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Review Article

PROGRAMMED CHRONOKINETICS OF SALBUTAMOL SULPHATE FOR NOCTURNAL ASTHMA.

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ABSTRACT

Asthma symptoms are worsening at night. In fact, it has been estimated that incidence of asthma occurred 100 times more often at night than during the day. Many circadian-dependent factors appear to contribute to the worsening nocturnal asthmatic symptoms. For example, cortisol levels are lowest in the middle of the night and histamine concentration peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am.

We developed a formulation that relies on a combination of water soluble and water insoluble polymers, coated on to drug loaded beads to delay release by four to five hours after ingestion. This delivery device is a pulsatile drug delivery system and capable of releasing drug after predetermined time delay. The release of drug can characterize by proportioning drug concentration throughout night period in synchrony with biological rhythm determinants of asthma. Such coordination of biological rhythms with treatment is called chronotherapy and the delivery device is known as chronotherapy drug delivery system.

Developed formulation is a multiarticulate pulsatile system in which Salbutamol Sulphate is coated on non-pareil sugar seeds, using PVP-K-30 as a binder, followed by a middle layer of water insoluble ingredients and final coating of drug to immediate release. The water insoluble ingredients used were Propylene Glycol and Cellulose acetate Phthalate which delay release by 4 hours. It shows that 1 gm of pellets administered before sleep can provide relief from nocturnal asthma.

Keywords: PVP-K-30

INTRODUCTION:

The symptoms of chronic asthma are frequently worse around 4 am when, cosrtisol level is lowest whereas histamine concentration is at peaked in body[1]. Therefore, the objective of the present work was to formulate a pulsatile drug delivery which is capable of releasing drug after predetermine time-delay and can characterized by proportioning drug concentration throughout night in synchrony with biological rhythm determinates of Asthma[2].

Experimental work:

A) Formulation:

1) 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 (0.5%w/v) in Water: IPA (1:1) containing PVP-K-30(1%), as a binder, was sprayed over the cascading NPS till mass put on 1%. Hot air (60-70ºC) was blown to evaporate the solvent.

2) Dried pellets were sprayed with Cellulose acetate phthalate (2%w/v) and Ethyl cellulose (2%w/v) in Acetone till 4-6% weight gain. These pellets further coated with coating dispersion containing Propylene glycol (1.86% w/v), Span80 (0.66%w/v), Castor oil (0.125%w/v), Methylene dichloride (21.58%), Ethanol95% (20%w/v), Cellulose acetate phthalate (2%w/v) and Acetone (q.s.) till 4% weight gain. These two layers restrict release of drug from pellets up to 4 hours until it reaches to intestine[2.]

3) At last initial dose was encrusted, fourth layer, as similar as first layer, for immediate action[3].

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[4, 5].

B) 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[6]. Initially coated pellets

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(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[7,8].

C) In vitro releases characteristics study:

Release characteristics study was carried out as in USP XVII reciprocating cylinder (type III) dissolution apparatus. The volume of dissolution media was 900 ml in 1000 ml beaker[9,10]. The cylinder was adjusted to 100 rpm and temperature 37± 0.1ºC was maintained throughout the experiment[11]. 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[12,13].

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.

Release profile:

Table 1: reveals the release of drug from formulation

Time (hr.)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
% Drug released	0.37	1.32	2.9	2.85	2.85	0	0	0	1.46	2.27	2.77	2.64	2.6

Conclusion:

Initial drug release was observed in first 2 hours which can offer immediate relief, on the 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. So we can conclude that it can underlie the chronokinetic of nocturnal asthma.

Future Prospective:

Although systems performed quite well *in vitro*; their performance *in vivo* has not been tested. One major challenge will be to obtain a better understanding of the influence of the biological environment on the release performance of pulsatile delivery systems in order to develop simple systems based on approved excipients with a good *in vitro-in vivo* correlation.

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