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RESEARCH ARTICLE

Formulation and Evaluation of Chronomodulated Pulsatile Drug Delivery System of Salbutamol Sulphate

Anusha V[*1], Shanthi G[1], Khobragade DS[2]

[1]*Department of Pharmaceutics, Bharat Institute of Technology, Hyderabad, India.*

[2] *Department of Pharmaceutics, Vijaya College of Pharmacy, Hyderabad India.*

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ABSTRACT

Chronotherapy denotes the therapy in which the release of the drug in the body is allowed to match with the circadian rhythm of the disease, such that the required action of the drug is shown with minimal side effects. The main interesting fact of chronotherapy is its ability to deliver the drug in required concentrations during the time of its greatest need such that synchronizing circadian rhythm of diseases or symptoms. Pulsatile drug delivery system for Salbutamol sulphate was formulated initially as core tablets followed by formulation of pulsatile tablets using press-coated technology. Core tablets were formulated using various concentrations of superdisintegrant (Sodium starch glycolate, cross povidone) and diluents (MCC & Dicalcium phosphate). The core tablets were then compressed into pulsatile tablets using combinations of HPMC K 100M and Eudragit L 100, Eudragit S 100 in various concentrations. Core tablets were evaluated and based on the dissolution studies trial T3was optimized as it shows lower disintegration time and faster drug release. Then the pulsatile tablets were evaluated for various tests and drug release studies were conducted for 2 hours in 0.1N HCl followed by pH 6.8 buffer and the trial S6 was optimized which showed satisfactory greater lag time of about 6 hours with satisfactory drug release which contains a combination of HPMC K15M (20mg), Eudragit L 100 (50mg), Eudragit S100 (60mg). Pulsatile tablets were formulated utilizing press coated technology and the combination of polymers provided required lag time with satisfactory dissolution profile.

KEYWORDS

Pulsatile, Lag Time, Salbutamol Sulphate, Drug Release

INTRODUCTION

Chronotherapeutics discusses about the treatment method where the *in vivo* drug release is programmed to match the rhythms of disease such that to obtain the required therapeutic outcomes and abate side effects.[1-4] Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours and are synchronized according to internal biologic clocks related to the sleep-wake cycle. The best-known circadian rhythms include body temperature, hormone secretion, metabolism, sleep or wake cycle. Hence the drug release should match the circadian rhythm of the disease hence variation in disease state and drug plasma concentration should be considered in the development of drug delivery systems intended for the treatment of diseases with adequate dose at the appropriate time.

Chronotherapeutic delivery system is required to be formulated to suit drug release conditions in various diseases like cardiovascular diseases,

***Address for Correspondence:**
Anusha V,
Department of Pharmaceutics, Bharat Institute of Technology, Hyderabad, India.
E-Mail Id: anushav14@yahoo.com

Diabetes mellitus, Asthma, Arthritis, Peptic ulcer etc. In such cases pulsatile drug delivery system is used in which the dosage form releases the drug in a programmed pattern i.e. at appropriate time & at appropriate site of action.[5] Pulsatile Drug Delivery systems are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc.

Asthma is disease of lung airways (bronchi) characterized by hyper active responsiveness to a variety of stimuli and in this condition the airways constricts and becomes inflamed with excess mucus lining the passage.[6-8] The stimuli which may trigger the asthmatic condition includes exposure to allergens, cold air, moist air, emotional stress etc. Nocturnal asthma is condition where an exacerbation of the asthma is observed during the night times, such that worsening the functioning of the lung with increased airway response.[9-11] Usually, asthma attacks are more predominant in early mornings so it is annoying for a patient to take medicine at late night, hence in this condition there is a demand for pulsatile drug delivery system which release the drug at required time at proper site with efficient therapeutic action. Pulsatile drug delivery system offers various advantages like it provides extended activity, reduced side effects and dosage frequency, reduction in dose size, improved patient compliance, along with the main advantage of releasing the drug in required time in required quantity with satisfactory lag time.

