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Research Article

FORMULATION DESIGN, CHARACTERIZATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF TERBUTALINE SULPHATE: A MODIFIED MATRIX TECHNOLOGY

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ABSTRACT

Introduction: The sustained release formulation is more effective than conventional release tablet in nocturnal asthma. Nocturnal asthma arises at the night time or sleeping time. The dose of terbutaline sulphate is 15 mg/day with biological half life of 3-4 hrs leads to the dosing frequency 6-8 times in a day. To overcome the issue related to attack of nocturnal asthma in night time or while sleeping, a conventional dosage form fall short to control the same. Thus the sustained release formulation, once administered, is more effective to control the probable attack of nocturnal asthma for overnight. Material and Methods: The sustained release formulation of Terbutaline sulphate (TS) is developed by modified wet granulation technique with the aid of polymers viz. Hydroxy Propyl Methyl Cellulose (HPMC K4M), Ethyl cellulose, Eudragit RS 100 and Microcrystalline cellulose (MCC). Results and Discussion: Terbutaline sulphate is a selective β-2 adrenoceptor agonist & widely used in nocturnal asthma. The best formulation was TS_7 containing ethyl cellulose with eudragit RS 100 in context to the dissolution profile, release kinetics and drug content. The prepared sustained release matrix tablet of terbutaline sulphate IP may be used in the treatment of bronchial & night time asthma. Conclusion: The present study concludes the better results of in vitro release for 12 hrs. It follows higuchi model of release kinetics, mean the drug release from matrix.

KEYWORDS: Preformulation Studies, Terbutaline Sulphate, In-vitro release profile, ANOVA, Release kinetics.

INTRODUCTION

The approach of sustained release formulation is to achieve slow release of drug over an extended period of time[1]. Asthmatic problem creates variable air flow obstruction & this problem widespread in the lungs. In which the sleep-related worsening of asthma is common[2]. The symptoms are arising throughout the day & worsen during sleep in individual patients. If it is not control than patient come under risk of health problems like as respiration trouble & rapid eye movement (REM) with the tiny apneic pauses. The asthmatic deaths and respiratory are arrest mostly observed in night. It is treated by the help of specific asthmatic treatment. As compared to conventional, the sustained release oral dosage form has greater attention for controlling the systems of nocturnal asthma[1, 3].

Terbutaline sulphate is a selective β_2 adrenoceptor agonist. TS acts on β_2 adrenoceptor of bronchial muscle at therapeutic dose. No reaction is reported on β_2 adrenoceptor of heart. Selectivity has further increased by inhaling the drug**.** The drug is used to prevent and manages asthmatic attack[4].

Asthmatic Pathophysiology

Inflammation in airway is most common symptom of asthma. The inflammatory mediators are released by the exposure to specific allergens, exercise, irritants, and cold air. Two types of responses may be observed on the behalf of inflammatory mediators:

1. Asthmatic response of early-phase.
2. Asthmatic response of late-phase.

Management of Nocturnal Asthma

The following goals may be set to manage the nocturnal asthma

1. Control symptoms so as including exercise to maintain normal activity level.
2. Establish plans for the prevention and management of exacerbations.
3. Avoid adverse effects from asthma medications.
4. Asthma management program conducted & educate to the patients.
5. Establish plans for chronic management and regular follow-up care[5].

MATERIALS AND METHODS

Terbutaline sulphate was provided as a sample from Ananta Drugs & Pharmaceutical Pvt. Ltd., Sri Ganganagar, Eudragit RS 100 was provided by Alembic Pharmaceutical Ltd., Vadodara, Dibasic calcium phosphate (DCP), Micro Crystalline Cellulose (MCC), Sodium benzoate, Stearic acid, Talc was obtained from ONS Pharmaceutical Pvt. Ltd. Jaipur, Rajasthan.

Preparation of standard calibration curve of TS

10mg of TS was weighed, dissolved in small amount of phosphate buffer pH 7.4 and volume was made upto 100ml with phosphate buffer pH 7.4. The solution was scanned using UV-Visible spectro-photometer. From this stock solution, the working solutions of 10, 20, 40, 60, 80 and 100µg/ml were prepared. Afterward absorbance was measured at λmax 276nm[6].

