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DESIGN AND DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEMS FOR SALBUTAMOL SULPHATE

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Abstract: Pulsatile drug delivery systems for salbutamol sulphate were prepared with a view to release the salbutamol around 4am with a lag time of 6 hours after it's administration (10pm). In this investigation pulsatile drug delivery systems were formulated with two different approaches namely press coated systems and modified pulsin cap technique as they are simple and easy to prepare when compared with other techniques. Press coated systems were prepared with different ratios of swelling and rupturable polymers [HPMC: Eudragit]. The lag time was dependent on composition of these polymers and the desired lag time was observed form the formulation containing only Eudragit. Modified Pulsin cap is based on cross linked hard gelatin capsules with formaldehyde and filled with hydrogel plug. The hydrogel plug was prepared with different ratios of swellable polymer HPMC and diluent Dicalciumphosphate. The lag time was dependent on the polymer and diluent ratio. The desired lag time was observed form the formulation containing HPMC: DCP (3:1) ratio. The blends were examined for micromeritic properties and the finished dosage forms were subjected to various quality control tests. The lag time of the drug release decreased by increasing the inner swelling layer and increased by the rupturing layer levels. Pulsin cap technique was found to be more suitable to achieve prolonged lag time when compared with the compression coated tablets.

Keywords: Pulsatile drug delivery systems, salbutamol sulphate, asthma, press coated, pulsin cap.

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INTRODUCTION

Asthma is an inflammatory disease of the airways in which the mucous membrane and muscle layers of the bronchi become thickened and the mucous glands enlarge, reducing air flow in the lower respiratory tract. During an asthmatic attack spasmodic contraction of bronchial muscle constricts the airway and there is excessive secretion of thick sticky mucus which further reduces the airway. Inspiration is normal but only partial expiration is achieved, so the lungs become hyper- inflated and there is severe dyspnoea and wheezing. The duration of attacks usually varies from a few minutes to hours and very occasionally days. In severe acute attacks the bronchi may be obstructed by mucus plugs, leaks the bronchi may be obstructed by mucus plugs, leading to acute respiratory failure, hypoxia and possibly death. [1] The incidence of nocturnal asthma is more at early hours as per the earlier reports; hence to treat asthma effectively and to improve the patient compliance, pulsatile drug delivery systems are required.

The treatment of asthma generally includes oral liquids, inhalation therapy, conventional oral dosage forms, fast release dosage forms like tablets, capsules. But oral administration is the most widely accepted route of delivery due to its ease of administration, convenience, compatibility and patient compliance.

Salbutamol sulphate is a short acting β_2 receptor blocker has $t_{1/2}$ of 2.8 hr. [2, 3] used for the relief of bronchospasm in conditions such as asthma.

This study attempts to design and develop a pulsatile drug delivery system of salbutamol sulphate, for the treatment of nocturnal asthma as it is inconvenient to take the medication at midnight. The maintenance of constant drug level is not always desirable for the optimal therapy. A drug should be delivered only when and/or where it is needed at the minimum required dose. A reasonable and an acceptable rationale is a delivery system capable of releasing drugs in a pulsatile fashion rather than as a continuous delivery. So this study attempts to design and evaluate a pulsatile drug delivery system and aimed to have a lag time of six hours i.e., the system is taken at the bed time and expected to release the drug after a period of 6 hr i.e., at 4.00 am when the asthma attacks are more prevalent.

MATERIALS AND METHODS:

Salbutamol sulphate, Flow Lac 100, Tablet Tose-70, DCL-21, Spray Dried Lactose, Avicel,Di Basic Calcium Phosphate, Microlac 100, Cross Caramullose Sodium, HPMC(3000-5600 cps) and Eudragit L 100 were obtained as gift samples from M/S Natco pharma Ltd., Hyderabad and other chemicals like Magnesium Stearate, Talc, Ethanol, Gelatin capsules '1' size were purchased locally.

Preparation of core tablet:

The core tablets were prepared by direct compression technique. The composition of the tablets was showed in [Table I]. All the excipients were passed through sieve No. 60. The required ingredients were weighed accurately and mixed thoroughly for 5 min. The resulting blends were subjected to the following micromeritic properties. The blends having desired flow properties were compressed to form a tablet using 5mm compression tool with Cadmach single stroke tablet machine (Hoko-25 Type).

