ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Design, Development and Characterization of Salbutamol Sulphate Extended Release Matrix Tablets

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ABSTRACT

Extended release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. Salbutamol sulphate is antiasthmatic agent used in the asthma and chronic obstructive pulmonary diseases (COPD). The extended release tablets of Salbutamol sulphate prolongs drug absorption in the upper gastrointestinal tract and permits once daily dosing inpatient with asthma. This newer formulation may enhance patient compliance with oral therapy compared to conventional tablets of Salbutamol sulphate. Extended release matrix tablets of Salbutamol sulphate were formulated by using different combinations of polymers like Ethyl cellulose (EC) and Xanthan gum by direct compression method. The formulated tablets were subjected to different evaluation parameters *viz.*Hardness test, Friability test, Drug content uniformity and *Invitro* dissolution studies. Formulations F1-F7 containing Ethyl cellulose and Xanthan gum in different concentration shows the extended drug release for up to 12 hrs, among these formulations, F7 shows 97.78% of drug release at the end of 12 hours. This finding reveals that above a particular concentration of Ethyl cellulose and Xanthan gum are capable of providing extended drug release.

Keywords: Salbutamol sulphate, Ethyl cellulose, Xanthan gum and matrix tablets.

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ISSN: 0975-8585

INTRODUCTION

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration which leads to higher level of patient compliance. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration. [1]

During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. [2] The oral controlled release formulation have been developed for those drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation. As these will release the drug slowly into the GIT and maintain a constant drug concentration in the plasma for a longer period of time. The sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. [3]

Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs. There are several reasons for attractiveness of these dosage forms *viz.* provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, Reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. [4] Extended release drug delivery system (ERDDS) have emerged as an effective means of enhancing the bioavailability and controlled delivery of many drugs. ERDDS play an important role in reducing the dosing frequency as well as by enhancing the biological half life of specific certain drugs. [5]

MATERIAL AND METHOD

Materials

The drug Salbutamol sulphate was obtained as a gift sample from Elegant Drugs Pvt. Ltd., Banglore, Karnataka. Polymers Ethyl cellulose and Xanthan gum were purchased from Evonic Degussa and Titan Biotech Ltd., Bhiwadi (Rajasthan). All other chemicals and reagents used were obtained from commercial sources and were of analytical grade.

Method

Establishment of Calibration plot

ISSN: 0975-8585

In order to conduct the *in vitro* drug dissolution studies, the calibration plot of pure drug using different solvents viz. 0.1N HCl, phosphate buffer (pH 6.8) and Distilled water were constructed. For this, 10 mg of Salbutamol sulphate was accurately weighed and transferred into a 10mL volumetric flask containing approximately 5 mL of 0.1N HCl. Flask was then gently shaken to dissolve its contents and volume was finally made up to 10 mL using the same solvent and was labelled as stock solution "A". 1 mL of this solution was pipette out in another volumetric flask and volume was made up to 10 mL with 0.1N HCl in order to obtain the resulting solution of 100 µg/mL, it was than labelled as stock solution "B". Finally by using stock solution "B", solutions of various concentrations such as 20, 40, 60, 80, 100, 120, 140, 160 µg/mL were prepared. 0.1N HCl was taken as blank and absorbance of different dilutions were taken at 277nmSimilarly, standard plots of pure Salbutamol sulphate were also constructed at the same λ_{max} using phosphate buffer and distilled water.

Table 1, 2 and 3 enlisted the standard curve data and Fig. 1, 2 and 3depicted the corresponding standard plot of Salbutamol sulphate in 0.1N HCl, phosphate buffer (pH 6.8) and distilled water respectively.