Formulation design of TS tablet

The preparation of sustained release tablet was carried out by modified wet granulation technique with starch paste. All the ingredients, previously passed through sieve #60 were weighed except stearic acid and talc. Terbutaline sulphate was mixed with required quantities of polymers (Eudragit RS 100, Ethyl cellulose and HPMC K4M) and Dibasic calcium phosphate, as shown in Table 1, in mortar for 5 min. Afterward starch paste was added drop by drop to prepare a suitable mass for granulation. The wet mass was then passed through sieve #10 and dried at 50°C for 30 minutes. The dried granulated material was further passed through sieve #22 to prepare granules of uniform size. The stearic acid and talc were incorporated in the dried uniform size granules. The granules equivalents to 200 mg were weighed and tablet was compressed with single punch tablet machine[7, 8].

Table 1: Composition of Sustained Release Tablet of Terbutaline sulphate

Ingredients (mg)	TS_1	TS_2	TS_3	TS_4	TS_5	TS_6	TS_7
Terbutaline sulphate IP	7.5	7.5	7.5	7.5	7.5	7.5	7.5
HPMC K4M	50	-	-	-	-	-	-
Ethyl cellulose	9	15	15	30	-	30	35
Eudragit RS 100	-	15	30	15	30	30	30
Dibasic calcium phosphate	63	77	69.5	69.5	77	62	59.5
Micro Crystalline Cellulose	62.5	77.5	70	70	77.5	62.5	60
Sodium benzoate	2	2	2	2	2	2	2
Stearic acid	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4

Pre-compression Study

Bulk density: The bulk density is the ratio of total mass of the granulated material/powder to the bulk volume of granulated material/powder. The bulk density was determined by bulk density apparatus. Pour the granules/powder into a calibrated measuring cylinder and measure the volume of granules/powder. The unit of bulk density is gm/ml. The bulk density can be mentioned as following;

$$\text{Bulk Density } (\rho_b) = \frac{\text{Mass of the powder (M)}}{\text{Volume of the bulk powder } (V_b)}$$

Tapped density: Take & weigh approximately 100 g of the terbutaline sulphate granules with 0.1% accuracy. Pour the granules into a dry graduated cylinder of 250 ml, without compacting, then the measuring cylinder place on tapped density apparatus and start for 50 taps, then carefully measure the tapped volume of powder. Then again proceed for 50 taps, if necessary and read the settled apparent volume (V_t) to the nearest graduated unit. The unit of tapped density is gm/ml. The tapped density can be mentioned as following;[9, 10]

$$\text{Tapped Density } (\rho_t) = \frac{\text{Mass of the powder (M)}}{\text{Tapped Volume of the powder } (V_t)}$$

Compressibility Index & Hausner's Ratio: These parameters are used to measure the tendency of powder to be compressed and the flow ability of granule. In which relative importance was measured under inter-particulate interaction[11]. Carr's index (Compressibility index) & Hausner's ratio may be calculated by following formula;

$$\text{Carr's Index (I)} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_b}$$

Angle of repose: The fixed funnel and free-standing cone methods employ a funnel that is secured with its tip at a given height H, above graph paper that is placed on a flat horizontal surface. Take approximately 80-100 gm of dried granules of TS & carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Then radius of the conical pile was marked, and height was measured for calculate the angle of repose according to following formula[11, 12, 13].

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Post-compression Study

Description of Tablet (Shape): It is determined by magnifying lens to measure the tablet shape[9].

Thickness of Tablet: It was measured by Vernier Caliper. Ten tablets from each formulation were randomly used to measure the thickness. The unit of thickness was in mm.

Determination of drug content: Twenty tablets were crushed in a glass mortar pestle and 200 mg of the powdered material equivalent to 7.5mg of the TS was dissolved in 50 ml of 7.4 pH phosphate buffer with stirring for 24 hrs. Afterward 5 ml of sample was withdrawn, filtered and determine drug content by UV-visible spectrophotometer at 276 nm[6].

$$\text{Drug content (\%)} = \frac{G_{act}}{G_{powder}} \times 100$$

Hardness: Ten tablets were randomly taken, and the hardness was determined by Monsanto hardness tester. The unit of this tester is kg/cm^2 [14].

Friability

Thirty-three tablets were taken (equivalent to 6.5gm as per IP) & weigh accurately by calibrated weighing balance. Tablets were placed into Roche friabilator. It was operated at 25 rpm for 4 minutes (100 revolutions), then dedust carefully and weigh accurately by using previously calibrated weighing balance. The range of the friability should not be more than 1% according to Indian pharmacopoeia (I.P.). The friability may be determined by the following formula:[15]

$$\text{\% F} = 1 - \frac{W_o}{W} \times 100$$

Weight variation of tablets: Twenty tablets randomly taken from each formulation batches and weighed individually on calibrated weighing balance[16]. The average weight of the 20

tablets was calculated. The variation should not be more than 7.5 % according to IP for these formulations[15].