Micromeritic evaluation:

Bulk density:

5gms of blend was weighed and it was transferred to a measuring cylinder. It was subjected to three tappings. The bulk volume was noted. [4] The bulk density was calculated by the formulae

Bulk Density= *Bulk weight/Bulk Volume*

Carr's index (%):

5gms of blend was weighed and it was transferred to a measuring cylinder and then it was subjected to 100 tappings. The tapped density and poured density were noted. [4] Carr's index was calculated by the following formulae

Carr's Index (%) = *Tapped Density- Poured Density/Tapped Density X 100*

Hausner's ratio:

5gms of blend was weighed and it was transferred to a measuring cylinder and then it was subjected to 100 tappings. The tapped density and poured density were noted. [4]Hauser's ratio was calculated by the following formulae

Hausner's Ratio = *Tapped Density/ Poured Density*

Angle of repose:

5gms of blend was taken and it was poured into a hollow cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. Then height and diameter of the heap formed were noted down. [4]The angle of repose (θ) was calculated by the formulae

Angle of repose (θ) $=Tan^{-1}\frac{h}{r}$

Evaluation of tablets

Weight variation:

Twenty tablets were collected at random and were weighed collectively and individually. From the collective weight, average weight was calculated. [5] The percent weight variation was calculated using the formulae

% Weight Variation= *Average weight- Individual weight/ Average weight*

Hardness:

Hardness of the tablet was determined using the Monsanto hardness tester. The

lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. [6] The hardness was computed by deducting the initial pressure from the final pressure.

Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. 10 tablets were selected, dedusted and weighed. Then they were placed in a drum and rotated for 100 times. Then tablets were dedusted to remove loose dust and were reweighed. [5] The percentage friability was calculated by formulae

% Friability= Initial weight – Final weight/ Initial weight X 100

Content of active ingredient:

Ten tablets of salbutamol sulphate containing the equivalent of 40mg of salbutamol were collected randomly, powdered and shaken with 60ml of water for 1hr. The resulting solution was diluted to 100ml and then filtered. The filterate was suitably diluted and analysed for salbutamol at 276nm. [5]

Content uniformity:

Ten tablets, each containing equivalent to 4mg salbutamol were collected randomly and analysed for the content of salbutamol separately in each case according to the procedure described in content of active ingredient. [5] The same procedure is followed for another ninteen tablets

Disintegration:

Six tablets were collected randomly and introduced one tablet into each tube separately, added a disc to each tube. Suspended the assembly in the beaker containing water and operated the apparatus for 15min [5]

Dissolution studies on core tablet:

Dissolution studies were performed for different core tablets which were formulated using different diluents are by employing paddle method. The temperature was maintained at 37±0.5°c and paddle was set at 50 rpm. The dissolution medium used was 7.4 P^H phosphate buffer and about 5ml of sample was withdrawn at a sample interval of 5min up to 30min and sample was replenished with fresh dissolution medium. The collected samples were analysed at 276nm. The dissolution studies were carried out in triplicate. [7]

Preparation of compression coated tablets:

Pulsatile drug delivery systems for salbutamol sulphate were prepared with compression coating technique by employing the core tablet prepared with the diluents DCP and combination of P^H sensitive polymer Eudragit L 100 and hydrophilic polymer HPMC as matrix forming material. The composition of the

prepared compression coated tablets was showed in Table II

Accurately weighed (150mg) amount of the polymer mixture was placed in 12mm die. The selected core tablet F_6 was placed at the centre with the help of forceps. Then another portion of Eudragit L 100:HPMC mixture equivalent to 150mg was accurately transferred into the die cavity the resulting blend was subjected to compression by employing CMD 3-16 Station Rotary Tableting Machine.

Evaluation of compression coated tablets:

The prepared compression coated tablets were evaluated for the weight variation, hardness, friability, content of active ingredient and content of uniformity as per the procedures mentioned earlier.

Dissolution Studies:

The dissolution studies on the coated tablets were performed upto 7 hrs with different dissolution media *viz* 0.1N Hcl (0-2 hrs), 6.8 P^H Phosphate buffer (2-5 hrs) and 7.4 P^H Phosphate buffer (5-7 hrs).The dissolution studies were conducted at 370.5c using paddle type apparatus (50 rpm).5ml of aliquot were withdrawn at 30min time interval and replenished with fresh dissolution media. The samples were analysed at 276 nm for the estimation of Salbutamol sulphate.

