FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY OF SALBUTAMOL SULPHATE

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ABSTRACT

Advancement in drug delivery could come from innovate improvement to existing drug delivery system. Because of reduce frequency of administration sustain release dosage from enjoy convenience and ambulatory patient compliance. Developed formula is a multiple unit based pulsatile delivery of Salbutamol Sulphate which can offer a solution for exhibiting chronopharmacological behavior of asthma, extensive first-pass metabolism and necessity of night-time dosing. So we can conclude that it can underlie the chronokinetic of nocturnal asthma. Among five Batches Specific amount 4% CAP and 2% EC batch gives late release than predetermined time. They release their higher dose after 6 hours. So that batch SF2 is accurate batch for Nocturnal Asthma according to pulsatile drug delivery system.

Keywords: pulsatile drug delivery system, Salbutamol Sulphate, Nocturnal Asthma, chronopharmacology.

1. INTRODUCTION

Asthma is a chronic condition involving the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus, often in response to one or more triggers. These episodes may be triggered by such things as exposure to an environmental stimulant (or allergen) such as cold air, warm air, moist air, exercise or exertion, or emotional stress.[1] Some asthmatics that have severe shortness of breath and tightening of the lungs never wheeze or have strider and their symptoms may be confused with a COPD-type disease.[2]

Signs of an asthmatic episode include wheezing (tachypnea), prolonged expiration, a rapid heart rate (tachycardia), rhonchous lung sounds (audible through a stethoscope), the presence of a paradoxical pulse (a pulse that is weaker during inhalation and stronger during exhalation), and over-inflation of the chest. During a serious asthma attack, the accessory muscles of respiration may be used, shown as in-drawing of tissues between the ribs and above the sternum and clavicles, and the presence of a paradoxical pulse.[3]

In many cases, a physician can diagnose asthma on the basis of typical findings in a patient's clinical history and examination. Asthma is strongly suspected if a patient suffers from eczema or other allergic conditions—suggesting a general atopic constitution—or has a family history of asthma. While measurement of airway function is possible for adults, most new cases are diagnosed in children who are unable to perform such tests.[4] Diagnosis in children is based on a careful compilation and analysis of the patient's medical history and subsequent improvement with an inhaled bronchodilator medication. In adults, diagnosis can be made with a peak flow meter (which tests airway restriction), looking at both the diurnal variation and any reversibility following inhaled bronchodilator medication. In the Emergency Department doctors may use a capnography which measures the amount of exhaled carbon dioxide, along with pulse oximetry which shows the amount of oxygen dissolved in the blood, to determine the severity of an asthma attack as well as the response to treatment.[5]

Symptomatic control of episodes of wheezing and shortness of breath is generally achieved with fast-acting bronchodilators. These are typically provided in pocket-sized, metered-dose inhalers (MDIs). In young sufferers, who may have difficulty with the coordination necessary to use inhalers, or those with a poor ability to hold their breath for 10 seconds after inhaler use, an asthma spacer is used.[6] A nebulizer which provides a larger, continuous dose can also be used. Nebulizers work by vaporizing a dose of medication in a saline solution into a steady stream of foggy vapour, which the patient inhales continuously until the full dosage is administered. There is no clear evidence, however, that they are more effective than inhalers used with a spacer.[7]

Pulsatile drug delivery system have a number of advantages like to maintain constant plasma drug level, Time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis. Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.[8]

The present study was aimed for chronopharmaceutics. The symptoms of chronic asthma are frequently worse around 4 am when, cortisol level is lowest whereas

histamine concentration is at peaked in body. Therefore the objective of the present work was to formulate a pulsatile drug delivery of Salbutamol Sulphate which is capable of releasing drug after predetermine time delay and can characterized by proportioning drug concentration throughout night in synchrony with biological rhythm.[9]

2. MATERIALS AND METHODS

2.1 Determination of solubility of the drug

The study was carried out in glass vials of 20 ml capacity. Each vial charged with 10 ml of distilled water and different dissolution media and excess quantity of salbutamol sulphate. The vials were closed with rubber closures and kept for equilibrium at 25°C ±2°C for a period of 24 hrs with continuous shaking; the solutions were then filtered and analyzed for the drug content by spectrophotometrically at respective wavelength. The studies were repeated in triplicate (n=3) and mean was calculated.[10]

