International Journal for Pharmaceutical Research Scholars (IJPRS)

V-10, I-3, 2021 ISSN: 2277 - 7873

RESEARCH ARTICLE

Formulation and Characterization of Pulsatile Drug Delivery System of Terbutaline Sulphate

Radhika Reddy, Deeksha saini, Shilpa Elsa Mathew, Akanksha Ghodke, Madhavi Borasi*

* Lakshmi Narain Collage of Pharmacy (RCP), Indore, India

Manuscript No: IJPRS/V10/I3/00004, Received: 14/09/2021, Accepted: 21/09/2021, Published: 20/10/2021

ABSTRACT

The endeavor of the present study was to formulate and evaluated an oral pulsatile drug delivery system of Terbutaline sulphate intended for treatment of asthma attack. Mostly asthma attack occurs at mid night (nocturnal asthma), hence it is very inconvenient for patients to take medication at mid night. To overcome this problem pulsatile form of immediate and burst release of a drug is suitable, which provides drug release at the time of attack and at a target site. With the help of pulsatile delivery system, drug releases with a lag time of few hours and a burst release of drug at the peak duration (early morning hours) of asthmatic attack. Solution layering technique assisted spherical shaped Terbutaline sulphate loaded non pareil seeds of immediate release and enteric release polymer. Five batches were formulated using varying concentrations of cellulose acetate phthalate and constant concentration of ethyl cellulose (2%) in acetone till 2-6% weight gain. These layers restrict the release of the drug from pellets in stomach and provided sufficient lag time to the formulation. All the batches were characterized for drug content and *in- vitro* release. The results indicated efficient pulsatile drug release i.e. drug release after lag time of 8 hours post administration (first 2hrs in acidic medium and 6hrs in basic medium).

KEYWORDS

Nocturnal Asthma, Circadian rhythm, Pulsatile delivery, Terbutaline sulphate, Cellulose acetate phthalate, Solution layering technique, Lag time, Burst release

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment strategies of asthma indicates that airway resistance increases progressively at night in asthmatic patients. In normal lung function, circadian changes are seen, which reaches a low point in the early morning hours.

*Address for Correspondence:
Radhika Reddy,
Lakshmi Narain Collage of Pharmacy (RCP),
Indore,
India.

The worsening of asthma at night, is commonly referred to as nocturnal asthma (NA).

The dose is administered at bedtime but should release drug during morning hours. The bronchi divide into smaller bronchi, and then into bronchioles which ultimately terminate in the alveoli – the folded membranes where gas exchange takes place. The bronchi and bronchioles have a muscular layer in the wall which allows them to contract. In an acute asthma attack, this muscular layer contracts and leads to narrowing of the airways. The symptoms of asthma are mostly found at night than during the day. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol levels reached maximum at the time of

© Copyright reserved by IJPRS

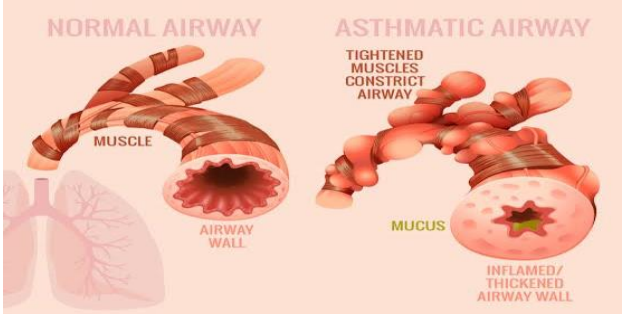


Fig: 1 Normal Airway & Asthmatic Airway

awakening and were lowest in the middle of night and histamine concentration were found maximum at the time of 4:00 am.

Approach to achieve Chronotherapeutic Drug Release Various methods have been developed and applied to design chronotropic system to achieve pulsatile drug release. These methods are mainly classified into three major categories.

- Time controlled chronotropic systems.
- Stimuli induced pulsatile drug delivery systems.
- Externally regulated pulsatile drug delivery system.

