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Formulation and Evaluation of Salbutamol Sulphate Extended Release Tablets

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A B S T R A C T

In the present investigation, an attempt was made to formulate and characterize the oral sustained release matrix tablets of salbutamol sulphate in order to improve efficacy, reduce the frequency of administration and better patient compliance. Salbutamol sulphate selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vaso constrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Matrix tablets of Salbutamol sulphate were formulated using different concentrations of hydrophilic polymers such as HPMCK4M, HPMC K15, HPMC K100 and prepared by Wet granulation method. The powder blend was evaluated for precompression properties. The tablets were evaluated for thickness, weight variation test, hardness, friability, and drug content and *in-vitro* drug release profile over a period of 12 hours. Along with physical properties, the dynamics of water uptake and erosion degree of tablets were also studied. The in-vitro drug release study revealed that, all the formulations showed extended release for 12 hours but most successful formulation of the study was found to be optimized with drug to polymer combination (0.5:0.5) 1:1 which includes HPMCK4M and HPMC K100, extended the drug release up to 12 hours. Formulation 'F10' follows Higuchi's kinetics indicating zero-order release which can be achieved when drug diffusion is rapid compared to the constant rate of solvent induced relaxation and swelling in the polymer. Results indicated that the prepared sustained-release tablets of Salbutamol sulphate could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

Keywords: Salbutamol sulphate, Extended release, HPMCK4M, HPMC K15, HPMC K100 etc

A R T I C L E I N F O

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1. Introduction

The term controlled-release drug product was previously used to describe various types of oral extended-release dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery. Sustained release (S.R)/ Controlled release (C.R) pharmaceutical products have gradually gained medical acceptance and popularity. General approaches to manufacturing an extended-release drug product include the use of a matrix structure in which the drug is suspended or dissolved, the use of a rate controlling membrane through which the drug diffuses, or a combination of both [1-2].

Salbutamol is a beta (2)-adrenergic agonist and thus it stimulates beta (2)-adrenergic receptors. Binding of albuterol to beta (2)-receptors in the lungs results in relaxation of bronchial smooth muscles. It is believed that salbutamol increases cAMP production by activating adenylate cyclase, and the actions of salbutamol are mediated by cAMP [3-5]. Salbutamol sulphate has a half-life of 1.6 Hrs, which increases the frequency of administration as an immediate release dosage form [6]. So, the aim of the present research work was to formulate and evaluate salbutamol sulphate extended release tablets using HPMCK4M, HPMC K100 in varying ratios and to extend the drug release up to 24hrs.

2. Materials and Methods

All the matrix tablets, each containing 32 mg of Solbutamol sulphate, were prepared by Wet granulation method. Accurately weighed drug and diluent mixed thoroughly by adding granulating agent, then wet mass was passed through the 18 mesh seive and finally added talc and magnesium stearate to the granules. The powder blend was then lubricated with magnesium stearate and talc for 2 minutes and compressed into tablets on a 16-station rotary tabletting machine using 6-mm round, flat-faced punches. The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 200mg with different drug polymer ratios and combination of polymers given in table no-1. The various polymers used were HPMC K4M, HPMC K15, HPMC K100. MCC (water-insoluble) was used as a diluent for the preparation of matrix tablets.

Evaluation

Precompression parameters [7-10]

a) Angle of Repose

The angle of repose of precompression blend was determined by the funnel-method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation

Tan θ = h/r

Where,

h and r are the height and radius of the powder cone, θ is the angle of repose .

Table 2: Angle of Repose

S.No	Angle of Repose	Properties
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Poor flow

b) Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal (Lachman et al., 1987).The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0

Tapped density = W/V_f

Where,

W= Weight of the powder

V_0 = Initial volume

V_f = final volume

c) Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is (Lachman et al., 1987).

CI = (TD-BD) x 100/TD

Where,

TD is the tapped density and BD is the bulk density.

Table 3: Carr's Index Values

S.No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

d) Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and, as such, could be used to predict powder flow properties (Lachman et al., 1987). Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index

Hausner's Ratio= Tapped density/ Bulk density

Post-compression parameters [10-15]

a) Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was

measured by using vernier caliper. Average thickness and standard deviation values were calculated.

b) Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

c) Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

%Friability was calculated as follows

% Friability = $(W_1 – W_2) \times 100/W_1$

Where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

d) Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = $(W_A–W_I) \times 100/ W_A$

As the total tablet weight was 250 mg, according to IP 1996, out of twenty tablets ±7.5 % variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

e) Drug Content (Assay)