2.2 Determination of λ_{max} in mixture of Distilled Water:Isopropyl Alcohol

Stock solution of salbutamol sulphate containing 2mcg,4mcg,6mcg,8mcg and 10 mcg/ml in mixture of Distilled Water:Isopropyl Alcohol(50:50)was prepared and the standard solution of salbutamol sulphate containing 2mcg, 4mcg, 6mcg, 8mcg and 10 mcg/ml in mixture of Distilled Water:Isopropyl Alcohol(50:50) was prepare. The above solutions were scanned between 200 nm to 400 nm in a double beam UV/ Visible spectrophotometer to get UV spectra. UV spectra showed λ_{max} at different wavelength. Averege λ_{max} is considered as λ_{max} of salbutamol.

2.3 Preparation of Calibration Curve:

Stock solution of salbutamol sulphate containing 2mcg,4mcg,6mcg,8mcg and 10 mcg/ml in mixture of Distilled Water:Isopropyl Alcohol(50:50)was prepared and the standard solution of salbutamol sulphate containing 2mcg,4mcg,6mcg,8mcg and 10 mcg/ml in mixture of Distilled Water:Isopropyl Alcohol(50:50) was prepared and analyzed spectrophotometrically at 276 nm.[11]

2.4 Identification of drug by Thin Layer Chromatography Method

Salbutamol Sulphate, was analysed by TLC as per Indian Pharmacopoeia. Silica gel 60 chromatographic plate was used for this method. The mobile phase used for the system was Phenol: H_2O with the ratio of 4:1.The sample solution was Preparation by dissolving 100mg of salbutamol sulphate in 10 ml of methanol, and the solution was spotted on the plate and subjected to ascending chromatography. The drug was detected by visualizing agent potassium permanganate ($KMnO_4$), Dragendroff's reagent.[12]

2.5 Loss on drying

Percentage loss on drying was determined by using crucible 1 gm of salbutamol sulphate was placed in weighed crucible and heated at 105°C for 3 hours. After 3 hrs crucibles were weighed again to determined loss on drying.[13]

2.6 Formulation Development:

A pulsatile drug delivery of salbutamol sulphate was prepared by coating Nonpareil seeds (NPS) approximately 14/16#.It was prepared in three stages.

2.6.1. Drug loading:

Drug loading was carried out by solution layering techniques, using conventional coating pan. The weighted non-pareil seeds (NPS) of approximately 14/16# were charged into pan and Salbutamol Sulphate solution (1%w/v) in Water: IPA (1:1) containing PVP-K-30(2%), as a binder, was sprayed over the cascading NPS till mass put on 1%. Hot air (60-70ºC) was blown to evaporate the solvent.[14]

2.6.2. Coating of Drug loaded pellets:

Dried pellets were sprayed with solution of Cellulose acetate phthalate (2%w/v,4%w/v,6%w/v,8%w/v,10%w/v) and Ethyl Cellulose (2% constant) in Acetone till 4-6% weight gain. These layers restrict release of drug from pellets up to 4 hours until it reaches to intestine.

Coating of cellulose acetate phthalate is done by 2%w/v, 4%w/v, 6%w/v, 8%w/v and 10%w/v in acetone and Ethyl Cellulose took at 2% constant in each batch. Different five batches were made.[15]

Table 1: Formula of Coating solution*

Material	Qty(g/l)	Scale % w/v item
Cellulose Acetate Pthalate	60.0	6.0
Propylene Glycol	18.65	1.86
Span 80	6.0	0.66
Oil castor	1.25	0.125
Tio2	53.3	5.33
Methylene chloride	215.0	21.58
Acetone	1 liter	Q.S

* 2% Ethyl Cellulose was added in each batches.

2.6.3. Final drug loading:

At last initial dose was encrusted, fourth layer, as similar as first layer, for immediate action. For that Salbutamol Sulphate solution (1%w/v) in Water: IPA (1:1) containing PVP-K-30(2%), as a binder, was sprayed over the cascading NPS till mass put on 1%. Hot air (60-70ºC) was blown to evaporate the solvent.