Preparation of pulsatile drug delivery systems with pulsin caps technology:

Pulsatile drug delivery systems were also prepared by employing pulsin cap technique. The '1' size hard gelatin capsules were selected and then caps and bodies were separated. The capsule bodies were exposed to formaldehyde solution for a period of 24 hours to form a Schiff's base in between amine group of gelatin and aldehyde group of formaldehyde in a dessicator. The resulting capsule body was found to be insoluble in biological fluids. The caps were packed in muslin cloth and kept in a coating polymer solution for overnight to get the deposition (2%w/w) of P^H sensitive polymer on the caps. Caps were coated with the Eudragit L 100 (2%solution in acetone) by dip coating technique. The formaldehyde treated capsule bodies were filled with different formulations consisting of 4mg salbutamol sulphate, varied proportions of HPMC and DCP [Table III].Then the cap was firmly placed into the capsule body.

Evaluation of pulsin cap formulations

The formulated pulsin cap formulations were subjected to various quality control tests such as weight Variation, content of active ingredient, content uniformity and dissolution studies. These tests were carried by following the procedures as described earlier.

RESULTS AND DISCUSSION:

Pulsatile drug delivery systems for salbutamol sulphate were prepared with a view to release the salbutamol at 4am from the administered dosage form for effective treatment of noctural asthma. Pulsatile drug delivery systems were designed with compression coating technique and modified pulsin cap technology and the results are reported here.

Studies on core tablets of salbutamol sulphate:

Salbutamol sulphate core tablets were formulated with direct compression technique by employing different commercially available direct compressible diluents. The blends containing the salbutamol and the direct compressible diluents were subjected to micromeritic evaluation and the results are shown in table IV. These blends exhibited good flow property and hence compressed to form tablet. The prepared tablets were evaluated for various quality control tests and the results were depicted in [Table IV]. All the tablets complied weight variation, friability, content of active ingredient and content uniformity test. The tablets formulated with the diluents DCL failed to disintegrate within the specified 15 min disintegration time, however the remaining tablets passed the disintegration test. The formulations were further subjected to dissolution studies in 7.4P^H phosphate buffer. The dissolution profile was showed in Fig 1. The dissolution rate followed first order kinetics. The dissolution rate was found to be influenced by the diluents employed in the formulation of tablets. Based on the release rate of salbutamol sulphate, the diluents can be ranked as DCP>Microlac 100>Tablet Tose 70>Avicel>Spray dried lactose>Flow Lac 100> DCL-21. The formulations containing DCP showed relatively better dissolution rate, hence the core tablet containing DCP (F_6) was selected for further studies.

Studies on compression coated tablets:

Compression coated tablets of salbutamol sulphate were formulated with compression coating technique by employing different proportions of P^H sensitive polymer Eudragit L 100 and the hydrophilic swellable polymer HPMC as coating material and the tablet formulated with DCP(F_6) as core material. All the formulated tablets were subjected to various quality control tests and the obtained data was showed in [Table V]. All the formulations complied the pharmacopoeial requirements. The dissolution studies on these formulations were conducted in 0.1N HCl for 0-2hours, 6.8 P^H phosphate buffer (2-5), 7.4 P^H phosphate buffer (5-7 hours). The dissolution profile was showed in Fig 2.The formulation containing only Eudragit maintained a lag time of 5 hours and the drug was released after 5 hours. The lag time was found to be increased with the concentration of Eudragit L 100 and the release rate was found to be increased with

the reduction of HPMC content. Thus pulsatile drug delivery systems formulated with only Eudragit L 100 can be exploited for pulsatile drug delivery systems for a lag time of 5 hours.

Studies on pulsin cap technique:

The capsule bodies which were prepared by exposing to formaldehyde solution were filled with the granules formulated with the hydrogel polymer HPMC and the diluents DCP in different proportions. The capsules were evaluated for various quality control tests and the results were showed in table VI.The capsules satisfied weight variation, drug content and content uniformity requirements. The dissolution profile was shown in fig 3. All the capsules maintained a lag time of 5 hours and the lag time were further extended with the proportional increase in the content of hydrogel polymer. The capsule contains 3:1 ratio of HPMC: DCP showed the required lag time of 6 hours and then the drug was released completely. Thus these formulations were found to be more suitable to achieve the required lag time and then for the complete release of salbutamol.

CONCLUSION:

The lag time of salbutamol sulphate can be achieved upto 5 hours with compression coating technique by employing Eudragit L 100 as coating polymer and pulsin cap technique. But Pulsin cap technique was found to be more suitable to achieve prolonged lag time when compared with the compression coated tablets as lag time for pulsin cap was found to be influenced by the amount of hydrogel incorporated into the capsule, by changing the proportion of hydrogel polymer in the formulation, the required lag time can be achieved.