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount. Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to average weight of three tablets of Salbutamol sulphate was transferred to a 100 ml volumetric flask containing 6.8 pH phosphate buffer solution and the volume was made upto the mark. From this 10ml was taken and shaken by mechanical means using centrifuge at 3000rpm for 30min. Then it was filtered through whatman filter paper. From this resulted solution 1 ml was taken, diluted to 10 ml with 6.8 pH Phosphate buffer solution and absorbance was measured against blank at 276 nm.

f) In -vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml of and the phosphate buffer pH 6.8 upto 24 hours and temperature was maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. And drug content in each sample was analyzed by UV-visible spectrophotometer at 276 nm.

g) Stability Studies

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human life.The ICH tripartite guidelines have established long term stability testing to be done at 25^0C/60%RH for 12 months. Accelerated stability testing should be done at 40^0 C/75%RH for 6 months and stability testing at intermediate storage conditions should be done at 30^0C/65%RH. The following table shows different storage conditions and period of stability testing.

Table 4: ICH Guidelines for stability study

Study	Storage Condition	Duration
Long term	25±2°C, RH 60±5%	12 months
Intermediate	30±2°C, RH 65±5%	6 months
Accelerated temperature	40±2°C, RH 75±5%	6 months

3. Results and Discussion

The present investigation was under taken to formulate and evaluate extended release tablets of Salbutamol sulphate. Using various polymers like HPMC K100M, HPMC K15M, HPMC K4M, tablets were prepared along with other additives. Wet granulation method was used for the preparation of tablets. A total number of 12 formulations were prepared and evaluated.

To retain tablet for long period, most of the excipients selected must be water soluble by nature. Excipient was used a bulking agent to achieve the desired tablet weight. Talc was employed as a lubricant and magnesium stearate used as glidant.

Pre compressional studies:

The results obtained by evaluating the powder blends of drug and excipients are shown in table no – 5. Bulk density and tapped density were found in the range 0.52-0.56 g/cc and 0.62-0.69 g/cc respectively. The value of hausner's ratio was in between 1.16-1.25 (< 1.3) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 19.65-25.8 showing that blend of powder mass was Good flowing.

Weight variation and Thickness:

The average weight in all the 12 formulations was found to be 96.7mg to 101.3 mg. In all 12 formulations no tablets were outside the ±10%of tablet weight in weight variation test. The thickness varies between 2.4 to 2.72 mm. In all formulations tablet thickness of all formulations was within ±5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 5 to 6 kg/cm^2 for all the formulations. Assay was performed and percent drug content of all the tablets were found to be between 96.5 % and 100.38% which was within the acceptable limits. Results are tabulated in table no-6.

***In vitro* dissolution:**

In vitro dissolution studies are performed for extended release tablets of Salbutamol sulphate using 0.1N HCl as buffer and USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of polymer. F10 (HPMC K15M with HPMC K4M) showed optimum release profile

indicating it to be the best formulation in present research and recorded 98.6% drug release respectively in 12 hrs. results are tabulated in table no-7 and fig no-1 to 4

Drug Release Kinetics:

In vitro drug release data of all extended release formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table no-8 and plots shown in fig no – 5,6,7. From the above data, it can be seen that F10 follows Higuchi's kinetics indicating zero-order release which can be achieved when drug diffusion is rapid compared to the constant rate of solvent induced relaxation and swelling in the polymer.

Stability Studies:

There was no significant change in physical and chemical properties of the tablets of formulation F10 after 3 Months. Parameters quantified at various time intervals were shown in table no-10.

