for all the evaluation parameters were found to be complying with pharmacopoeial specifications.

Table 4: Result of evaluation of tablets for various parameters

Formulations	Parameters						
	Avg. wt (gm)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	% Drug Content	
						SS	TH
C1	825±2.81	9.16	3.65±0.05	7.42	0.52	92.19	96.01
C2	821±2.61	9.65	3.70±0.12	6.83	0.46	94.48	95.29
C3	812±3.52	9.82	3.75±0.07	7.21	0.40	95.73	95.82
C4	822±3.56	9.13	3.60±0.17	6.18	0.63	92.01	96.41
C5	826±2.80	9.26	3.75±0.09	5.84	0.52	97.75	93.51
C6	816±2.15	9.57	3.85±0.04	6.93	0.28	98.23	97.86
C7	816±2.15	9.28	3.80±0.80	8.11	0.34	98.97	97.05
C8	831±3.21	9.66	3.75±0.15	7.82	0.37	98.28	98.62
C9	827±2.30	9.77	3.78±0.18	6.90	0.30	98.22	95.74

All values are the mean of three readings. (**SS**-Salbutamol Sulphate, **TH**-Theophylline)

Water uptake study:

The percentage of water uptake study for the formulations C1, C4 and C7 were carried out. As the amount of HPMC was increased, the water retaining capacity also increased which lead to higher percentage of water uptake. Thickness, length and width were found to be increased in swelling characteristics study. Diffusion of drug significantly depends on the water content of the tablet. This may be due to the mobility of the polymer chain strongly depending on the water content of the system. At high water content relaxation of polymer chain takes place with the volume expansion giving high swelling to the system. Also this higher water content could predict the higher penetration of the gastric fluid into the tablet, leading to faster CO_2 gas generation and thus reducing the floating lag time. Consequently, faster and higher swelling of the tablet led to increase in dimension of the tablet as well as diffusion pathways and thus increasing diffusion rates. Therefore, the drug release was found to be high initially and then gradually decreased.[18]

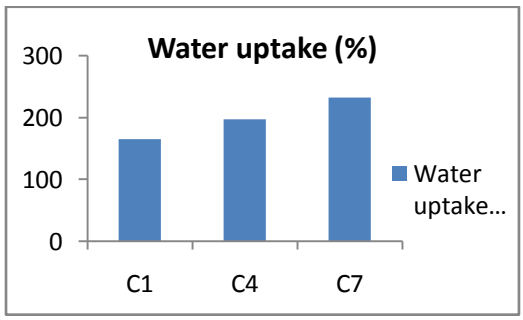


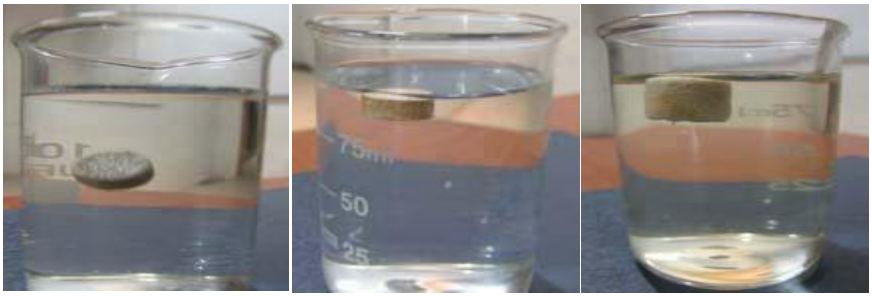
Figure 2: Water uptake study

Table 5: Water uptake study

Formulation	Water uptake (%)
C1	165
C4	197
C7	232

***In vitro* buoyancy studies:**

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N HCl). The combination of sodium bicarbonate and citric acid Provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC), thus decreasing the density of the tablet below 1, which made the tablet buoyant. The tablets with higher concentration of citric acid shows decreased BLT followed by tablet disintegration and erosion (C1 to C3) due to insufficient matrix of HPMC K100M to entrap the gas generated by the effervescent mixture. Increase in the concentration of HPMC K100M decreases the BLT, but the Influence of concentration of HPMC K100M was not distinctly far more significant than that of citric acid. With reference to buoyancy studies results it can be concluded that the batch containing optimum amount of



Initial after 8 min after 12 min

Figure 3 : In vitro buoyancy study of batch C7

Table 6: Buoyancy Lag Time

Formulation	BLT (sec)	TFT (Hr)
C1	303	6
C2	247	4
C3	189	3
C4	481	10
C5	367	7
C6	306	5
C7	725	12
C8	669	10
C9	543	8

Sod.bicarbonate, Citric acid HPMC K100M polymer showed good floating lag time (FLT) and total floating time (TFT). The results of *in vitro* buoyancy studies are tabulated in table.6 and the following Figure 3. Shows the floating behavior of the tablet from batch C7.