Table I

Composition of Salbutamol core tablets

S.no	Ingredient	Quantity(mg per tablet)						
		F1	F2	F3	F4	F5	F6	F7
1.	Salbutamol sulphate	4	4	4	4	4	4	4
2.	Flow lac 100	65	-	-	-	-	-	-
3.	Tablet tose-70	-	65	-	-	-	-	-
4.	DCL-21	-	-	65	-	-	-	-
5.	Spray dried lactose	-	-	-	65	-	-	-
6.	Avicel	-	-	-	-	65	-	-
7.	Di calcium phosphate	-	-	-	-	-	65	-
8.	Microlac 100	-	-	-	-	-	-	65
9.	Cross caramallose sodium	5	5	5	5	5	5	5
10.	Magnesium stearate	1	1	1	1	1	1	1
Total weight		75	75	75	75	75	75	75

Table II

Composition of compression coated tablets containing selected salbutamol core tablet (F6)

Ingredients	Quantity(mg per tablet)				
	CCT_1	CCT_2	CCT_3	CCT_4	CCT_5
UPPER LAYER					
HPMC	150	100	75	50	-
EUDRAGIT L 1OO	-	50	75	100	150
CENTRAL CORE(F_6)					
LOWER LAYER					
HPMC	150	100	75	50	-
EUDRAGIT L 1OO	-	50	75	100	150
TOTAL WEIGHT	375	375	375	375	375

Table III

Compositions of pulsin cap formulations containing Salbutamol

S.no	Ingredient	Quantity (mg per capsule)				
		PC_1	PC_2	PC_3	PC_4	PC_5
1.	Salbutamol sulphate	4	4	4	4	4
2.	DCP	65	48.75	32.5	16.25	-
3.	HPMC	-	16.25	32.5	48.75	65
	Total	69	69	69	69	69

Table IV

Micromeritic properties of the blends and physical characteristics of salbutamol core tablets

Properties	Formulation						
	F1	F2	F3	F4	F5	F6	F7
Bulk density (g/cm^3)	0.543	0.510	0.531	0.595	0.333	0.416	0.465
Angle of repose(^{o})	28.76	29.50	37.66	25.64	30.96	47.46	18.72
Carr's index(%)	19.5	16.2	25.63	14.26	24.48	15.75	18.56
Hausner's ratio	1.243	1.194	1.344	1.166	1.324	1.37	1.22
Average weight (gm)	74.5 ±1.7	74.7 ±1.8	75.2 ±1.9	75.1 ±2.1	74.9 ±2.0	74.7 ±1.7	74.8 ±2.2
Hardness(Kg/m)	4.2	4.3	4.0	4.1	4.7	4.4	4.8
Friability (%)	0.53	0.55	0.57	0.62	0.66	0.62	0.59
Drug content (%)	98.56	98.34	98.86	99.34	98.29	98.44	99.67
Content uniformity (%)	97.54 ±1.7	98.35 ±1.9	99.36 ±2.0	98.48 ±2.1	99.23 ±1.8	98.79 ±1.5	97.86 ±1.6
Disintegration time (min)	6	5	>15	6	5	3	4

Table V

Physical characteristics of compression coated tablets containing Salbutamol core tablet

Parameter	Formulation				
	CCT_1	CCT_2	CCT_3	CCT_4	CCT_5
Average weight (mg)	374.5±2.1	374.6±2.3	374.8±2.0	374.3±1.9	374.7±2.4
Hardness (kg/meter)	6.7	6.2	6.4	6.5	6.6
Friability	0.33	0.35	0.37	0.46	0.37
%Drug content	97.58	98.54	98.23	99.68	99.43
Content uniformity	96.64±1.6	97.45±1.8	99.46±1.9	98.58±1.9	99.33±2.0

Table VI

Quality control test report of pulsin cap containing salbutamol sulphate

Formulation	Average weight (mg)	% Drug content	Content of uniformity
PC_1	107.53±1.3	99.76	98.65±1.9
PC_2	108.21±1.9	98.76	99.67±2.1
PC_3	107.67±1.7	99.87	98.65±2.2
PC_4	108.19±2.0	99.65	97.65±1.8
PC_5	107.97±1.9	98.67	98.65±1.6

Figures

Fig 1 Dissolution profile of salbutamol sulphate core tablets formulated with different diluents