Table 1: Standard plot data in 0.1N HCl

S No.	Conc. (µg/mL)	Absorbance
1	20	0.1301
2	40	0.2512
3	60	0.3814
4	80	0.5132
5	100	06312
6	120	0.7415
7	140	0.8823
8	160	0.9912

Table 2: Standard plot data in phosphate buffer (pH 6.8)

S No.	Conc. (µg/mL)	Absorbance
1	20	0.1101
2	40	0.2311
3	60	0.3441
4	80	0.4322
5	100	0.5330
6	120	0.6502
7	140	0.7615
8	160	0.9012

Table 3: Standard plot data in distilled water

S No.	Conc. (µg/mL)	Absorbance
1	20	0.1291
2	40	0.2412
3	60	0.3842
4	80	0.5121
5	100	0.6333
6	120	0.7612
7	140	0.8817
8	160	0.9896

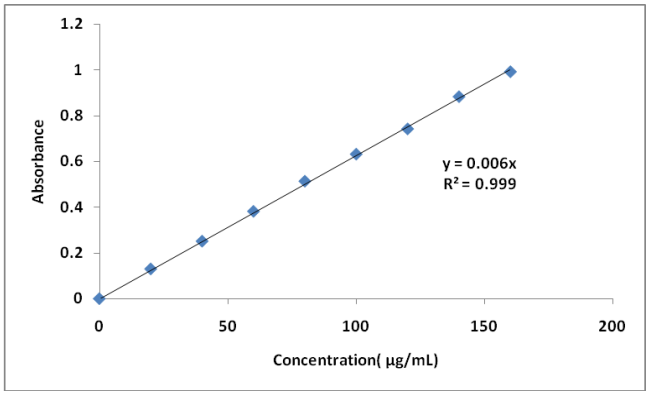

Fig 1: Standard plot of Salbutamol sulphate in 0.1N HCl

ISSN: 0975-8585

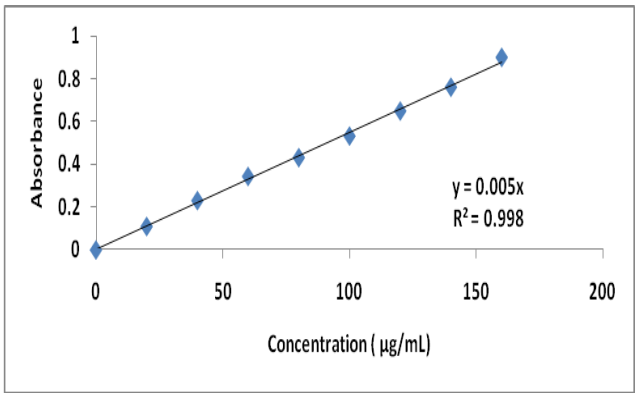

Fig 2: Standard plot of Salbutamol sulphate in phosphate buffer (pH6.8)

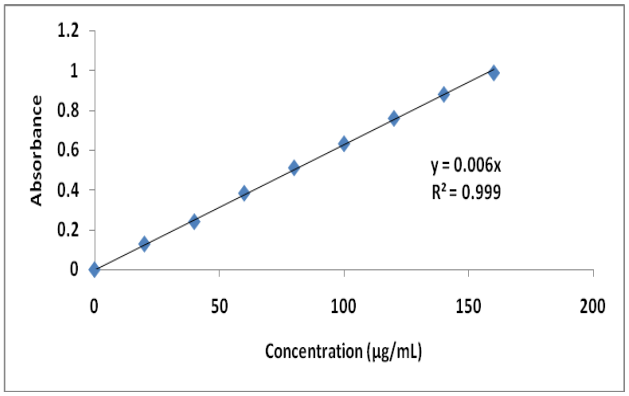

Fig 3: Standard plot of Salbutamol sulphate in distilled water

Preparation of Extended Release Tablet of Salbutamol Sulphate

Extended release tablets of Salbutamol sulphate (F1-F7) were prepared by developing the formulae using variable concentrations of different polymers *viz.* Xanthan gum and Ethyl cellulose as shown in table 4. The concentration of Salbutamol sulphate was kept constant for all batches of formulations. Salbutamol sulphate and all excipients were weighed accurately except talc and magnesium sterate, after that blended in mortar with the help of pestle for 5-10 min. After the mixing of drug with excipient, required amount of talc and magnesium stearate were added and further mixing was done for 4-5 min. The gross weight of each formulations was kept 200 mg.