MATERIAL AND METHODS

Materials

Salbutamol Sulphate was gifted by Natco chemicals Hyderabad. Microcrystalline cellulose, Dicalcium phosphate, Sodium starch glycolate, crosscarmellose sodium, Magnesium stearate, talc gifted by S D FINE chemicals. HPMC K15M, Eudragit L100, Eudragit S 100 were obtained from colorcon India Ltd and Evonik industries Mumbai respectively. All other chemicals and reagents used were of A.R. grade.

Method

Formulation of Core Tablets of Salbutamol Sulphate

The core tablets containing Salbutamol Sulphate were formulated using the composition shown in (Table 1).Accurately weighed quantity of drug (4 mg) and other ingredients like croscarmellose Sodium, sodium starch glycolate, dicalcium phosphate, micro crystalline cellulose, talc and magnesium stearate were taken according to their trials and passed through sieve and the mixture was dry blended for 10 minutes and directly compressed in to 90 mg tablet using 6 mm punch on a rotary tablet machine.

Table 1: Composition of Core Tablets

Ingredients (mg)	T1	T2	T3	T4	T5	T6
Salbutamol sulphate	4	4	4	4	4	
Sodium starch glycolate	2	3	4	-	-	-
Cross carmellose sodium	-	-	-	2	3	4
Microcrystalline cellulose	80	80	80	-	-	-
Di calcium phosphate	-	-	-	80	80	80
Magnesium stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Total weight	90	90	90	90	90	90

Evaluation of Core Tablets

The tablets were evaluated for pre-compression and post-compression parameters.

Pre Compression Studies

The blend of tablets was evaluated for pre-compression properties before compression of the tablet.

Angle of Repose

Angle of repose was determined by funnel method, where a funnel is fixed to a stand and it is adjusted up to the required height and blend was filled into the funnel by closing the tip of the funnel with finger.[12,13] After filling the funnel completely the finger is released and blend was allowed to pass until they form a pile, then the angle of repose can be calculated.

Bulk Density

The bulk density was measured by taking 50 g of blend was taken into 100 ml calibrated measuring cylinder and then bulk density was calculated by calculating the volume occupied then dividing weight by volume.[14,15]

Tapped Density

The tapped density was measured by dividing weight by volume but the final volume was measured after tapping the cylinder for fixed number of tappings as per the pharmacopeia guidelines until a constant volume was obtained using tap density apparatus (Electrolab®, India).[16-18]

Compressibility Index

Compressibility index was determined after determining bulk and tapped density by using the following formula

Carr's index (%) = [(TD-BD)] / TD x 100

Hausner's Ratio

Hausner's ratio was determined by using the following formula

Hausner's ratio = TD / LD

Post-Compression Evaluation of Core Tablets

The formulated core tablets were evaluated for all required test for tablets such as hardness, friability, weight variation test, thickness, disintegration time and in-vitro dissolution study.

Weight Variation

Weight variation for tablets was calculated by taking twenty tablets at random and they were weighed individually and the average weight was calculated then it is compared with the individual weights of the tablet. Weight variation was calculated using the formula.

$$\text{Weight variation} = \frac{(\text{Weight of Tablet-average weight})}{\text{Average weight of Tablets}} \times 100$$

Tablet Thickness

Tablet thickness was determined using a screw gauge micrometer and the limit and the variation should be ±5% of the standard value.

