A KINETIC STUDY ON THE DISSOLUTION CHARACTERISTICS OF MATRIX TABLET FORMULATED WITH SALBUTAMOL SULPHATE FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT:

Aims: The objective of the present study was to develop Salbutamol sulphate matrix tablet for sustained release dosage form, for the treatment of Chronic Obstructive Pulmonary Disease (COPD).

Methods: Simultaneous equations were formed to calculate the concentration values of Salbutamol sulphate and drug compatibility study was performed through Infrared spectroscopy. The matrix tablets were prepared by wet granulation method using two hydrophobic polymers such as Ethyl cellulose and Acrycoat S-100 in varying ratios. Results and Conclusions: The granules showed satisfactory flow properties. All the seven tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for tested parameters. The results of formulation F-4 (Ethyl cellulose and Acrycoat in 2:1 ratio) could extend the release of Salbutamol sulphate up to 12 hr and was found comparable to marketed sustained release products. Model fitting analysis (Zero order, Higuchi and Korsmeyer-Peppas model) for all the formulations were performed and it was seen that all the formulations predominantly follow the Higuchi model. While comparing with the 'n' values of all the formulations of Korsmeyer-Peppas model, Fickian/Diffusion controlled release was observed in case of F-4 and F-5, whereas for the other formulations non-Fickian transport was observed.

Keywords: Salbutamol sulphate, matrix tablet, Acrycoat S 100, Ethyl Cellulose, Fickian Diffusion

INTRODUCTION

The objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of therapeutic effect in the face of uncertain fluctuations in-vivo environment in which drug release takes place [(1)].

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient's convenience [(2)].

The drug release time can be prolonged according to one of the following mechanisms-

1. Changing the physical properties such as- solubility and stability of the drug molecules,
2. Forming a complex of drug molecules with ion exchange resins,

3. Incorporating drug molecules in slowly disintegrating or inert porous matrices,
4. Coating drug molecules with pharmaceutical polymers that have a barrier function for the diffusion of drug molecules,
5. Osmotic pumps [3].

Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials [2]. Drug release occurs either by diffusion through the matrix or by erosion of the matrix or by a combination of both diffusion and erosion [4].

Salbutamol sulphate (SS), a short acting highly selective beta 2 adrenoceptor agonist is having bronchodilating property. It is widely used in the management of Chronic Obstructive Pulmonary Disease (COPD) which includes- bronchial asthma, chronic bronchitis and emphysema [5]. It is almost completely absorbed from the gastrointestinal tract after oral administration. It is reported to have plasma half-life 2.85±0.85, time of peak plasma concentration occurs about 30 minutes after an oral dose. It is also reported that SS having plasma protein binding 7±1% and undergoes considerable first pass metabolism. The drug as sulphate is soluble in 1 to 4 of water, due to the hydrophilic nature it is readily excreted through urine[6-9]. These bio-pharmaceutical and physicochemical properties reveal that SS is an ideal candidate to develop into a controlled release system.

SS is a basic drug, so maximum absorption is taking place into the intestine. As the drug is hydrophilic and undergoes first pass metabolism, so our main objective is to deliver the drug as much as possible in intact form into the main site of absorption. So in this present work two hydrophobic polymers (Ethyl cellulose and Acrycoat S-100) in different ratios are used as matrix forming agent to protect the drug from hepatic metabolism.

Present study is undertaken to prepare SS matrix tablet for sustained release dosage form, which will prolong the drug release leading to minimize the incidences of nocturnal and early morning asthmatic attacks, exhibit patient convenience and provide a cost effective product, thus ensuring an effective treatment for prevention of COPD.

AIM

Salbutamol sulphate conventional release tablets are administered 2 to 4 mg three to four times daily and their duration of action are last for 4 to 6 hours [9]. So the aim of this work was to design, formulate and develop a novel oral monolithic controlled release tablet dosage form that may be toiled to provide quasi steady state drug release over an extended period of time [10].