Table 4: Various Formulations of Extended Release Tablets of Salbutamol Sulphate

Ingredients (mg)	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Salbutamol sulphate	8	8	8	8	8	8	8
Xanthan gum	60	80	100	-	-	-	50
Ethyl cellulose	-	-	-	60	80	100	50
Lactose	126	106	86	126	106	86	86
Magnesium stearate	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

All batches of prepared tablet were evaluated for various parameters like hardness, friability, content uniformity and *invitro* dissolution studies. The Results of All batches of prepared tablets of Salbutamol Sulphate for different parameters *viz.* hardness, friability and content uniformity are shown in table 5 and table 6 representing the result of *in vitro* dissolution studies.

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Table 5: Evaluation of Salbutamol sulphate extended release matrix tablets

Formulation Code	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)
F1	5.7±0.25	0.45±0.065	98.02±0.70
F2	5.5±0.36	0.55±0.096	99.28±1.998
F3	5.7±0.32	0.64±0.060	97.76±0.872
F4	5.1±0.12	0.65±0.057	94.54±0.870
F5	5.6±0.15	0.50±0.095	101.04±1.29
F6	5.5±0.26	0.34±0.098	101.64±1.310
F7	5.3±0.21	0.45±0.035	99.78±0.773

All values are mean ± SD of three determinations

Table 6: *In vitro* drug release profile

Time(h)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	20.43±0.35	21.56±0.08	22.67±0.18	21.48±0.18	23.78±0.27	20.89±0.26	21.38±0.22
2	26.56±0.30	29.56±0.23	27.19±0.03	27.32±0.19	30.22±0.30	27.22±0.18	29.54±0.13
3	31.21±0.12	35.43±0.77	33.86±0.42	35.22±0.12	36.18±0.15	35.75±0.17	36.66±0.30
4	38.31±0.18	44.95±0.17	39.60±0.49	43.77±0.15	42.56±0.33	42.79±0.21	43.98±0.36
5	46.57±0.26	52.12±0.43	47.86±0.27	52.99±0.37	50.38±0.36	49.04±0.18	51.37±0.44
6	53.86±0.11	59±.0.13	56.78±0.17	58.27±0.33	58.01±0.17	55.27±0.23	59.75±0.31
7	58.48±0.28	63.76±0.44	62.41±0.20	61.45±0.23	65.39±0.35	61.48±0.33	67.36±0.23
8	65.77±0.11	68.27±0.34	69.17±0.08	69.71±0.05	72.59±0.25	67.33±0.32	75.55±0.41
9	71.68±0.21	72.54±0.10	76.33±0.17	73.01±0.39	80.11±0.34	74.37±0.33	83.11±0.32
10	79.54±0.30	78.45±0.20	81.01±0.39	79.94±0.32	87.52±0.32	80.61±0.24	89.66±0.28
11	85.43±0.17	89.14±0.30	76.50±0.11	84.29±0.11	89.48±0.31	86.88±0.13	94.82±0.29
12	86.38±0.22	92.49±0.33	74.28±0.26	90.29±0.38	86.51±0.08	84.47±0.43	97.78±0.29
16	81.61±0.40	87.89±0.26	71.55±0.35	85.61±0.32	81.31±0.26	79.55±0.19	93.08±0.40
20	77.36±0.28	81.45±0.31	68.30±0.10	80.25±0.26	76.27±0.41	74.22±0.12	89.33±0.22
24	72.62±0.39	76.56±0.30	64.87±0.29	75.66±0.16	71.99±0.18	69.51±0.26	86.69±0.25

Tablet Hardness:

Tablet hardness indicates the pressure which is needed to break the tablet. The hardness (Kg/cm^3) of prepared tablets was determined by using Monsanto hardness tester. The average hardness and standard deviation was determined. Hardness of 4 kg is considered to be minimum for a satisfactory tablet. [6]

Friability:

Friability test is performed to evaluate the ability of the tablet to withstand wear and tear in packing, handling and transporting. Friability test was done by Roche Friabilator. Randomly picked twenty tablets were weight (W_o) and were subjected to combined effect of attrition and shock by utilizing a plastic chamber(25 rpm) dropping the tablets at a distance of 6