Tablet Hardness

The hardness of the formulated tablets was determined using Monsanto hardness tester. The strength and resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness of the tablet formulated (Lachman, 1991).[19,20]

Tablet Friability

Friability was measured using Roche friabilator. Friability evaluates the ability of the tablet to with stand abrasion during packaging, handling and shipping. Required quantities of tablets were taken based on their weights and the procedure was followed according to USP. The tablets initial weight is noted then the tablets were placed in the friabilator and allowed to rotate for 4min with 25rpmand the loss in weight before rotation and after rotation indicates the friability losses and the acceptable range is between 0.5-1.0 percent.[21-23]

%Friability = (W1-W2)/W1 X 100

Where, W1= weight of tablets before test

W2 = weight of tablets after test

Tablet Disintegration Time

Disintegration time was determined using disintegration test apparatus. One tablet each was placed in all the 6 tubes of the basket and a disc was added to each tube and the apparatus was run using pH 6.8 phosphate buffer maintained at 37°±2°C. The time taken in seconds for complete

disintegration of the tablet with no mass remaining in the apparatus was considered as the disintegration time.[24-26]

Formulation of Pulsatile Tablets by Press Coated Technology

The core tablets were evaluated and based on the evaluation results of core tablets, the formulation T3 was optimized as it shows lower disintegration time with good dissolution profile and satisfactory integrity among all formulations of core tablet hence it is further selected for formulating pulsatile tablets.

The core tablets were compressed using polymer blend which has composition of HPMC K15 M and Eudragit L100 and Eudragit S100 in different concentrations.[27,28]

Half of the coating polymer material was placed in the die cavity, then the core tablet was carefully sited in the centre of the die and cavity was filled on the top with the other half of the coating polymer material.[29,30]

Then the tablet was compressed using Rimek tablet machine, with 9mm punch. The compositions are shown in Table 2.

Evaluation of Compression Coated Tablets

The compression coated tablets were evaluated for various evaluation test as follows.

Weight Variation Test

Weight variation for tablets was calculated by taking twenty tablets at random and they were weighed individually and the average weight was calculated then it is compared with the individual weights of the tablet. Weight variation was calculated using the formula.

$$\text{Weight variation} = \frac{(\text{Weight of Tablet-average weight})}{\text{Average weight of Tablets}} \times 100$$

The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

Thickness

Tablet thickness was determined using a screw gauge and the limit and the variation should be ±5% of the standard value**.**

Hardness Test

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Lag Time Determination by Rupture Test

The time taken for the outer coating to rupture is defined as the lag time of the pulsatile tablet. It was determined by using the USP II paddle dissolution apparatus.

Table 2: Composition of pulsatile tablets

S. No	Polymer in upper layer (mg)	S1	S2	S3	S4	S5	S6	S7
1.	HPMC K15M	130	100	80	60	40	20	10
2.	Eudragit L 100	-	30	50	50	50	50	50
3.	Eudragit S100	-	-	-	20	40	60	70
	Polymer in lower layer(mg)							
4	HPMC K15M	130	100	80	60	40	20	10
5	Eudragit L 100	-	30	50	50	50	50	50
6	Eudragit S100	-	-	-	20	40	60	70
Total tablet weight= 350mg								

initially 900 ml of 0.1 N HCl was taken as media and was carried for 2 hours at 37.0 ± 0.5°C, 50 rpm followed by phosphate buffer pH 6.8. The time at which the outer coating layer starts to rupture was noted and considered as the lag time.[31-33]

In Vitro Drug Release

In vitro drug release was determined using USP II apparatus (Paddle type). The dissolution test was done using 900 ml of 0.1N HCl for 2 hours followed by phosphate buffer (pH 6.8) at 37 ± 0.5 ^{0}C.

The speed of rotation of paddle was set at 75 rpm. At a preset time interval samples of about 5ml were withdrawn, and absorbance of solution was determined by using UV spectrophotometer at 276 nm and drug release was calculated.

RESULTS AND DISCUSSION

Evaluation of Tablets

Pre Compression Studies of Core Tablet

The powder blend was evaluated and angle of repose was between 28.3^o to 31.2^o, bulk density was between 0.497 to 0.52 gm/ml, tap density was between 0.632 to 0.641 gm/ml, Carr's index and Hausner's ratio were satisfactory as shown in (Table 3) indicating good powder flow properties.

