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### Original Article

# Design, Development and Evaluation of Extended Release Tablets of Anti-asthmatic Agents using various Polymers

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**ABSTRACT:** The aim of this investigation was to define and assess Salbutamol sulphate and Theophylline framework tablets, prolonged discharge dosage form, for the treatment of Chronic Obstructive Pulmonary Disease (COPD). Powder blends of the drugs (Salbutamol sulphate and Theophylline) and polymers (HPMC K100M and Xanthan Gum) were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose which shows satisfactory results. The direct compression method was used for the preparation of Extended-release tablets using hydroxyl propyl methyl cellulose (HPMC K100M), a semi-synthetic polymer, and xanthan gum (a natural polymer) in changing ratios keeping the total weight 250 mg for each tablet. The fabricated tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability and drug content. The results of all these tests were found to be satisfactory as per guidelines mentioned in the standards. The *in-vitro* dissolution study was carried out for 24 hours using type II dissolution apparatus. Among all the formulation, F7 shows 97.16 ± 0.59 % of drug release at the end of 12 hours. This finding reveals that above a particular concentration of HPMC K100M and xanthan gum are capable of providing extended drug release from the dosage form.

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## INTRODUCTION

Salbutamol sulphate is a sympathomimetic molecule that works on the  $\beta_2$ -adrenergic receptor and demonstrates site-particular absorption in the stomach. Hence it is utilized as a bronchodilator in the treatment of reversible bronchospasm, acute asthma and for symptom relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD)[1]. The drug has plasma half-life ranges from 2-3 hr and the maximum plasma drug concentration occurs within 2.5 hr. It is given orally at a dose of 2-4 mg, three or four times a day.

Theophylline has anti-inflammatory as well as bronchodilator activity for moderate to severe reversible bronchospasm[2]. It relaxes the bronchial muscle and hence plays a vital role in the treatment and prevention of asthma and COPD. The drug is well absorbed from GIT with 90-100% bioavailability and has a

narrow therapeutic index with a short half-life (8 hrs in adults)[3,4].

The traditional tablet gives just a solitary and a transient burst of medication. A pharmaceutical impact is viewed as long as the measure of medication is inside the Therapeutic range. So, it is chosen to set up an ER tablet of the drugs[4].

ERDDS allows a moderate release of the medication over a broadened timeframe or the medication is absorbed over for an extended time. Extended-release dosage form initially releases an adequate amount of drug to bring about the necessary blood concentration (loading dose,  $D_L$ ) for the desired therapeutic response and therefore, a further amount of drug is released at a controlled rate (maintenance dose,  $D_M$ ) to maintain the said blood levels for some desirable period. Extended-release drug delivery system (ERDDS) has emerged as an effective means of enhancing the bioavailability and controlled delivery of many

drugs. Extended-release drug delivery system assumes an essential part in diminishing the dosing recurrence by enhancing the biological half-life of drug agents. As of late, different endeavours were made to diminish the dosing recurrence of certain patent medications by this approach[5,6].

The Present study deals with the formulation, development and evaluation of Salbutamol sulphate and theophylline matrix tablet for extended drug delivery resulting in minimization of occurrences of nocturnal and early morning asthmatic attacks, superior patient compliance, a pharmaco-economic NDDS and for powerful treatment of Chronic Obstructive Pulmonary Disease[7].

## MATERIALS AND METHOD

### MATERIALS

The drugs Salbutamol sulphate and Theophylline were obtained as a gift sample from Elegant Drugs Pvt. Ltd., Karnataka and Koves India Ltd. Chennai. Polymers HPMC K100M and Xanthan gum were purchased from Leon Chem., Bengaluru,

**Table 1: Formulations of ER Tablets of Salbutamol Sulphate and Theophylline**

Ingredients (mg)	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Salbutamol sulphate	4	4	4	4	4	4	4
Theophylline	100	100	100	100	100	100	100
HPMC K100M	40	50	60	-	-	-	50
Xanthan gum	-	-	-	50	75	100	75
Lactose	100	90	80	90	65	40	15
Magnesium stearate	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4
Total weight	250	250	250	250	250	250	250

### Compression of Extended Release Tablets of Salbutamol Sulphate and Theophylline

Extended-release tablets of Salbutamol sulphate and theophylline (F1-F7) were prepared by direct compression method. The powder blend of different batches (F1-F7) has illustrated in table 1, were compressed by using rotary tablet punching machine. The diameter of punches and die was 8 mm and the weight of tablets remained kept constant i.e. 250 mg. The compressed tablets were of convex round shaped. 100 tablets of each batch were prepared initially. The prepared tablets were evaluated for different parameters of evaluation[11,12].

## RESULTS AND DISCUSSION

### Evaluation of Tablets

All groups of manufactured tablets were assessed for different parameters like hardness, friability, thickness, weight variation, content consistency, *in-vitro* dissolution tests.