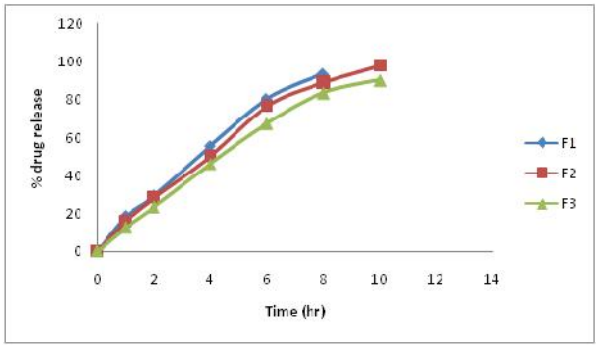

Figure 1: *In-vitro* release profile of F1, F2, F3

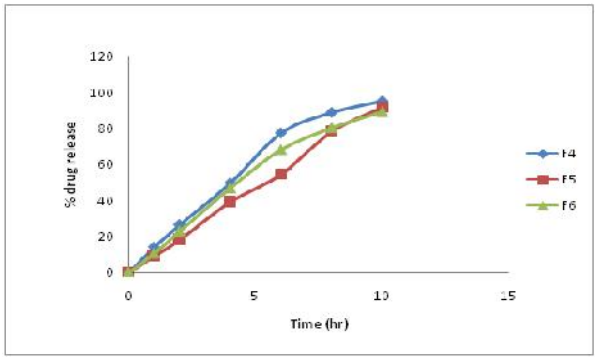

Figure 2: *In-vitro* release profile of F4, F5, F6

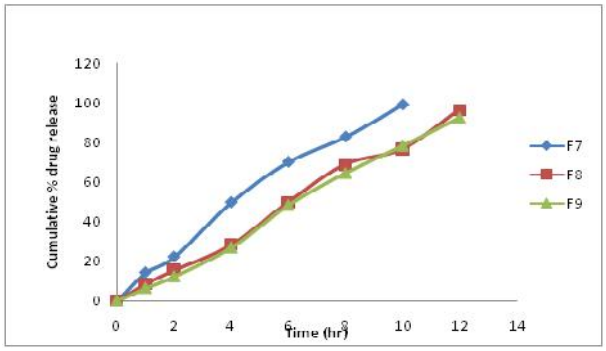

Figure 3: *In-vitro* release profile of F7, F8, F9

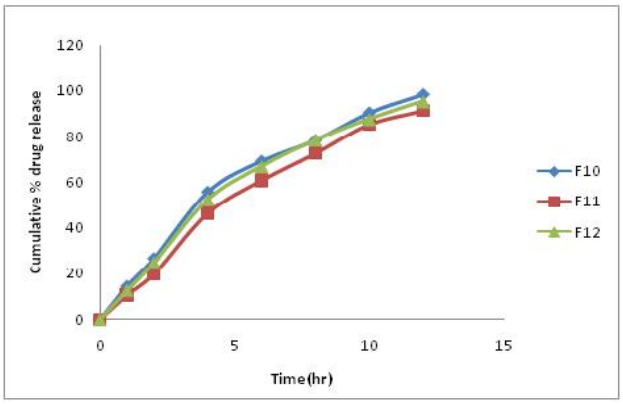

Figure 4: *In-vitro* release profile of F10, F11,F12

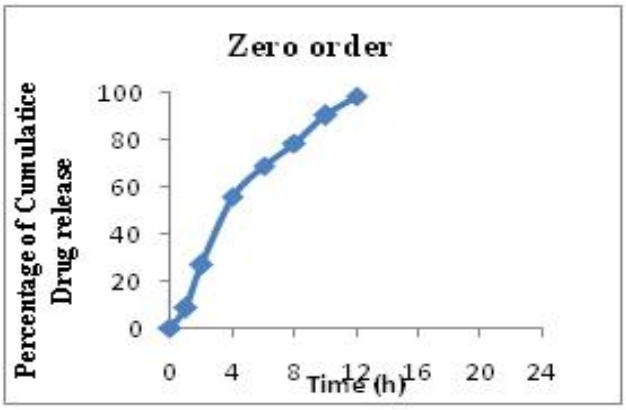

Figure 5A: Mathematical modeling for formulation F10

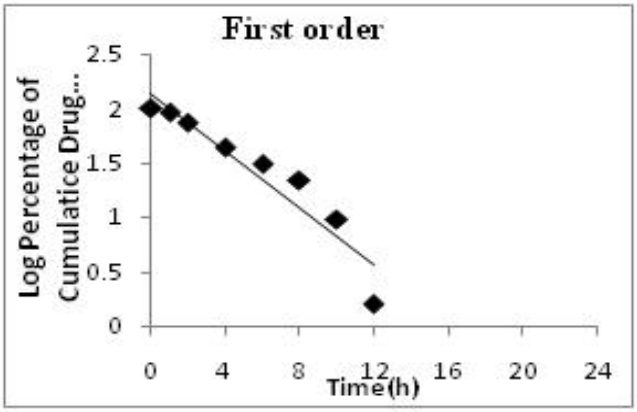

Figure 5B: Mathematical modeling for formulation F10

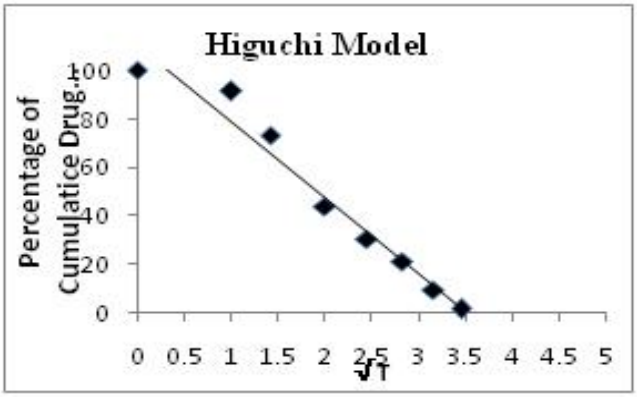

Figure 5C: Mathematical modeling for formulation F10

Table 1: Composition of Matrix Tablets

Ingredients (in mg)	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Salbutamol sulphate	4	4	4	4	4	4	4	4	4	4	4	4
HPMC K15	4	-	-	8	-	-	12	-	-	4	-	4
HPMC K4M	-	4	-	-	8	-	-	12	-	4	4	-
HPMC K 100	-	-	4	-	-	8	-	-	12		4	4
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lactose mono hydrate	79	79	79	75	75	75	71	71	71	75	75	75
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. Stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100	100	100	100

Table 5: Precompression parameters

Formulation Code	Bulk Density	Tapped Density	Carr's Index	Hausner Ratio	Angle of Repose
F1	0.55	0.65	1.25	0.25	23.45
F2	0.54	0.62	1.19	0.16	19.65
F3	0.56	0.64	1.23	0.18	22.35
F4	0.54	0.63	1.12	0.11	20.69
F5	0.50	0.67	1.24	0.22	20.82
F6	0.53	0.64	1.23	0.18	20.72
F7	0.51	0.67	1.24	0.19	20.89
F8	0.52	0.69	1.3	0.23	20.78
F9	0.56	0.68	1.21	0.17	22.6
F10	0.52	0.66	1.16	0.16	22.3
F11	0.51	0.62	1.18	0.18	24.6
F12	0.52	0.63	1.2	0.19	25.8

Table 6: Post compression parameters

Formulation Code	Thickness (mm)	Weight Variation (mg)	Friability (%)	Hardness	%Drug content
F1	2.41	100.65	0.16	5.4	96.19
F2	2.45	99.67	0.18	5.5	99.69
F3	2.43	98.89	0.17	5.3	99.77
F4	2.35	101.05	0.25	5.6	100.38
F5	2.54	99.12	0.22	5.3	99.38