EXPERIMENTAL SECTION

Materials

Salbutamol sulphate was obtained as a gift sample from INGA Laboratories P. Ltd., Mumbai. Acrycoat S-100 and Ethyl cellulose (EC) were gift samples received from COREL PHARMA-CHEM, Gujrat. And S.D. Fine- Chem. Limited, Mumbai, respectively. All other chemicals and reagents used were obtained from commercial sources and were of analytical grade.

Methods [2]

Compatibility study

IR spectra of pure drug, drug and polymers and the formulations were obtained using IR spectrophotometer (FTIR – 8400S, SHIMADZU) to establish the compatibility of ingredients.

Preparation of Matrix Tablet of Salbutamol Sulphate

Different tablet formulations were prepared by wet granulation technique. The compositions of each batch of tablet formulation were shown in the following Table 1.

Table 1: Preparation of Tablets

INGREDIENTS (mg/tablet)	F-1 (1:1)	F-2 (1:2)	F-3 (1:3)	F-4 (2:1)	F-5 (2:3)	F-6 (3:1)	F-7 (3:2)
Salbutamol Sulphate	12	12	12	12	12	12	12
EC	25	17	13	33	20	37	30
Acrycoat S-100	25	33	37	17	30	13	20
Lactose	35	35	35	35	35	35	35
Talc	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1

All the powders were passed through USP 100 mesh sieve. Required quantity of drugs, polymers and diluents were mixed thoroughly and a sufficient quantity of binding agent (0.1% w/v of respective polymers in Isopropyl alcohol) was added slowly to get dough mass. The mass was sieved through USP 20/35 mesh and dried at 60^0C for 1hr. the dried granules retained on 35 mesh were mixed with 10% fines, 2% Talc and 1% Magnesium Stearate. Tablets were compressed using 6 mm round concave punches to get the tablets having the hardness between 5 to 7 kg/ cm^2.

EVALUATION OF GRANULES [11]:

1. Measurement of Angle of Repose:

Angle of repose was determined by funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated by using the formula:

$$\theta = \tan^{-1} (h / r)$$

This was done thrice, from that average angle of repose and standard deviation was calculated. (Table 2)

2. Bulk Density:

Apparent bulk density (ρ_b) was measured by pouring the pre-weighed (M) blend into a graduated cylinder. The bulk volume (V_b) of the blend was determined. Then the bulk density was calculated by using the formula : $\rho_b = M / V_b$

This was done thrice, from that average bulk density and standard deviation was calculated. (Table 2)

3. Tapped Density:

The measuring cylinder containing a known mass (M) of blend was tapped for a fixed time, and the minimum volume (Vt) occupied in the cylinder was measured. The tapped density ρt was calculated by using the following formula : $\rho_t = M / Vt$

This was done thrice, from that average tapped density and standard deviation was calculated. (Table 2)

EVALUATION OF THE FORMULATIONS [1,12] :

The tablets were evaluated for Appearance, Weight variation, Thickness, Diameter, Hardness, and Friability to meet the Pharmacopoeial standards. (Table 3)

1. Determination of Weight Variation of the tablets:

Twenty tablets were selected at random from each batch and were weighed accurately and average weights were calculated. Then the deviations of individual weights from the average weight and the standard deviation were calculated.

2. Determination of Thickness and Diameter of the tablets:

Thickness and diameter of ten randomly selected tablets from each batch were measured with a Slide Calipers. Then the average diameter and thickness and standard deviation were calculated.

3. Determination of Hardness of the tablets:

Five tablets were sampled randomly from each batch and the hardness was determined by using Monsanto Hardness Tester. Then average hardness and standard deviation was calculated.

4. Determination of Friability of the tablets:

Twenty tablets were sampled randomly from each batch and the friability was determined using Roche type Friabilator. A pre-weighed tablet sample was placed in Friabilator which was then operated for 100 revolutions (25 rpm). The tablets were then dusted and reweighed. Then percentage friability was calculated.