Post Compression Studies of Core Tablet

Core tablets were evaluated for various tests like the weight variation and the tablet weight was found between 88.7-90.81mg, the hardness was found to be 4.8kg/cm^2, thickness was found up to 3.17mm, the friability was found up to 0.198 to 0.328% and the disintegration time was between 20 to 82 sec and content uniformity between 96.9 to 99.4% and all the results were tabulated as shown in Table 4.

Evaluation of Compression Coated Tablets

Compression coated tablets were evaluated for various tests like the weight variation and the tablet weight was found between 348-350 mg, the hardness was found around to be 5.5kg/cm^2, thickness was found up to 4.98mm, and dissolution studies were conducted and lag time was found up to 96 to 372 min all the results were tabulated as shown in Table 5. The dissolution studies were performed and dissolution profile of compression coated tablet was shown in Figure 1. Asthma requires a medication in such a fashion that the drug is released in a pulsatile manner such that it provides an initial lag time and release the required quantity of drug in correct time at the proper site, with satisfactory therapeutic efficiency.[34-37]

Table 3: Evaluation of Pre-Compression Properties of Core Tablet

Formulation trial	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (%)	Hausnner's ratio
T1	29.72±0.24	0.498±0.02	0.638±0.04	21.9±0.3	1.28±0.24
T2	29.20±0.28	0.502±0.04	0.641±0.02	21.6±0.28	1.27±0.24
T3	28.32±0.2	0.497±0.06	0.637±0.02	22±0.32	1.28±0.32
T4	30.8±0.32	0.498±0.04	0.640±0.04	22.1±0.34	1.28±0.4
T5	31.2±0.32	0.52±0.04	0.640±0.06	18.75±0.34	1.23±0.32
T6	30.8±0.22	0.50±0.04	0.632±0.05	20.88±0.31	1.26±0.29

Table 4: Evaluation of Core Tablets

Trails	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)	Disintegration time (sec)
T1	90.81±1.74	3.17±0.013	4.8±0.112	0.328 ± 0.001	98.11±0.47	64.11 ± 0.029
T2	89.19±1.45	3.17±0.016	4.7±0.022	0.289 ± 0.003	96.99 ±0.27	39.22 ± 0.017
T3	90.17±1.11	3.15±0.018	4.7±0.047	0.198 ± 0.001	99.44±0.39	20.23 ± 0.028
T4	88.71±1.50	3.17±0.018	4.7±0.043	0.297 ± 0.001	97.17 ±0.62	82.44 ± 0.035
T5	89.28±1.29	3.14±0.033	4.8±0.027	0.310 ± 0.003	97.68 ±0.22	59.34 ± 0.042
T6	90.22±1.69	3.14±0.029	4.7±0.022	0.299 ± 0.003	97.99±0.32	42.39 ± 0.019

Table 5: Evaluation of Press-Coated Pulsatile tablets of Salbutamol Sulphate

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Lag Time(min)
S1	348.29±1.8	4.98±0.03	5.4±0.041	96
S2	348.36±1.0	4.95±0.03	5.4±0.042	155
S3	350.08±1.0	4.93±0.02	5.3±0.052	215
S4	348.09±1.5	4.94±0.04	5.4±0.041	255
S5	350.04±1.4	4.94±0.04	5.3±0.039	278
S6	349.92±1.0	4.98±0.06	5.4±0.041	372
S7	348.44±1.0	4.98±0.06	5.5±0.041	312