#### Tablet Hardness

The crushing strength (Kg/cm<sup>2</sup>) of prepared tablets was determined by using Monsanto hardness tester. The hardness test was performed for each batch of prepared tablets in the triplicate

Evonic Degussa and Titan Biotech Ltd., Bhiwadi. All other chemicals and reagents used were obtained from commercial sources and were of analytical grade.

## METHOD

### Formulation of Extended Release Tablet of Salbutamol Sulphate and Theophylline

Extended-release tablets of Salbutamol sulphate and Theophylline (F1-F7) were prepared by developing the formulae using variable concentrations of different polymers viz. HPMC and Xanthan gum as shown in table 1. The concentration of Salbutamol sulphate and Theophylline was kept constant for all batches of formulations. The Drugs (Salbutamol sulphate and Theophylline) and all excipients were weighed accurately except talc and magnesium stearate, after that blended in a mortar with the help of pestle for 5-10 min. After the mixing of drug with the excipient required amount of talc and magnesium stearate were added and further mixing was done for 4-5 min. The gross weight of each formulation was kept 250 mg[8,9,10].

manner as shown in Table 2. The average hardness and standard deviation were determined. Tablet hardness represents the pressure which is required to crush the tablet. The Hardness of 4 kg is thought to be least for an acceptable tablet[13,14,15].

### Friability

Friability test was finished by Roche Friabilator. Twenty tablets were weight ( $W_0$ ) and were subjected to the joined impact of wearing down and stun by using a plastic chamber that revolves at 25 rpm dropping the tablets at a separation of 6 inches with each revolution, operated for 100 revolutions. The tablets were dusted and reweighed ( $W$ ) after fulfilment of 100 revolutions. The percentage friability (Table 2) was calculated using following formula.

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

Friability test is performed to assess the capacity of the tablet to withstand wear and tear in packing, handling and transporting.

### Thickness

Ten tablets from each batch of formulations were selected randomly and thickness of tablets was measured using Vernier calliper. The average value of thickness was calculated and illustrated in Table 2[16].

**Weight Variation**

For uniformity of weight, twenty tablets from each batch of the formulation were selected at random and determined their individual weights by using electronic balance. Then, average weight and standard deviation of the tablets was calculated and shown in Table 2 [17].

**Uniformity of Drug Content**

Assay of extended-release tablets of Salbutamol sulphate and Theophylline was done in distilled water to find out the number of drugs present in one tablet. For this test, 5 tablets were weighed and powdered in a glass mortar and 250 mg of the powder equivalent to 4 mg of Salbutamol sulphate and 100 mg of Theophylline drugs were placed in two stoppered 100 mL volumetric flasks and dissolved in 100 mL water. The resulting solutions were filtered, and absorbance was measured at  $\lambda_{\max}$  277 nm for Salbutamol sulphate and  $\lambda_{\max}$  271 nm for Theophylline using UV visible spectrophotometer. The concentration of Salbutamol sulphate in milligram per millilitre (Table 2) was obtained from standard calibration plot of the drug [18,19,20].

**In-vitro drug release studies**

*In-vitro* release of Salbutamol sulphate and Theophylline from extended-release tablets were determined using USP type II dissolution apparatus in 900 mL of phosphate buffer (pH 6.8) at the constant temperature of  $37^{\circ} \pm 0.5^{\circ}\text{C}$  at 50 rpm. Aliquots (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 aliquots were filtered, and the absorbance of solutions was measured by using a double beam ultra-violet spectrophotometer at 277 nm for Salbutamol sulphate and 271 nm for Theophylline against fresh phosphate buffer solution as a blank. All the studies were conducted in triplicate and percent drugs release were calculated by using the following formulae and shown in Table 3 [21,22,23].

$$\% \text{ Drug Release} = K \times \text{Absorbance}$$

Where K can be calculated by using the equation as follows

$$K = \frac{\text{Std. conc.} \times \text{vol. of the dissolution media} \times \text{dilution factor}}{100 / \text{std. abs.} \times \text{dose} \times 1000}$$