5. Determination of Drug Content Uniformity:

Three tablets were selected randomly from each batch and taken separately into three 100 ml volumetric flasks. In each flask 100 ml of Phosphate buffer pH 6.8 was poured and kept for 24 hrs. After filtering the solutions, the absorbance of the filtrate was measured at 225 nm. From these absorbances, drug content was determined and average and standard deviation was calculated.

6. Determination of Mass Degree of Swelling [2] :

Each tablet from all formulations were pre-weighed and allowed to equilibrate with 100 ml of water for 5 hrs. Then the tablet was removed, blotted using tissue paper and weighed. The Mass Degree of Swelling was then calculated by using the following formula-

Q = Mass of swelling gel / Mass of dry the powder

Where,

Q = Mass Degree of Swelling

7. *In-vitro* Dissolution Studies of the tablets:

In-vitro drug release studies were carried out using tablet dissolution test apparatus USP Type-I (Paddle Type) at 100 rpm. The dissolution medium consisted of 900 ml of Phosphate buffer pH 6.8 and dissolution carried out for 12 hrs. maintaining the temperature at $37^0C \pm 1^0C$. Aliquots of 5 ml were withdrawn at 30 minutes intervals and an equivalent amount of fresh dissolution media equilibrated at the same temperature was replaced. These aliquots were filtered and the absorbance of the filtrate was measured in each case at about 275 nm against fresh pH 6.8 Phosphate buffer solutions as blank. Finally the Cumulative percentage of drug release was calculated. (Table 4) (Figure 1,2)

In-vitro dissolution studies were also carried out with the marketed sustained release products (ASTHALIN SA-8mg and VENTORLIN 8mg). (Figure 3,4)

RESULTS AND DISCUSSION

Table 2: Evaluation of Granules

Batch Code	Angle of Repose (θ)	Bulk Density (ρ_b) (g/cm^3)	Tapped Density (ρ_t) (g/cm^3)
F – 1	28.2761 ± 0.6635	0.3282 ± 0.0318	0.4524 ± 0.0825
F – 2	26.8946 ± 1.4113	0.3002 ± 0.0106	0.3861 ± 0.0298
F – 3	27.3089 ± 1.4164	0.3158 ± 0.0398	0.4139 ± 0.0758
F – 4	25.1293 ± 1.6721	0.3264 ± 0.0120	0.4186 ± 0.0349
F – 5	27.8269 ± 1.6296	0.2845 ± 0.0253	0.3690 ± 0.0429
F – 6	26.3839 ± 1.3576	0.3072 ± 0.0226	0.3987 ± 0.0502
F – 7	26.2352 ± 0.9686	0.3009 ± 0.0200	0.3861 ± 0.0298

Table 3: Physico-chemical characteristics of prepared tablets

Batch Code	Weight Variation		Diameter Variation (mm)	Thickness Variation (mm)	Hardness (kg)	Friability (%)	Drug Content Uniformity (%)	Mass Degree of Swelling
	Average Weight (mg)	Highest Percentage Deviation						
F - 1	101.15 ±2.54	- 4.10282	6.14±0.13	4.24±0.09	6.0±0.71	0.005	99.67±0.02	1.0583
F - 2	101.75 ±2.09	-3.6855	6.16±0.18	4.22±0.18	6.6±0.55	0.00	99.35±0.02	1.0490
F - 3	101.30 ±2.85	5.626851	6.21±0.07	4.23±0.13	6.2±0.84	0.01	99.45±0.04	1.0667
F - 4	101.45 ±1.90	+ 3.499261	6.14±0.13	4.27±0.13	6.2±0.84	0.01	99.37±0.06	1.0505
F - 5	102.30 ±2.68	+ 5.571848	6.19±0.07	4.25±0.11	6.2±0.45	0.00	99.58±0.04	1.0792
F - 6	101.70 ±2.45	+ 5.211406	6.22±0.11	4.22±0.08	6.4±0.89	0.005	98.37±0.06	1.1000
F - 7	101.70 ±1.84	- 3.63815	6.18±0.12	4.25±0.08	6.4±0.55	0.00	98.69±0.06	1.0769