ISSN: 0975-8585

inch with each revolution, operated for 100 revolutions. The tablets were dusted and reweighed (W) after completion of 100 revolutions. The percentage friability was calculated using following formula. [7]

$$\% \text{ Friability} = W_0 - W / W_0 \times 100$$

Uniformity of Drug Content:

Assay of extended release tablets of Salbutamol sulphate was done in distilled water to find out the amount of drug present in one tablet. For this 5 tablets were weighed and powdered in a glass mortar and 200 mg of the powder equivalent to 8 mg of drug was placed in a stoppered 100 mL volumetric flask and dissolved in 100 mL water. The resulting solution was filtered and absorbance was measured at λ_{max} 277 nm using UV visible spectrophotometer. The concentration of Salbutamol sulphate in milligram per milliliter was obtained from standard calibration plot of drug. [6]

***Invitro* Drug Release Studies:**

In-vitro release of Salbutamol sulphate from extended release tablets were determined using USP type II (Paddle Type) dissolution apparatus in 900 mL of phosphate buffer of pH 6.8 at constant temperature of 37° ± 0.5°C at 50 rpm. Samples (5 mL) of the solutions were withdrawn from the dissolution apparatus at different time intervals and replaced with fresh dissolution medium to maintain the sink condition. These Samples were filtered and the absorbances of these solutions were measured by using a double beam ultra-violet spectrophotometer at 277 nm against fresh phosphate buffer solution as blank. [7] Comparison release profile of F1 to F7 has been depicted in Fig 4.

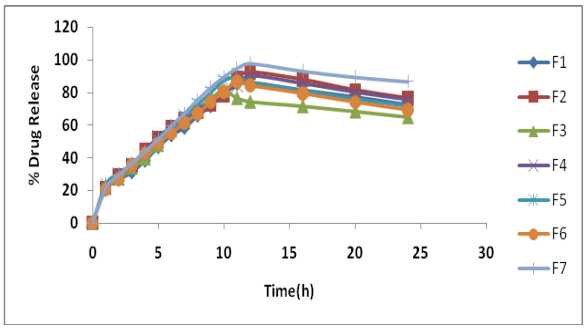

Fig 4: Dissolution profile of different formulations (F1-F7) of salbutamol sulphate

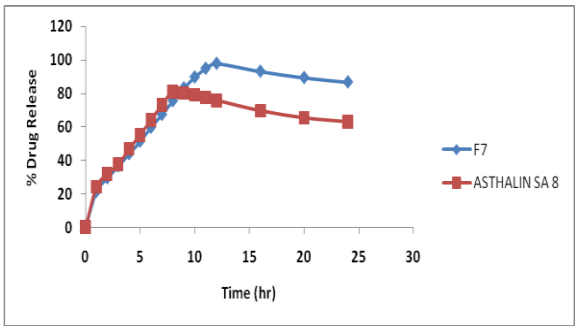

Fig 5: Comparison of % drug release profile of best formulation with marketed product

Comparison of Best Formulation

The promising formulations (F7) as found by evaluation studies were compared with marketed tablet. The marketed formulations showed drug release upto 8 hr whereas selected formulations (F7) extended drug release upto 12 hr and has better control over drug release

rate. Fig 5 portrays the respective release profile of ASTHALIN SA8 and selected formulations indicated that the release performance of F7 are rather better controlled and extended than the marketed formulation.

DISCUSSION

All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range. The hardness of all the tablets was within a range of 5.1±0.12 to 5.7±0.32 kg/cm^2. The loss in total weight in friability test was in a range of0.34±0.098 to0.65±0.057%. The percentage drug content for different tablet formulations varied from 94.54±0.870 to101.64±1.310 % was found to be within the limit. F-7 containing Ethyl cellulose and Xanthan gum (1:1 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, 97.78±0.29% drug was released from the formulation.

CONCLUSION

From the above results it can be concluded that formulation F-7 has achieved the objectives of prolonged drug release, patient convenience and cost effectiveness as extended 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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