Pulsatile drug delivery system

- Temperature sensitive pulsed- release delivery systems.
- Inflammation induced systems.
- Enzyme dependent pulsatile-release systems.
- Glucose concentration dependent insulin release systems.
- Intelligent gels responding to antibody concentration.
- pH sensitive pulsatile drug delivery systems.

Disease requiring pulsatile drug delivery

Circadian rhythm regulates many body functions in human, viz metabolism, behavior, physiology, sleep pattern, hormone production etc. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung functions, which reaches a low point in the early morning hours. In case of cardiovascular disease, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. Platelet's agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Circadian increases in the blood sugar level after meal has been observed in diabetes mellitus. Circadian variations seen in DOPA level in afternoon in case of attention deficit syndrome.

Material and Method

Terbutaline sulphate (Yarrow chem labs), Isopropyl alcohol (Lobachem Pvt. Ltd), Polyvinyl Pyrrollidone k30 (Lobachem Pvt. Ltd), cellulose acetate phthalate, Ethyl cellulose, Acetone, Propylene glycol, Span 80, Castor oil, Titanium di oxide, Methylene chloride. (Lobachem Pvt. Ltd).

Formulation and Development

A pulsatile drug delivery of Terbutaline sulphate was prepared by coating Non pareil seeds approximately 14/16#. It was prepared in three stages.

Drug loading

Drug loading was carried out by solution layering technique, using conventional coating pan. The weighed non-Pareil seeds of approximately 14/16# were charged into pan and Terbutaline sulphate solution (1%w/v) in water: IPA (1:1) containing PVP-k30 (2%), as a binder, was sprayed over the non pareil seed till mass put on 1% hot air (60-70^{o}c) was blown to evaporate the solvent.

Coating of drug loaded pellets

Dried pellets were sprayed with the solution of cellulose acetate phthalate (2%w/v, 4%w/v, 6%w/v, 8%w/v, and 10%w/v) and ethyl cellulose (2% constant) in Acetone till 2-6% weight gain. These layers restrict release of

IJPRS/V10/I3/00004

© Copyright reserved by IJPRS

drug from pellets up to 6 hours until it reaches to intestine.

Final drug loading

At last an initial dose was encrusted, fourth layer, as similar as the first layer, for immediate action. For that Terbutaline sulphate solution (1%w/v) in water: IPA (1:1) containing PVP-K30 (2%), as a binder, was sprayed over the non pareil seed till mass put on 1%, Hot air (60-70ºc) was blown to evaporate the solvent. The solution was applied at pressure 20 psi. The speed of revolution of coating pan was 20-30 rpm. Hot air was supplied by hair dryer which, was placed at a distance of 15 cm from pan.

Table 1: Composition of coating solution

	Quantity (g/ml)				
Material	**F1**	**F2**	**F3**	**F4**	**F5**
Cellulose acetate phthalate	2%	4%	6%	8%	10%
Ethyl cellulose	2%	2%	2%	2%	2%
Propylene glycol	1.86 ml	1.86 ml	1.86 ml	1.86 ml	1.86 ml
Span 80	0.66 ml	0.66 ml	0.66 ml	0.66 ml	0.66 ml
Castor oil	0.125 ml	0.125 ml	0.125 ml	0.125 ml	0.125 ml
Titanium di oxide	0.533g	0.533g	0.533 g	0.533 g	0.533 g
Methylene chloride	20 ml	20 ml	20 ml	20 ml	20 ml
Acetone	q.s	q.s	q.s	q.s	q.s

Table 2: Processing conditions for coating

S.no.	**Parameter**	**Range**
1.	Inlet air temperature	45-60 ºC
2.	Outlet air temperature	30-40 ºC
3.	Spray rate	0.5-2 g/min
4.	Spray nozzle diameter	0.5 mm
5.	Speed of coating pan	20-30 rpm

Result and discussion

Preformulation

IJPRS/V10/13/00004

© Copyright reserved by IJPRS

Melting point determination

The melting point of Terbutaline sulphate was found to be 118-120ºC which is same as reported in literature.

Determination of wavelength using UV spectrophotometric analysis

The maximum wavelength of Terbutaline sulphate was found to be 275nm. The reported wavelength is 276-280nm.