Table 4: *In-vitro* Dissolution Profile of Formulations (1-7) and Marketed Brands

Batch Code	Zero Order		Higuchi		Korsmeyer-Peppas			t_{50} (hr)	t_{77} (hr)	X_{60} (mg)
	R^2	K_0	R^2	K_H	n	K	R^2			
F – 1	0.8548	7.0681	0.9693	30.0865	0.6643	1.2535	0.9904	2.5	5.5	32.5149
F – 2	0.8642	7.1888	0.9739	30.2940	0.6572	1.5713	0.9932	3.0	5.5	32.0090
F – 3	0.8519	6.7017	0.9647	28.1130	0.5758	1.9449	0.9842	2.5	5.5	32.4507
F – 4	0.8724	7.3681	0.9783	31.8546	0.5021	1.5196	0.9948	2.5	6.0	32.8142
F – 5	0.8479	7.2591	0.9714	30.6192	0.4503	4.4182	0.9932	3.0	5.0	31.9739
F – 6	0.8548	6.9925	0.9699	29.5619	0.6634	1.2469	0.9860	2.5	5.5	32.3314
F – 7	0.8683	7.1372	0.9713	30.0583	0.6240	1.2932	0.9901	3.0	5.5	32.4315
ASTHALIN-SA	0.9507	7.5532	0.9771	30.5910	0.4978	1.4643	0.9956	4.0	7.0	30.1446
VENTORLIN	0.9373	7.4393	0.9725	30.2510	0.4669	1.500	0.9945	3.5	6.5	32.9453