The solutions were applied at pressure 20 psi. The speed of revolution of coating pan was 58-60 rpm. Hot air was

supplied by hair dryer which, was placed at a distance of 15 cm away from pan.[16]

2.7 Evaluation:

2.7.1. Drug Content:

An UV spectrophotometer method based on measurement of absorbance at 276 nm in 100 ml of phosphate buffer pH 6.8 was used for the estimation of Salbutamol Sulphate in pellets. Initially coated pellets (900mg) dissolved in phosphate buffer by keeping the flask on shaker for 2 hours whereas time duration for final coated pellets (1gm) was 5-6 hours. Both are evaluated separately against blank.[17]

Table 2: Drug content in each formulation

Total Drug Content (mg)	
%CAP and 2%EC	Drug (mg)
2	6.603
4	6.431
6	6.672
8	6.534
10	6.568

2.7.2. *In-vitro* releases characteristics study:

Release characteristics study was carried out as in USP I basket type apparatus (type I) dissolution apparatus. The volume of dissolution media was 900 ml in 1000 ml beaker. The cylinder was adjusted to 100 rpm and temperature 37± 0.1ºC was maintained throughout the experiment. 0.1 N HCl (pH 1.2) was used as dissolution media for first two hours in which the initial dose, fourth layer, releases. At the end of second hour dissolution fluid replaced by phosphate buffer of pH 6.8 (KH_2PO_4/NaOH) and the apparatus was further operated for four hours. 10 ml aliquots were withdrawn after every 30 minutes interval and replaced with equal amount of fresh dissolution. Samples were filtered and estimated by UV spectrophotometer at 276 nm.[18]

2.7.3. Flow properties:

The flow properties from a material result from many forces. There are many types of forces that can act between solid particles: frictional forces, surface tension forces, mechanical forces caused by interlocking of particles of irregular shapes, electrostatic forces and cohesive or vander vaals forces. These forces can affect granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy and surface area. The two methods for determining the flow properties are angle of repose and hopper flow rate measurements.[19]

2.7.4. Angle of repose:

Angle of repose is the tan inverse of angle between height of pile of powder and the radius of the base of conical pile.

$$\text{Tan } \theta = h/r$$

Values for angle of repose less than or equal to 30 degrees suggest a free flowing material and angles greater than or equal to 40 degrees suggest a poorly flowing material.[20]

2.7.5 Loss on drying:

Percentage loss on drying was determined by using crucible.1 gm of salbutamol sulphate was placed in weighed crucible and heated at 105°C for 3 hours. After 3 hrs crucibles were weighed again to determined loss on drying.[21]

3. RESULTS AND DISCUSSION

Initial drug release was observed in first 2 hours which can offer immediate relief, on the other hand if symptoms of asthma are worse at morning than delayed release, after 4 hours, will cure it. Developed formula is a multiple unit based pulsatile delivery of Salbutamol Sulphate which can offer a solution for exhibiting chronopharmacological behavior of asthma, extensive first-pass metabolism and necessity of night-time dosing.[22]

To find out the drug release, the calibration curve was plotted in 0.1N HCl and phosphate Buffer solution (pH 6.8). Figure 1 showed the calibration curve of salbutamol sulphatein 0.1N HCl solution. The Calibration curve were linear and regration co-efficient was found to be 0.9998 in case of 0.1 N HCl, while 0.9975 in case of phosphate buffer solution (pH 6.8) as shown in Figure 2.

To study the better release of the drug, five batches were prepared on the basis of the Cellulose Acetate Pthalate (CAP) and ethyl cellulose (EC). Batch SF1 contain 2% CAP and 2%EC, SF2 contain 4% CAP and 2%EC, SF3 contain 6% CAP and 2%EC and Final batch SF5 contain 10% CAP and 2%EC. Table 3 showed amount of drug released through different formulation.