Swelling index: The matrix tablet was weighed individually (designated as W_0), placed in a beaker containing 200ml of pH 7.4 phosphate buffer at 37°C±1°C. At one hour time intervals until 12 h, the matrix tablets were removed from beaker, excess surface buffer was removed carefully using the tissue paper, weighed and replace in the beaker. The swollen matrix tablets were re-weighed (Wt), and % swelling index (SI) was calculated by following formula[17].

$$\text{Swelling Index (\%)} = \frac{W_t - W_o}{W_o} \times 100$$

Table 2: Absorbance of Terbutaline sulphate in Phosphate buffer pH 7.4

Concentration (µg/ml)	Absorbance
10	0.082
20	0.173
40	0.337
60	0.494
80	0.650
100	0.829

In-Vitro Drug Release Profile

The in vitro drug release profile of sustained release tablets was determined by USP apparatus 2 (Paddle). The basket was allowed to rotate at a speed of 50 rpm, at temperature 37 ± 0.5°C. 5 ml of sample was withdrawn at a predetermined interval i.e.; at 5, 10, 15, 30, 45, 60, 120, 180, 240, 360, 480, 600, and 720 minutes and the volume of dissolution medium (Phosphate buffer pH 7.4) was maintained 900ml by replacing the equivalent quantity of dissolution medium to the vessel at each time. The filtered samples were subjected to the absorbance determination by UV spectrophotometer at λmax 276 nm[17].

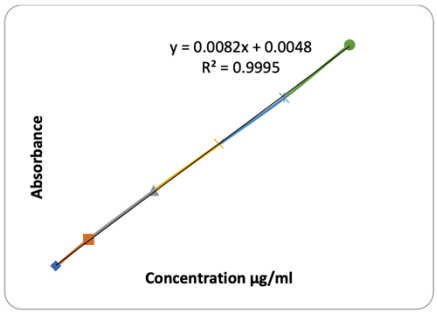

Figure 1: Standard calibration curve of Terbutaline sulphate

Table 3: Results of The Evaluations of Pre-Compression Stage

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner ratio	Angle of repose
TS_1	0.4166	0.4545	8.33	1.09	25.4
TS_2	0.3846	0.4166	7.68	1.08	27
TS_3	0.50	0.5555	9.99	1.11	27.1
TS_4	0.3571	0.4166	14.28	1.16	25.8
TS_5	0.4545	0.50	9.10	1.10	25.6
TS_6	0.40	0.4347	7.98	1.08	28.2
TS_7	0.3703	0.4166	11.11	1.12	24.3

Table 4: Results of The Physical Evaluations of Post-Compression Stage

Batch No.	Thickness (mm)	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Swelling index (%)
TS_1	3.52	201	5.09	0.36	97.66	71
TS_2	3.50	190	5..76	0.32	98.33	78.72
TS_3	3.52	198	5.23	0.36	96.83	94.11
TS_4	3.53	203	5.46	0.28	97.16	97.01
TS_5	3.53	208	5.10	0.41	96.66	75
TS_6	3.51	188	5.01	0.31	98.16	94.73
TS_7	3.51	197	5.16	0.40	99.12	90.81

Table 5: In-vitro Release Profile of Formulations of Terbutaline Sulphate

% Cumulative Release at Different Time Intervals							
Time	**TS_1**	**TS_2**	**TS_3**	**TS_4**	**TS_5**	**TS_6**	**TS_7**
5 min.	0	0	0	0	7.5	0	0
10 min	0	1.5	3	1.5	7.54	0	0
15 min.	0	3	6.01	6	13.58	4.5	1.49
30 min.	1.5	6.02	10.55	10.54	21.11	7.52	6
45 min.	4.5	13.55	16.59	16.59	31.69	9.06	10.54
60 min.	6.03	18.1	19.65	21.15	40.79	12.09	15.09
90 min.	10.55	28.67	30.2	30.2	51.4	18.11	18.14
120 min.	16.59	45.25	40.77	40.78	60.5	22.66	22.68
180 min.	25.65	61.9	54.39	57.39	72.61	36.22	33.22
240 min.	33.23	74.09	75.52	71.04	86.23	48.32	45.3
360 min.	39.32	86.25	89.21	89.2	96.87	63.46	61.93
480 min.	51.4	96.88	96.9	98.38	-	83.11	75.59
600 min.	62	-	-	-	-	98.3	89.25
720 min..	72.62	-	-	-	-	-	98.4