F6	2.60	96.46	0.3	6.0	96.5
F7	2.63	98.99	0.48	5.6	99.49
F8	2.72	99.76	0.25	5.5	98.17
F9	2.46	99.13	0.42	5.0	99.38
F10	2.62	98.45	0.02	5.5	97.3
F11	2.54	99.78	0.12	6	96.4
F12	2.20	99.56	0.14	5.5	98.6

Dissolution Profiles of Formulations:

Table 7: *In-vitro* release profile of drug with various polymers

Time (hr)	% drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	18.45	15.92	12.6	14.05	9.2	10.64	14.25	8.56	6.45	8.5	10.6	12.6
2	28.2	28.15	23.4	26.41	18.15	22.85	22.10	15.50	12.40	26.7	19.8	24.8
4	55.6	50.24	46.9	49.66	39.24	46.98	49.60	28.24	26.92	55.8	46.4	52.4
6	80.4	76.5	67.34	77.47	54.5	68.34	70.02	49.76	48.34	69.3	60.8	66.9

8	93.6	88.92	83.52	88.9	78.28	80.50	82.65	68.80	64.52	78.4	72.6	78.4
10	-	97.74	90.2	95.32	91.74	89.44	98.9	76.52	78.3	90.4	85.3	87.6
12	-	-	-	-	-	-	-	96.2	92.4	98.4	91.2	95.3

Table 8: Kinetic Analysis of Dissolution Data

Formulation code	**Mathematical models (Kinetics)**				
	Zero order	First order	Higuchi	Peppas model	
	r2	r2	r2	N	r2
F10	0.942	0.900	0.965	0.94	0.943

Table 9: Results of stability studies of optimized formulation F10

S.No	**Parameters**	**Initial**	**1 month**	**2 month**	**3 month**	**Limits as per specification**
1	400C/75% RH % Release	98	98.52	97.79	96.56	Not less than85 %
2	400C/75% RH Assay Value	98	97.96	96.22	96.00	Not less than 90 % Not more than110 %

4. Conclusion

Success of the In-vitro drug release studies recommends the product for further in-vivo studies, which may improve patient compliance. From the results, formulation F10 containing Salbutamol sulphate 4 mg with HPMC (K15M) 4 mg and HPMC K4M 4 mg evolved as the optimized formulation and it releases more than 97% drug in 12hrs. The optimized formulation F10 can be considered as a promising extended drug delivery system of Salbutamol sulphate providing nearly zero order drug release over a period of 12 hrs.

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