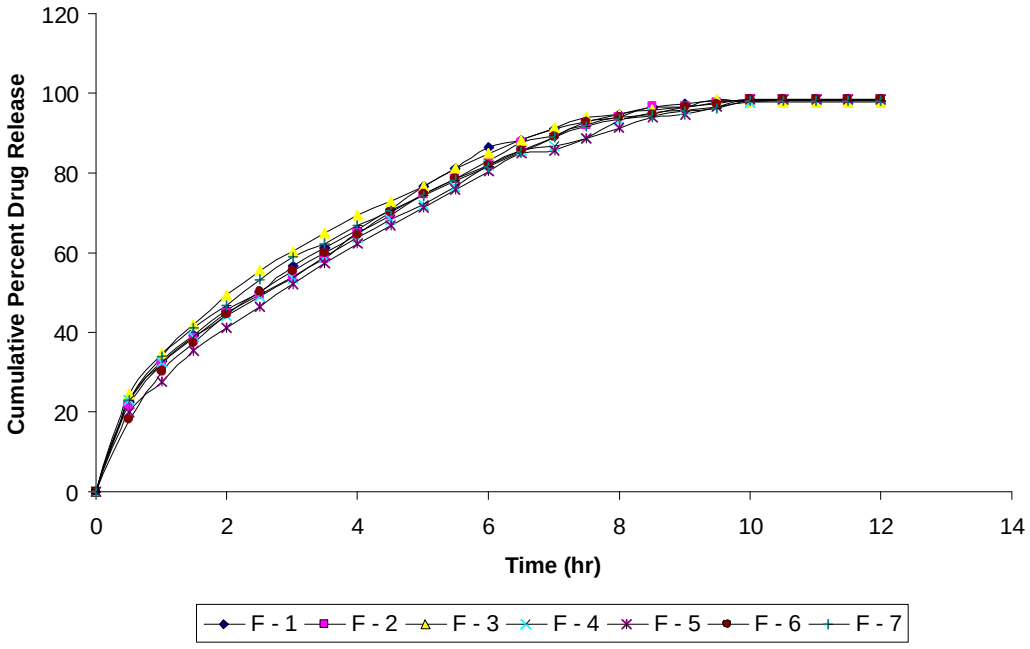

Figure 1: Release Profile of Salbutamol Sulphate from Formulation F-1 to F-7

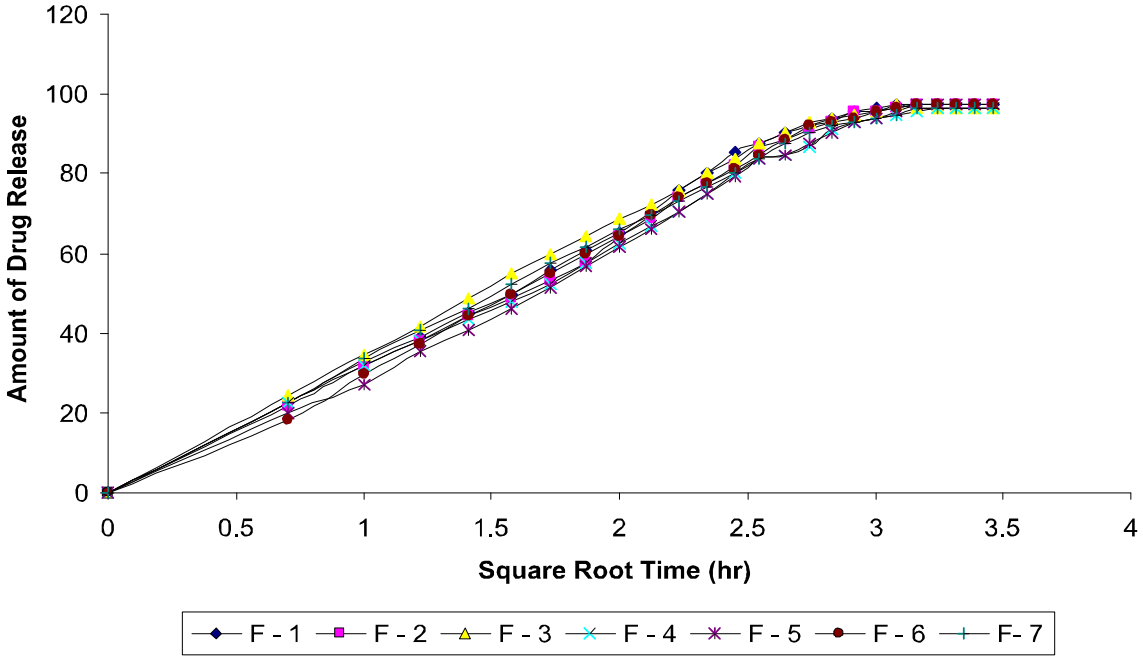

Figure 2: Release Profile of Salbutamol Sulphate from Formulation F-1 to F-7

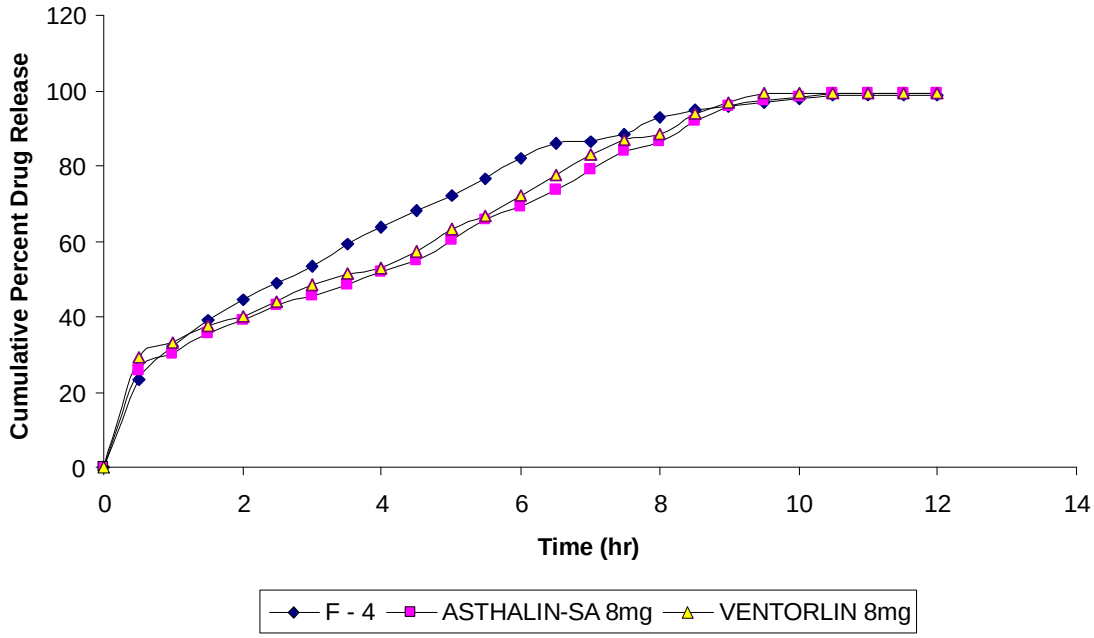

Figure 3: Release Profile of Formulation F-4 and Two Marketed Brand

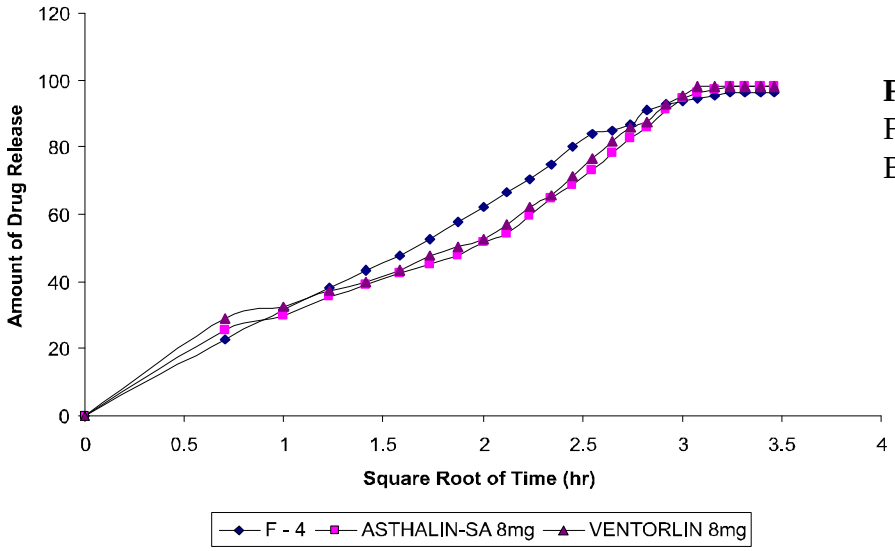

Figure 4: Release Profile of Formulation F-4 and Two Marketed Brand

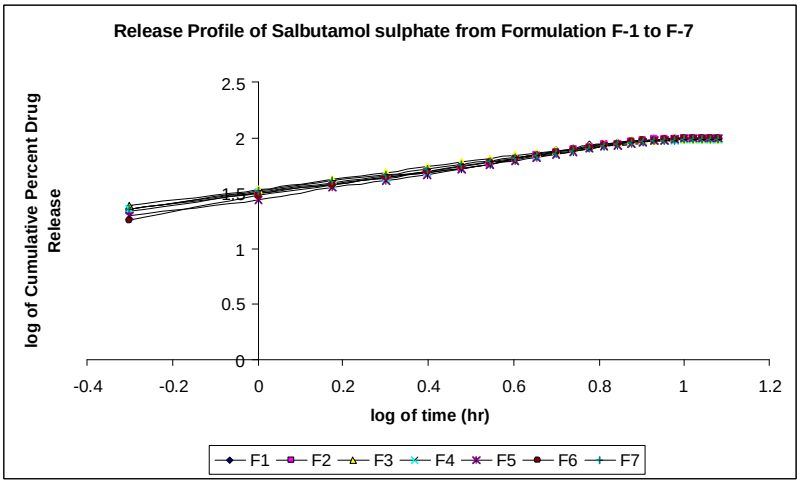

Figure 5: Release profile of Salbutamol sulphate from formulation F-1 to F-7.

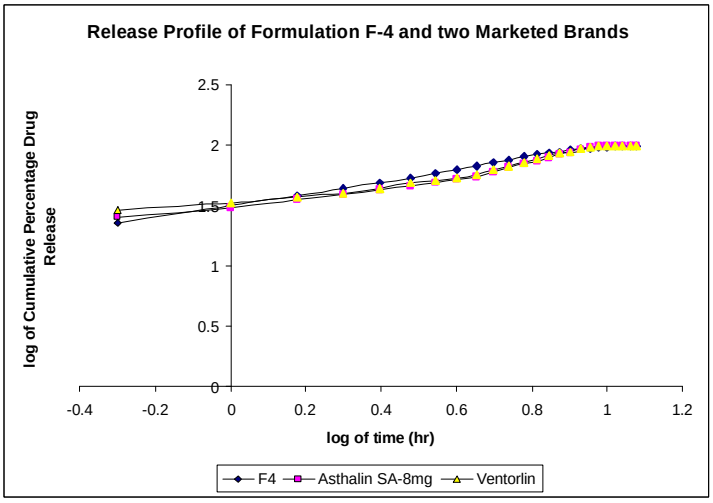

Figure 6: Release profile of formulation F-4 and two marketed brands

Table 5: Values of Formulation F1 to F7

Log t	F1	F2	F3	F4	F5	F6	F7
-0.30103	1.355643	1.338058	1.388811	1.355643	1.300595	1.259594	1.355643