Preparation of calibration curves

The calibration curves of Terbutaline sulphate in various solvents e.g. Distilled water, Phosphate buffer 6.8 and 0.1 N HCl was prepared.

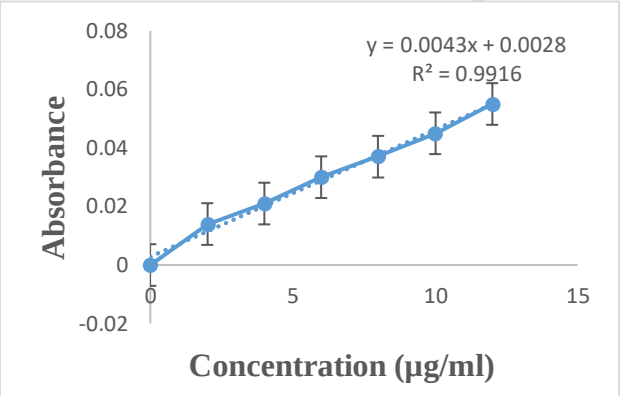
Table 3: Absorbance data of Terbutaline sulphate in distilled water at 275 nm

S.No	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.014 ± 0.001
3.	4	0.021 ± 0.001
4.	6	0.030 ± 0.001
5.	8	0.037 ± 0.001
6.	10	0.045 ± 0.001
7.	12	0.055 ± 0.0008

Determination of solubility of Terbutaline sulphate in various medium

The solubility of Terbutaline sulphate in various medium were studied and results of study shown in table 6.

Fig 2: Calibration curve of Terbutaline sulphate in distilled water



Drug-excipient interaction study

Table 4: Absorbance data of Terbutaline sulphate in phosphate buffer 6.8 at 278 nm

S.No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.035 ± 0.0008
3.	4	0.052 ± 0.0008
4.	6	0.074 ± 0.001
5.	8	0.097 ± 0.001
6.	10	0.116 ± 0.0008
7.	12	0.133 ± 0.001

The drug Terbutaline sulphate was found to be compatible with various excipients which were selected for formulation of pulsatile drug delivery. The compatibility was assessed by

IJPRS/V10/I3/

© Copyright reserved by IJPRS

TLC and retention factors of all ratio found similar. The Rf factor of Terbutaline is 0.34 and mobile phase is Chloroform: Methanol (4:1).

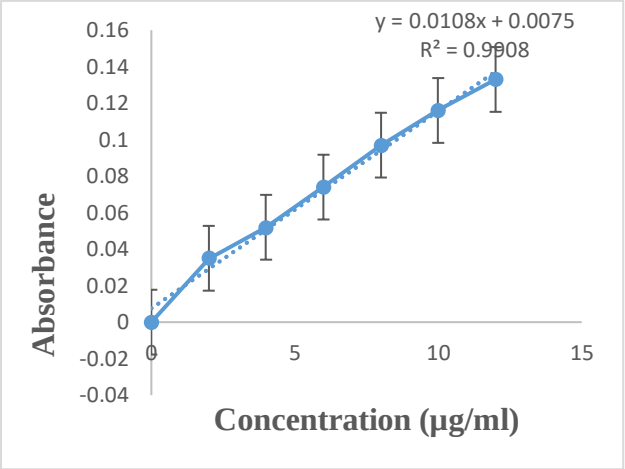


Fig 3: Calibration curve of Terbutaline sulphate in Phosphate buffer 6.8 at 278nm

Table 5: Absorbance data of Terbutaline sulphate in 0.1 N HCl at 273nm

S.No.	Concentration (µg/ml)	Absorbance
1.	2	0.013 ± 0.0008
2.	4	0.019 ± 0.0008
3.	6	0.024 ± 0.001
4.	8	0.029 ± 0.0008
5.	10	0.035 ± 0.001
6.	12	0.041 ± 0.001