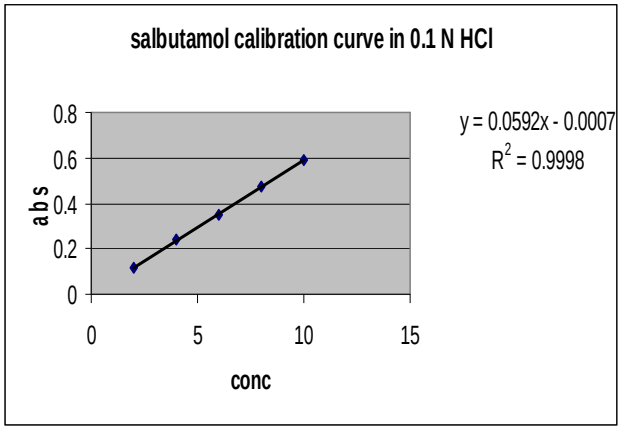

Figure 1: Calibration curve in 0.1 N HCl

Figure 2: Calibration curve in Phosphate buffer pH 6.8

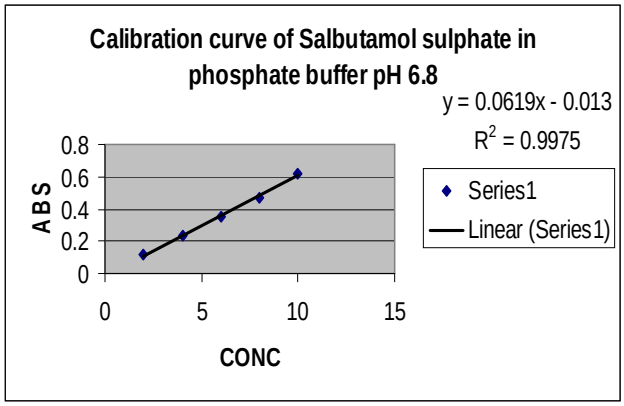

Table 3: Total amount of drug release in vitro study

Time (hrs)	Total drug release in vitro				
	SF1	SF2	SF3	SF4	SF5
0	0	0	0	0	0
0.25	0.324	0.29	0.24	0.27	0.28
0.5	1.3	1.27	1.04	0.95	0.97
1	2.98	2.93	2.67	2.73	2.85
1.5	3.25	3.14	3.03	2.96	2.96
2	3.31	3.53	3.38	3.48	3.18
2.5	3.31	3.53	3.38	3.48	3.18
3	3.31	3.53	3.38	3.48	3.18
3.5	3.31	3.53	3.38	3.48	3.18
4	3.47	3.61	3.57	3.48	3.18
4.5	4.24	4.06	4.00	3.59	3.18
5	4.89	4.9	4.43	3.87	3.225
5.5	5.81	5.29	4.97	4.39	3.89
6	6.36	6.32	5.87	5.09	4.57

Table: 4. Cumulative percentage release drug (%)

Time (hrs)	Cumulative percentage release drug (%)				
	SF1	SF2	SF3	SF4	SF5
0	0	0	0	0	0
0.25	4.9	4.5	3.59	4.13	4.26
0.5	19.6	19.75	15.59	14.54	14.78
1	45.15	45.56	40.02	41.8	43.44
1.5	49.24	48.83	45.42	45.32	45.12
2	50.15	54.89	50.67	53.29	48.47
2.5	50.15	54.89	50.67	53.29	48.47
3	50.15	54.89	50.67	53.29	48.47
3.5	50.15	54.89	50.67	53.29	48.47
4	52.57	56.14	53.52	53.29	48.47
4.5	64.24	63.14	59.97	54.97	48.47
5	74.09	76.2	66.41	59.26	49.08
5.5	88.03	82.27	74.51	67.22	59.29
6	96.36	98.28	88.00	77.94	69.66

Table 4 showed the cumulative amount of drug released through different batches. If we observe in the table 4, Batch SF1 showed 96.36 % cumulative release within 6 hours, when batch SF2 showed 98.28 % cumulative release. Batch SF3 showed 88 %, batch SF4 showed 77.94 % and batch SF5 showed 69.66% release up to 6 hours.

It seems that batch SF2 contain 4% CAP which gives better release according to chronopharmacological dose up to 6 hours. Batch SF2 which contain 2 % CAP which also gives near to predetermined dose, while Batch SF3, SF4, SF5 showed less release as compare to Batch SF1 and SF2.

4. CONCLUSION

From the above results, it can be concluded that the batch SF2 containing 4%CAP and 2%EC showed the maximum release of the drug and was the accurate batch for Nocturnal Asthma according to pulsatile drug delivery system.

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