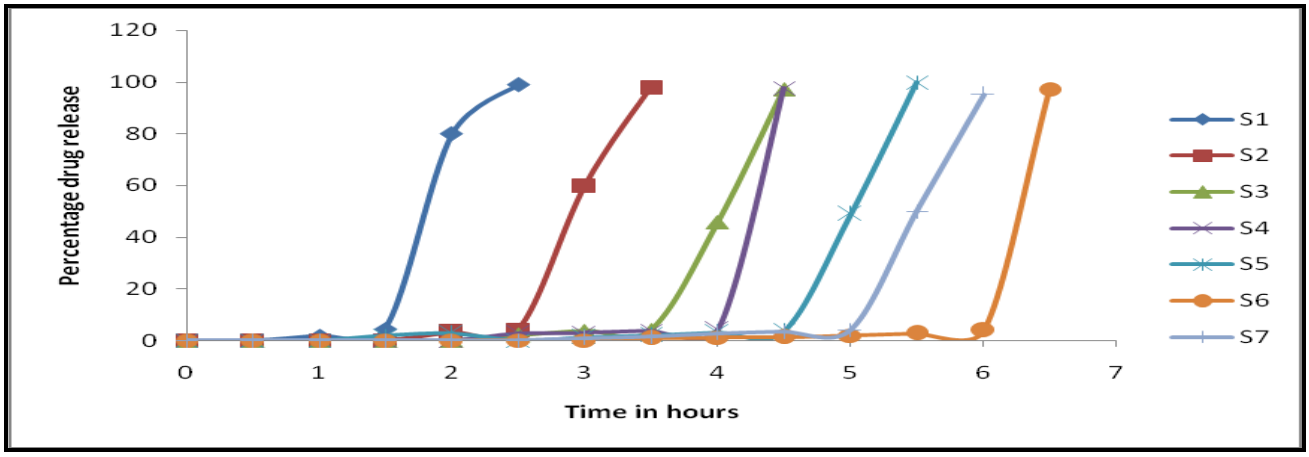

Figure 1: Dissolution Profiles of Compression Coated Pulsatile Tablets

In this study pulsatile tablets were prepared, which consist of two parts, the core tablet and its outer polymeric part. Core tablets of salbutamol were formulated by conducting different trials using sodium starch glycolate and croscarmellose sodium as super disintegrant in various concentration like 2mg,3mg,4mg along with diluents like microcrystalline cellulose, dibasic calcium phosphate and talc , magnesium stearate were used as glidant. The trial T3 was optimized which contains sodium starch glycolate 4mg as superdisintegrant, because as it shows lower disintegration time and good dissolution profile.

Core tablets were press coated using various polymers like HPMC K15M, Eudragit L 100and Eudragit S 100. In the initial trial S1 only HPMC K 15M was used as the polymer, in both the layers but the lag time was not satisfactory as it released the drug in the initial time points itself the probable reason may be due to hydrophilic nature of HPMC it may not provide the required lag time, hence further in trial S2 HPMC K 15M concentration was decreased and Eudragit L 100 was added to the formulation in little concentration used as the polymer, in both the layers but the lag time was not satisfactory as it released the drug in the initial time points itself, but the release was better compared to the first trial because of the nature of the eudragit L100, but it didn't provide sufficient lag time so that the study was continued further by varying the concentrations of Eudragit L 100 and HPMC.[38,39]

In further trials to obtain the required lag time HPMC K15M concentration was lowered and Eudragit L100 and Eudragit S 100 was used in combination which provided required lag time, hence the trial S6 was optimized which contains HPMC K15M (20mg), Eudragit L100 (50mg), Eudragit S 100 (60mg) per each layer of the coating material that is in upper and lower layer. Due to presence of combination of polymers it provided the lag time of about 5hours which may be due to the pH dependent nature of the polymers which predominantly ruptures at higher pH.[40-42] A drug delivery system with a lag time of around 5hours and pulsatile properties was successfully developed.

CONCLUSION

The aim of the study was to develop a pulsatile drug delivery system of Salbutamol sulphate for the management of Asthma. The Chronotherapeutic drug delivery system of salbutamol sulphate was prepared which provided desired lag time thus it can be taken at bedtime such that the drug will be released in the morning hours i.e. at the time of symptoms and useful for chronopharmaceutics of Asthma. The results indicated that amount of polymer in the formulation affects the drug release rate. The drug release was high-pitched and full after the lag time, which is mandatory for a pulsatile drug delivery system. Thus, the formulated pulsatile tablets will deliver the drug permitting to the need of the patient so as to give the highest therapeutic benefit of treatment.

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