***In vitro* dissolution studies:**

Total 9 formulations were prepared to study the effect of effervescence agent and HPMC K100M on the drug release profile. Formulations C1, C2, C3 were found to release more than 50% of drug in 1st hour and complete drug release was found in 6h, 4h and 3h respectively. Formulation C3 showed burst effect due to lower conc. of HPMC and higher conc. of citric acid. To overcome this burst effect, the concentration of HPMC was increased to minimize the burst effect and prolong the time required to release the complete drug (C4-C6). Formulation C4 showed, improved drug release and disintegrated within 10 hr with BLT upto 8min., whereas C5 and C6 showed the disintegration within 7h and 5h respectively, due to higher conc. of citric acid than C4. Further, the concentration of HPMC was increased to prolong the release rate (C7-C9). Formulation C8 and C9 showed the disintegration within 10 hr and 8hr with the average drug release of 29% and 32% respectively in 1st hour (for both the drugs), whereas formulation C7 showed 95% of average drug release within 12h with BLT of 12 min and average 22% drug release in 1st hour. This is due to lower concentration of citric acid than C8 and C9. This controlled release of drug from C7 could be attributed to the formation of a thick gel structure that delayed the drug release from the tablet matrix.

Thus, a formulation C7 was selected as the promising formulation, containing HPMC K100M (395 mg), sodium bicarbonate (82 mg) and citric acid (17 mg) , as it has achieved optimum *in vitro* buoyancy, floatability of more than 12 hrs as well as controlled and sustained *in vitro* drug release.

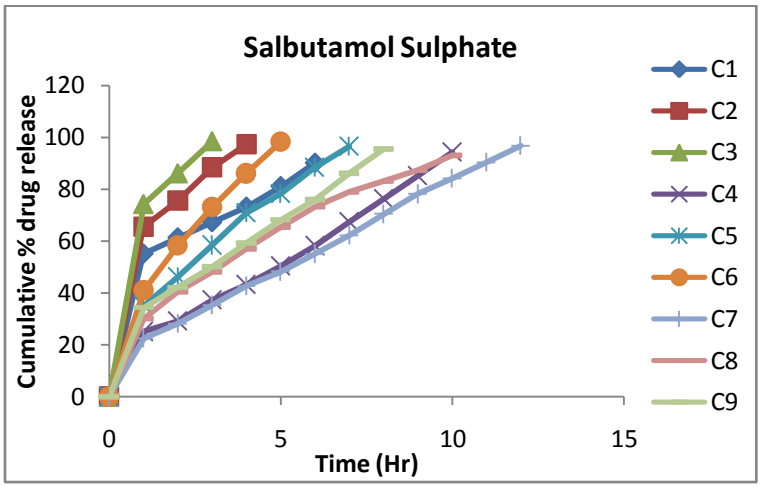


Figure 4: Cumulative % Salbutamol Sulphate release from formulations C1-C9.

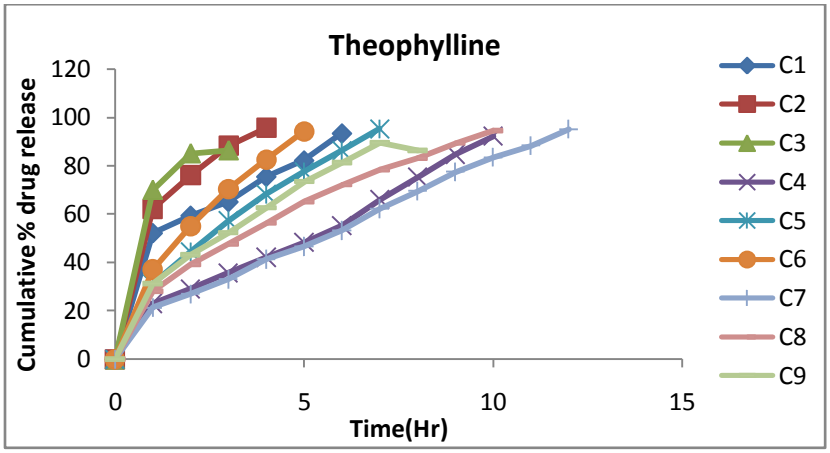


Figure 5: Cumulative % Theophylline release from formulations C1-C9.