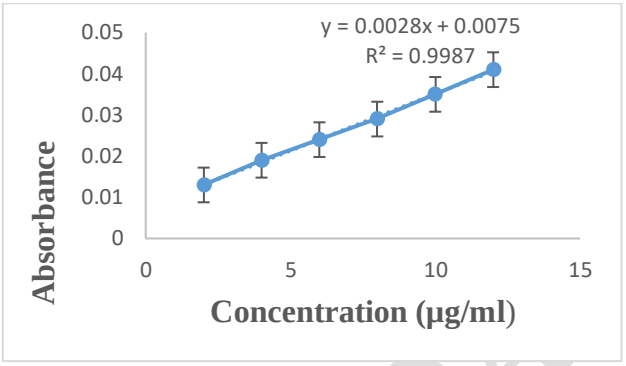


Fig 4: Calibration curve of Terbutaline sulphate in 0.1 N HCl at 273nm

Table 6: Solubility data of Terbutaline sulphate in different medium at 37°C

S.no.	Solvent	Solubility
1.	Distilled water	210.97 mg/ml
2.	Phosphate buffer 6.8	51.80 mg/ml
3.	0.1 N HCl	63.03 mg/ml

Evaluations of capsule filled coated pellets

% Drug content of each formulations

Table 7: % Drug content

S.No.	Different layers	Drug loaded in 1 pellet	% Drug Content
1.	Drug loading capacity	0.954 mg	95.4%
2.	Enteric coated layer	0.025 mg	2.5%
3.	Immediate layer	0.939 mg	93.9 %

IJPRS/V10/I3/00028

© Copyright reserved by IJPRS

Practical yield

Table 8: % practical yield in each formulation

S.No.	Formulation	Weight of pellets (gm)	Weight of drug polymer loaded pellets (gm)	% practical yield
1.	F1	2	2.06	97.08 %
2.	F2	2	2.05	97.5 %
3.	F3	2	2.03	98.5 %
4.	F4	2	2.04	98.03 %
5.	F5	2	2.020	99.0 %

***In – vitro* drug release study**

Table 9: In 0.1 N HCl Immediate release layer

S.No.	Time (hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
1	1 hr.	82.06	85.3	68.4	73.5	52.8
2	2 hr.	91.6	91.2	87.4	91.8	92.6

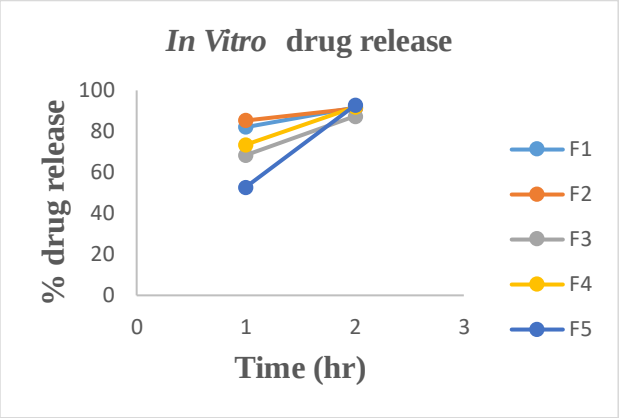


Fig 5: % *In vitro* drug release in 0.1 N HCl

Table 9: *In vitro* % drug release in pH 6.8 Phosphate buffer

Time (hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0.5					
1					
1.5					
2	80.9				
2.5					
3					
3.5		82.7			
4					
4.5			82.9		
5					
5.5				91.6	
6					91.7

IJPRS/V10/13/0008

© Copyright reserved by IJPRS

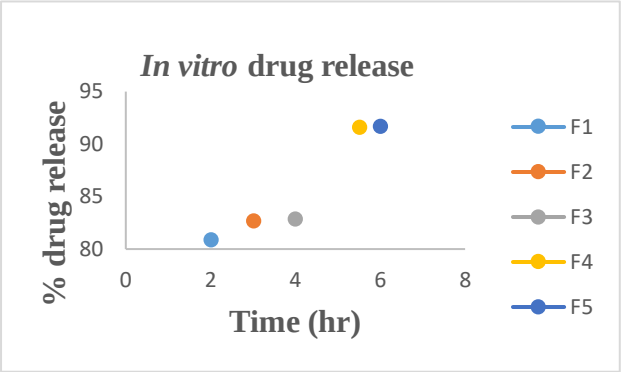


Fig. 6: % *In vitro* drug release in pH 6.8 PBS

In Phosphate buffer pH 6.8: Burst release layer

F1 contained 2 % CAP and EC 2% the drug release was found to be 80.9 % in 2 hrs, F2 contained 4 % CAP and 2% EC the drug release was found to be 82.7 % in 3.5 hrs., F3 contained 6% CAP and 2% EC drug release was found to be 82.9 % in 4.5 hrs., F4 contained 8% CAP and 2% EC drug release was found to be 91.6 % in 5.5 hrs. and F5 contained 10 % CAP and 2% EC drug release was found to be 91.7 % in 6 hrs.