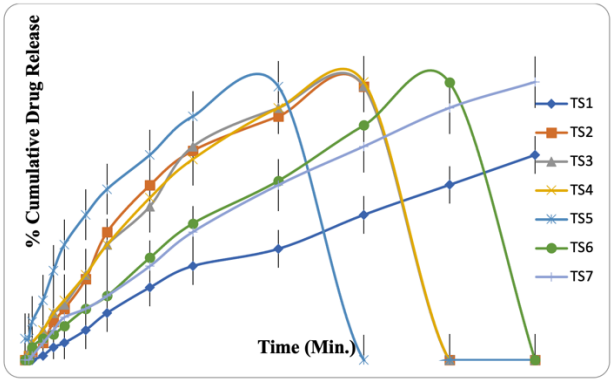

Figure 2: Scatter Chart of Comparisons of In-vitro profiles of TS_1–TS_7

Table 6: Data Summary of In-vitro Dissolution Profile by ANOVA

Formulations	N (Number of data)	Mean	Standard Deviation	Standard Error
TS_1	14	23.0993	24.8738	6.6478
TS_2	12	36.2675	35.4067	10.221
TS_3	12	36.8992	34.4608	9.948
TS_4	12	36.8975	34.4903	9.9565
TS_5	11	44.5291	31.613	9.5317
TS_6	13	31.0269	32.7565	9.085
TS_7	14	34.1164	34.2821	9.1623

Table 7: ANOVA Summary of In-vitro Dissolution Profile

Source	Degree of Freedom	Sum of Squares	Mean Square	F- Stat	P- Value
Between Formulations	6	3255.4546	542.5758	0.5103	0.7989
Within Formulations	81	86129.6465	1063.329		
Total	87	89385.101	-		

Table 8: In-vitro Dissolution Profile of SR Tablet (TS_7)

TIME	% Cumulative drug release
5 min.	0
10 min	0
15 min.	1.49
30 min.	6
45 min.	10.54
60 min.	15.09
90 min.	18.14
120 min.	22.68
180 min.	33.22
240 min.	45.3
360 min.	61.93
480 min.	75.59
600 min.	89.25
720 min.	98.4

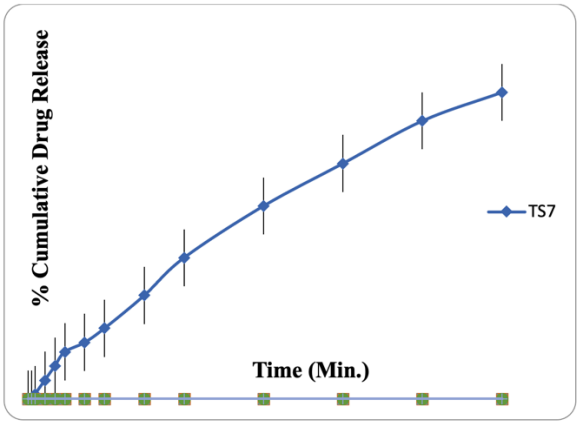

Figure 3: Scatter Chart of In-vitro profiles TS_7

Table 9: Data of Release Kinetic Models

Name of Model	Value of r^2
Zero order kinetic model	0.938
First order kinetic model	0.671
Higuchi Equation	**0.991**
Korsmeyer-Peppas Model	0.960

Table 10: % CDR of Optimized Formulation (TS_7)

Square Root of Time	% CDR
3.873	1.49
5.4772	6
6.7082	10.54
7.746	15.09
9.4868	18.14
10.9545	22.68
13.4164	33.22
15.4919	45.3
18.9737	61.93
21.9089	75.59
24.4949	89.25
26.8328	98.4

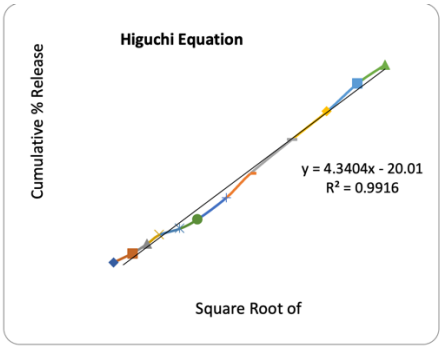

Figure 4: Scatter Chart of Higuchi Equation of Optimized Formulation (TS_7)

RESULT AND DISCUSSION

Standard calibration curve of Terbutaline sulphate: The absorbance of the different dilutions for drug sample was observed at the λmax 276 nm as data obtained are shown in Table 2 & Figure 1.