**Table 2: Evaluation of Salbutamol sulphate and Theophylline ER matrix tablets**

Formulation Code	Hardness (Kg/cm <sup>2</sup> )	Friability (%)	Weight Variation(mg)	Drug Content (%)		Thickness (nm)
				Salbutamol sulphate	Theophylline	
F1	5.5 ± 0.40	0.49 ± 0.068	249.6 ± 3.32	95.57 ± 0.56	97.42 ± 0.42	4.15 ± 0.11
F2	5.8 ± 0.35	0.46 ± 0.016	250.4 ± 2.25	99.67 ± 1.06	95.88 ± 0.36	4.27 ± 0.10
F3	5.1 ± 0.21	0.3 ± 0.073	248.7 ± 2.31	97.51 ± 0.66	99.65 ± 0.71	4.26 ± 0.07
F4	5.7 ± 0.25	0.45 ± 0.065	249.5 ± 2.31	98.02 ± 0.70	98.78 ± 0.22	4.34 ± 0.05
F5	5.5 ± 0.36	0.55 ± 0.096	249.2 ± 2.57	99.28 ± 1.998	97.75 ± 0.41	4.23 ± 0.09
F6	5.7 ± 0.32	0.64 ± 0.060	250.1 ± 2.71	97.76 ± 0.872	99.68 ± 0.39	4.19 ± 0.01
F7	5.6 ± 0.36	0.29 ± 0.065	251.9 ± 1.84	100.29 ± 0.979	98.16 ± 0.53	4.22 ± 0.05

All values are mean ± SD of three determinations

**Table 3: *In vitro* drug release study of Salbutamol sulphate and Theophylline**

Time (h)	Drugs	F1	F2	F3	F4	F5	F6	F7
0	Salbutamol sulphate	0	0	0	0	0	0	0
	Theophylline	0	0	0	0	0	0	0
1	Salbutamol sulphate	32.50 ± 0.33	26.49 ± 0.83	18.20 ± 0.53	23.22 ± 0.80	18.33 ± 0.65	14.87 ± 0.66	23.33 ± 0.65
	Theophylline	28.06 ± 0.39	21.80 ± 0.22	17.66 ± 0.61	23.34 ± 0.43	17.65 ± 0.73	14.57 ± 0.39	23.42 ± 0.31
2	Salbutamol sulphate	46.41 ± 0.34	36.50 ± 0.62	25.69 ± 0.40	36.56 ± 0.84	33.62 ± 0.44	28.21 ± 0.61	35.62 ± 0.44
	Theophylline	43.73 ± 0.63	32.08 ± 0.21	23.05 ± 0.47	35.43 ± 0.56	31.06 ± 0.32	27.44 ± 0.36	35.06 ± 0.13
3	Salbutamol sulphate	57.49 ± 0.62	44.24 ± 0.77	39.38 ± 0.82	58.01 ± 0.60	46.30 ± 0.84	41.31 ± 0.24	43.30 ± 0.84
	Theophylline	54.67 ± 0.45	39.11 ± 0.42	37.66 ± 0.29	55.89 ± 0.31	41.09 ± 0.53	39.09 ± 0.68	41.61 ± 0.12
4	Salbutamol sulphate	72.65 ± 0.13	59.50 ± 0.53	51.42 ± 0.19	72.59 ± 0.62	60.79 ± 0.52	58.29 ± 0.47	52.79 ± 0.52
	Theophylline	68.91 ± 0.32	57.38 ± 0.76	48.01 ± 0.35	68.43 ± 0.32	56.64 ± 0.81	56.70 ± 0.63	52.77 ± 0.31
5	Salbutamol sulphate	99.03 ± 0.56	71.34 ± 0.73	65.29 ± 0.07	87.52 ± 0.73	72.66 ± 0.36	76.05 ± 0.84	65.66 ± 0.36
	Theophylline	96.55 ± 0.43	69.65 ± 0.88	64.97 ± 0.46	82.43 ± 0.38	68.66 ± 0.63	73.88 ± 0.36	64.89 ± 0.66
6	Salbutamol sulphate	99.17 ± 0.63	81.29 ± 0.80	76.18 ± 0.73	99.09 ± 0.96	88.49 ± 0.29	81.73 ± 0.09	76.49 ± 0.29
	Theophylline	98.84 ± 0.56	77.03 ± 0.37	74.38 ± 0.75	95.03 ± 0.33	85.46 ± 0.52	79.67 ± 0.54	75.09 ± 0.14
7	Salbutamol sulphate	99.12 ± 0.78	99.08 ± 0.44	85.51 ± 0.78	99.44 ± 0.38	96.21 ± 0.18	83.24 ± 0.67	88.21 ± 0.18
	Theophylline	98.34 ± 0.67	96.48 ± 0.62	82.86 ± 0.44	95.39 ± 0.38	93.44 ± 0.35	82.89 ± 0.64	86.16 ± 0.23
8	Salbutamol sulphate	99.34 ± 0.45	99.85 ± 0.61	89.44 ± 0.91	87.32 ± 0.24	99.16 ± 0.59	84.06 ± 0.42	97.16 ± 0.59
	Theophylline	98.11 ± 0.31	97.64 ± 0.55	86.48 ± 0.39	95.38 ± 0.43	97.88 ± 0.36	82.32 ± 0.47	93.64 ± 0.17
12	Salbutamol sulphate	99.42 ± 0.35	99.59 ± 0.57	91.19 ± 0.65	99.35 ± 0.54	99.45 ± 0.34	86.16 ± 0.65	97.45 ± 0.34
	Theophylline	98.12 ± 0.81	97.36 ± 0.58	89.66 ± 0.21	96.45 ± 0.07	97.76 ± 0.66	83.78 ± 0.36	93.88 ± 0.51
24	Salbutamol sulphate	99.48 ± 0.18	99.55 ± 0.51	92.67 ± 0.87	99.99 ± 0.55	99.55 ± 0.36	89.01 ± 0.69	97.55 ± 0.36
	Theophylline	98.36 ± 0.44	97.63 ± 0.70	89.54 ± 0.11	96.32 ± 0.66	97.78 ± 0.58	85.69 ± 0.73	94.79 ± 0.57