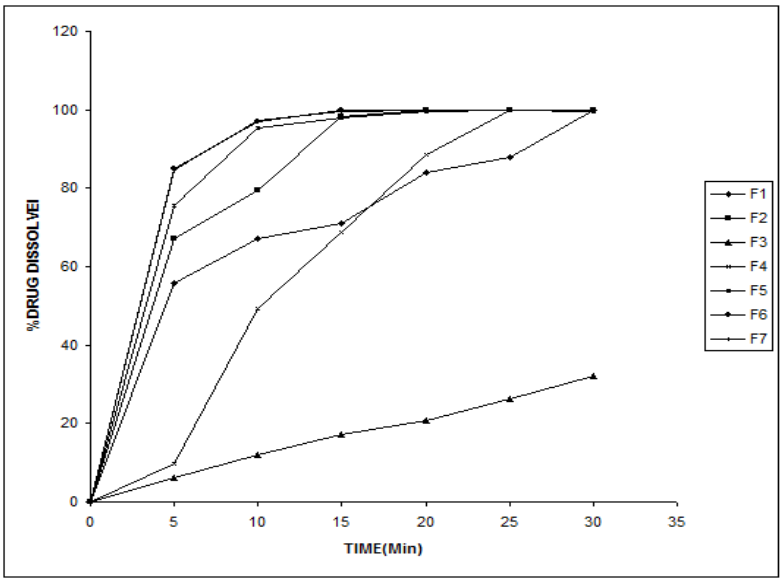


Fig 2 Dissolution profile of compression coated salbutamol sulphate tablets

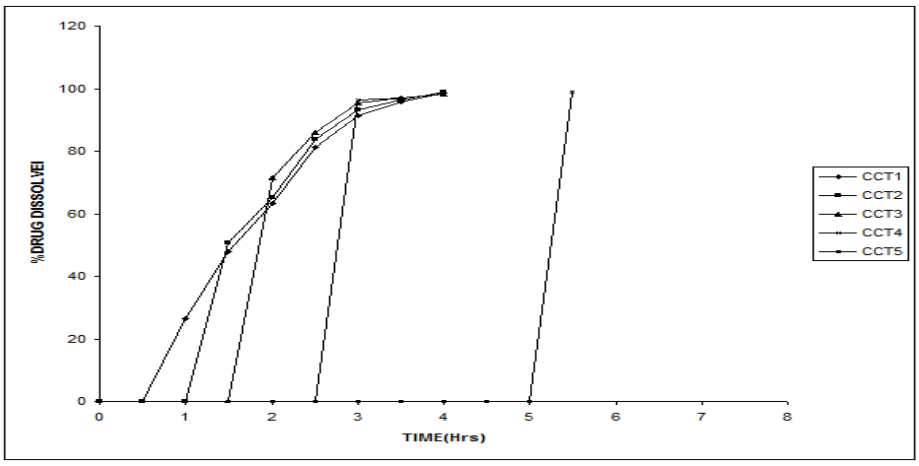
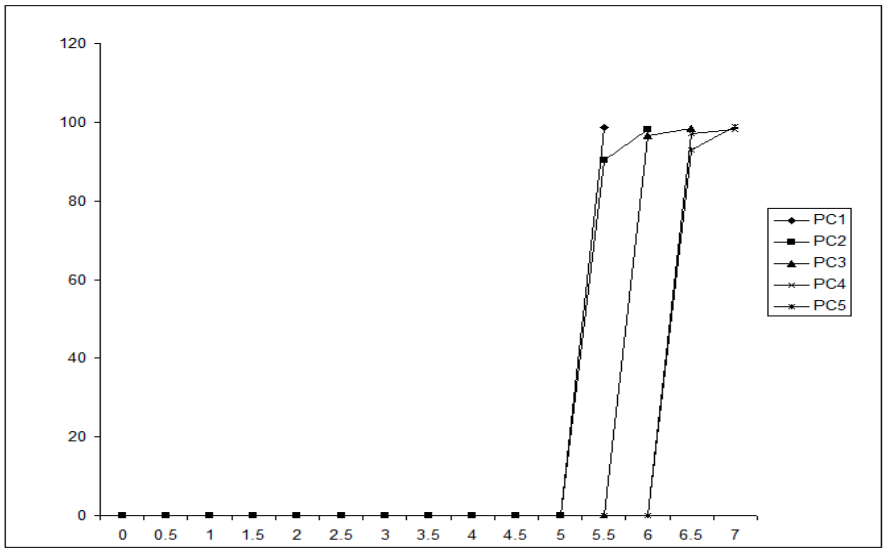


Fig 3 Dissolution profiles observed from pulsin cap containing salbutamol



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