Disintegration test for capsule

The disintegration time for hard gelatin capsule was found to be in the range of 2.5±0.816 to 10.33±0.471 min. in HCl.

Stability study

There were no changes in appearance and percentage drug content of pellets loaded capsules stored at different temperature 40ºC ±2% RH and 75 ºC ±5% RH.

Table 10: Stability studies

S.NO.	Parameter	Storage condition 40ºC±2% RH and 75 ºC ±5% RH
1.	Dissolution time	No change
2.	Disintegration time	No changes
3.	% Drug content	No change
4.	% Practical yield	No change

Conclusion

Over the past decades, it has been observed that asthmatic attack occur at mid night it is very difficult to take medication at mid night for patient or it is inconvenient for patient to take medicines repeatedly in an interval. To overcome such problems, an effort was made to formulate and evaluate time controlled pulsatile dosage form of Terbutaline sulphate. The drug loading of Terbutaline was processed with suitable carrier (non pareil seed) by employing solution layering technique. Solution layering technique assisted spherical shaped drug loaded non pareil seed of immediate release and enteric release polymers. With the use of non pareil

IJPRS/V10/I3/000004

© Copyright reserved by IJPRS

seed the delivery of a drug at the target site may be achieved by avoiding dose dumping.

Initial drug release was observed in first 2 hours in acidic medium which can offer immediate relief, on the other hand enteric coated polymers releases the drug with a lag time of 5-6 hours and a burst release in a single pulse. Burst release of the drug after a lag time (requirement for chronotherapeutics) was achieved with the developed formulation.

To study the better release of the drug, five batches were prepared on the basis of cellulose acetate phthalate and ethyl cellulose, it was found that the batch F5 (10% CAP and 2% EC) was the best as it showed 95.4% drug content and 91.7% drug release after lag time of 8 hours (first two hrs in acidic medium and 6 hrs in basic medium) This batch was accurate for treatment of nocturnal asthma according to pulsatile drug delivery system.

REFERENCE

1. Anonymous-www.pharmatutor.org-Art-2657
2. Ricciotti, E., & FitzGerald, G. A. (2011). Prostaglandins and inflammation. *Arteriosclerosis, thrombosis, and vascular biology*, *31*(5), 986-1000.
3. A review of Ayurvedic medicated oils,Ayur times Dr.Jagdev Singh.
4. Ghasemian, M., Owlia, S., & Owlia, M. B. (2016). Review of anti-inflammatory herbal medicines. *Advances in pharmacological sciences*, *2016*.
5. Mukherjee, P. K. (2002). *Quality control of herbal drugs: an approach to evaluation of botanicals*. Business Horizons.
6. Khandelwal, K. (2008). *Practical pharmacognosy*. Pragati Books Pvt. Ltd.
7. Pharmacopoeia, I. (2014). Ghaziabad: Indian Pharmacopoeial Commission. *Govt. of India-Ministry of Health and Family Welfare*, 1948.

IJPRS/V10/I3/00004

HOW TO CITE THIS ARTICLE

Reddy, R., Saini, D., Mathew, S. E., Ghodke, A., Borasi, M. (2021). Formulation and Characterization of Pulsatile Drug Delivery System of Terbutaline Sulphate. *International Journal for Pharmaceutical Research Scholars, 10(3);24 - 33.*

IJPRS/V10/I3/00004

© Copyright reserved by IJPRS

THIS PAGE IS INTENTIONALLY LEFT BLANK.

IJPRS/V10/I3/00004

© Copyright reserved by IJPRS