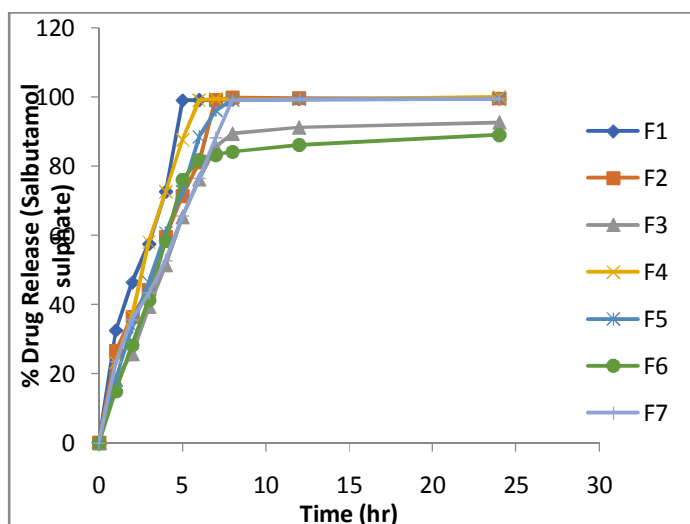


Fig. 1: Dissolution profile of various formulations (F1-F7) of salbutamol sulphate

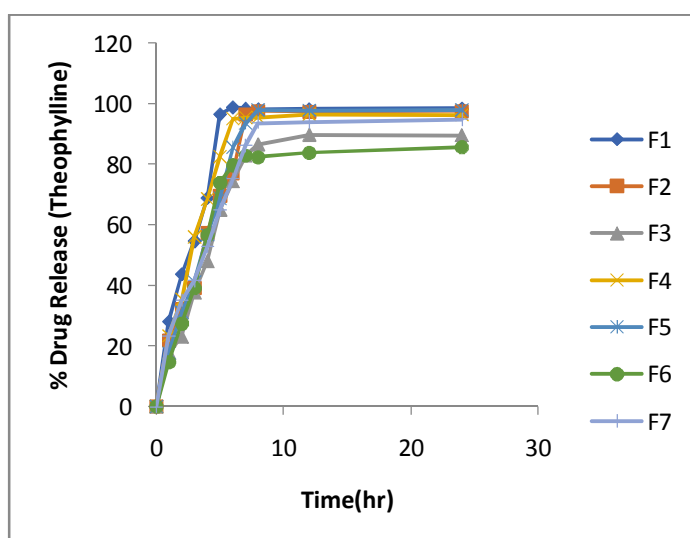


Fig. 2: Dissolution profile of various formulations (F1-F7) of Theophylline

## DISCUSSION

The present investigation was undertaken to formulate and evaluate Salbutamol sulphate and Theophylline matrix tablet for extended release dosage form. 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 means thickness values ranged from  $4.15 \pm 0.1$  to  $4.34 \pm 0.05$  mm. The hardness of all the tablets was within a range of  $5.1 \pm 0.21$  to  $5.8 \pm 0.35$  kg/cm<sup>2</sup>. The loss in total weight in friability test was in a range of  $0.29 \pm 0.065$  to  $0.64 \pm 0.060$  %. The percentage drug content for different tablet formulations varied from  $95.57 \pm 0.56$  to  $100.29 \pm 0.979$  % was found to be within the limit. The % age release of different formulations varied from  $84.06 \pm 0.42$  to  $99.85 \pm 0.61$  % for Salbutamol sulphate and  $82.32 \pm 0.47$  to  $98.11 \pm 0.31$  for Theophylline.

F-7 containing HPMC K100M and Xanthan gum (2:3 ratio) was selected as the optimum formulation based on the results of *in-vitro* dissolution studies. It is seen that at the end of 12 hr,  $97.16 \pm 0.59$  % of Salbutamol sulphate and 93.88 % of Theophylline 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 and thus improve the patient convenience by reducing dosing frequency. It was promised an ERT of Salbutamol sulphate and appears to be assessed further by conducting bioavailability studies in human volunteers and long-term stability testing

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