Kinetic treatment of dissolution profiles:

Formulation C7 showed the highest r^2 value observed in Korsmeyer-Peppas model (Table 7) and the n value was found to be in between 0.5 and 1.0 which indicated a non –fickian anomalous transport of drug release i.e, swelling as well as diffusion mechanism.

Table 7: Kinetic release data of different model for optimized formulation C7.

Formulations		Zero-Order	First-Order	Higuchi Model	Korsemeyer-peppas Model	
		r^2	r^2	r^2	r^2	n
C7	SS	0.979	0.575	0.972	0.978	0.623
	TH	0.986	0.587	0.962	0.975	0.638

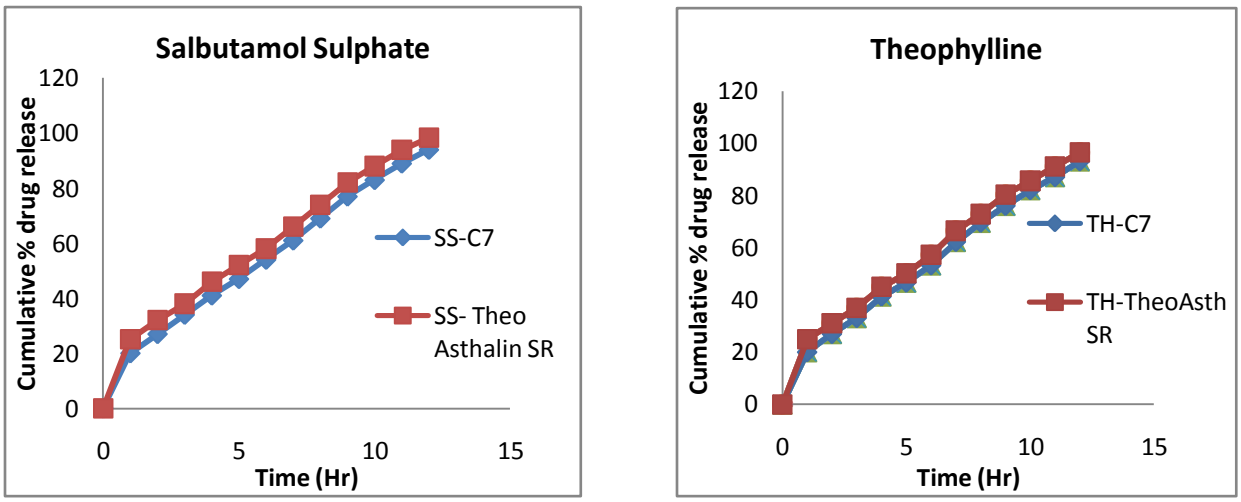


Figure 6: Comparative dissolution profile of Salbutamol sulphate and Theophylline from C7 batch with marketed formulation.

Comparison with Marketed Product.

Figure.6 shows Comparative dissolution profile of selected best formulation C7 with marketed brand **Theoasthalin-SR (**Cipla contains 4 mg of Salbutamol Sulphate and 300 mg of

Theophylline. The drug release from the formulation C7 and Theoasthalin–SR at 8hr was 69.71% and 72.50% respectively and complete drug release was observed at 12 hr in both the formulations. The developed formulation C7 and marketed formulation were found to have almost similar *in vitro* release profile. The similarity factor f_2 was found to be 73.17 for the developed formulation C7 and marketed formulation indicating that the release was almost similar to that of the marketed formulation.

CONCLUSION:

The addition of polymer HPMC K100M and gas generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the fed stomach, caused an enhancement in drug release. Diffusion and swelling of polymer is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent agent and polymer. The in vitro drug release profiles obtained for tablets (C7) showed FLT (12 min) and a prolonged floating duration (12 hrs) with controlled and sustained release of Salbutamol Sulphate and Theophylline. Therefore, the formulation can be scaled up to validate its industrial applicability and can become a promising gastroretentive drug delivery system against *Asthma*.

ACKNOWLEDGEMENTS

The authors are sincerely thankful to Gurunanak College of Pharmacy, Nagpur, for providing the laboratory facilities and moral support to carry out this research work.

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