0	1.514627	1.502441	1.53802	1.502509	1.436019	1.476846	1.526417
0.176091	1.591743	1.581563	1.620875	1.581563	1.549383	1.57108	1.611362
0.30103	1.657018	1.648272	1.690294	1.639397	1.611468	1.648223	1.665637
0.39794	1.69837	1.690426	1.743125	1.682335	1.665637	1.698327	1.721283
0.477121	1.750169	1.728768	1.777325	1.721365	1.713793	1.743165	1.763959
0.544068	1.783839	1.763997	1.80896	1.763959	1.757138	1.777325	1.790292
0.60206	1.81502	1.808893	1.838446	1.796581	1.790257	1.80896	1.820996
0.653213	1.849671	1.838446	1.860703	1.826891	1.820996	1.844079	1.844142
0.69897	1.88179	1.871345	1.881847	1.849733	1.849702	1.871374	1.866086
0.740363	1.906879	1.892044	1.906879	1.876628	1.876628	1.892044	1.886976
0.778151	1.935134	1.916512	1.925962	1.906852	1.901981	1.911749	1.906906
0.812913	1.944265	1.939699	1.944216	1.925962	1.925936	1.930598	1.925962
0.845098	1.957444	1.948711	1.957444	1.930674	1.930674	1.948662	1.944216
0.875061	1.966053	1.961758	1.970259	1.939774	1.944241	1.966006	1.957444
0.90309	1.97447	1.970282	1.974493	1.961711	1.957444	1.970305	1.966053
0.929419	1.982728	1.982705	1.978642	1.970282	1.970259	1.974493	1.970305
0.954243	1.986821	1.982773	1.982751	1.974493	1.974493	1.982728	1.974493
0.977724	1.990854	1.986821	1.990831	1.978642	1.982728	1.986821	1.978642
1	1.990876	1.990854	1.986866	1.982751	1.990831	1.990854	1.986799
1.021189	1.990876	1.990876	1.986843	1.986821	1.990876	1.990876	1.986843
1.041393	1.990876	1.990876	1.986843	1.986843	1.990876	1.990876	1.986843
1.060698	1.990876	1.990876	1.986843	1.986843	1.990876	1.990876	1.986843
1.079181	1.990876	1.990876	1.986843	1.986843	1.990876	1.990876	1.986843

Table 6: Values of F4 & two marketed brands

Log t	F4	Asthalin SA-8mg	Ventorlin
-0.30103	1.355643	1.404492	1.462098
0	1.502509	1.477425	1.515092
0.176091	1.581563	1.549567	1.571255
0.30103	1.639397	1.59191	1.601908
0.39794	1.682335	1.630387	1.639496
0.477121	1.721365	1.657209	1.682335
0.544068	1.763959	1.682425	1.706257
0.60206	1.796581	1.713877	1.721489
0.653213	1.826891	1.736125	1.757176
0.69897	1.849733	1.777289	1.796547
0.740363	1.876628	1.814986	1.821029
0.778151	1.906852	1.838478	1.855192
0.812913	1.925962	1.866057	1.886919
0.845098	1.930674	1.897	1.916486
0.875061	1.939774	1.921249	1.935185
0.90309	1.961711	1.93521	1.944265
0.929419	1.970282	1.961687	1.970189
0.954243	1.974493	1.978573	1.982705
0.977724	1.978642	1.986799	1.994805
1	1.982751	1.990854	1.994871
1.021189	1.986821	1.994849	1.994871
1.041393	1.986843	1.994871	1.994871
1.060698	1.986843	1.994871	1.994871
1.079181	1.986843	1.994871	1.994871

DISCUSSION

The present investigation was undertaken to design, formulate and evaluate Salbutamol sulphate matrix tablet for sustained release dosage form and compare with marketed product. IR study indicated good compatibility between drug, polymers and excipients.

The granules of different formulations were evaluated for Angle of repose, Bulk density and Tapped density. The granules indicated good flowability with an angle of repose values ranging from 25-28^0. The result of bulk density and tapped density are mentioned in Table-I and the results were within the limit.

All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values. The tablet mean diameter and mean thickness values ranged from 6.14±0.13 to 6.21±0.07 mm and 4.22±0.08 to 4.27±0.13 mm, respectively. The hardness of all the tablets was within a range of 6.0±0.71 to 6.6±0.55 kg/cm^2. The loss in total weight in friability test was in a range of 0.00 to 0.01%. The percentage drug content for different tablet formulations varied from 98.37±0.06 to 99.67±0.02% was found to be within the limit. The mass degree of swelling was found to be the maximum for F–6, indicating high swelling which helps in retarding the drug release from the formulation.

F–4 containing EC and Acrycoat S-100 (2:1 ratio) was selected as the optimum formulation on the basis of the results of in-vitro dissolution studies. It is seen that at the end of 12 hr, 98.62% drug was released from the formulation, whereas the two marketed sustained release products (ASTHALIN-SA 8mg and VENTORLIN 8mg) released 99.23%

and 99.44% respectively at the end of 12 hr, which is comparable to the fabricated formulation F-4.

Upon model fitting analysis (Zero order, Higuchi and Korsmeyer-Peppas model), it is seen that all the formulations predominantly follow Higuchi model as the R^2 values are near to unity.

As compared to the 'n' value, obtained from the Korsmeyer-Peppas model, Fickian/Diffusion controlled drug release is observed from F-4 and F-5 whereas for the other formulations non-Fickian transport are observed.

CONCLUSION

From the above results it can be concluded that formulation F-4 has achieved the objectives of prolonged drug release, patient convenience and cost effectiveness as a sustained release dosage form and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

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