The standard calibration curve of terbutaline sulphate was prepared to assure the drug sample where the λmax of the sample drug observed was 276 nm.

Evaluation of Pre-compression Parameters: In the pre-compression study, prepared powder/granules of TS1-TS7 were evaluated for various physical properties as shown in Table 3.

The bulk density & tapped density of various formulations were performed by tapped density apparatus. The range of bulk density indicates good packing character. The compressibility index of various design was found below 15 % and flow properties of the powder were analyzed by angle of repose. The observed value was found between 24.3-28.2.

The hausner ratio of all formulation was found below 1.18, indicates good flow properties of the powder.

Evaluation of Post Compression Parameters: All the formulations (TS1-TS7) were evaluated for post compression parameters mentioned in Table 4. The observed values were found within limit according to reference or I.P.

Thickness of various formulations was found 3.48 to 3.55mm & weight variation average was 197.85 mg. Hardness of formulations was found to be less than 1 %. Highest Drug content 99.12% was found in TS7. Swelling index was within range of 71 - 97.01.

In-Vitro Drug Release profile: Result shown in as per Table 5 & Figure 2.

The % cumulative drug release of TS7 formulation was found maximum 98.4% within 12 hrs.

ANOVA Analysis: The value of P is observed 0.7989. It means that the P- value is greater than 0.05, so these formulations are shown significant difference Table 6, 7 [18].

Selection of the Best Formulation

In-vitro drug rerelease data of TS7 formulation: The cumulative drug release of drug was observed and reported in Table 8 & Figure 3.

Release Kinetic Study: Optimized formulation (TS7) of sustained release tablet of terbutaline sulphate follows Higuchi model of drug release Table 10 & Figure 4. The value of r2 for Higuchi model was the maximum observed i.e. 0.9916 and the release kinetic of another models as shown in Table 9.

CONCLUSION

Proposed work was aimed to obtain desired therapeutic value and patient compliance. The physicochemical evaluations of all formulations were found with good flow properties according to the requirement. TS7 formulation was found with best in-vitro drug release formulation. Formulation TS7 includes the combination of Eudragit-RS 100 & ethyl cellulose was found a suitable candidate for the said objective. It follows Higuchi model conclude that the formulation release drug from matrix system. The sustained release of drug depends upon various polymer used in proposed research. Thus, the prepared formulation is useful to treat nocturnal asthma.

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REFERENCES

1. Pundir S, Badola A and Sharma D. Sustained release matrix technology and recent advance in matrix drug delivery system: A review. The International Journal of Drug Research and Technology. 2013; 3 (1):12-20.
2. J. Montplaisir, J. Walsh and J. L. Malo. Nocturnal asthma: Features of attacks, sleep and breathing patterns. The American review of respiratory disease. 1982; 125:18-22.
3. Harold K. Jorge M. A review article on Asthma. Allergy, Asthma & Clinical Immunology. 2011:2-9.
4. Kumar S, Singh L and Tyagi L. Formulation and evaluation of bilayer floating tablet of levocetirizine and terbutaline. World Journal of Pharmacy and Pharmaceutical Science; 7 (Issue 5), 1210-1228.
5. Kumar V. Kataria MK. Bilandi A. Nocturnal asthma & its management by chronotherapy. World Journal of Pharmacy and Pharmaceutical Science 2019; 570-585.
6. Bharti N. A thesis of a study of targeted pulmonary drug delivery system containing nanoparticles 2015; 98-102.
7. NM Harish, R Charyulu N. et al. Formulation design and optimization of sustained release tablets of terbutaline

sulphate. International Journal of Pharmaceutical Education and Research 2011; 259-266.
8. Kola R. Ramani D. B Kumar P. Formulation and in-vitro evaluation of terbutaline sulphate sustained release tablets. Indian Journal of Research in Pharmacy and Biotechnology 2013; 621-624.
9. Lachman L., Lieberman H. A., Kanig J. L. The Theory and Practice of Industrial Pharmacy. Chapter No. 8 Preformulation. Published by Varghese Publishing House, Bombay, 3rd Edition 1991; 293-303.
10. C.V.S. Subrahmanyam. A textbook of physical pharmaceutics. Chapter No. 6 Micrometrics. Vallabh prakashan, New Delhi; 215-230.
11. United States Pharmacopoeia 28 NF 23. The Official Compendia of Standards. Published by United States Pharmacopeial Convention. Inc. Rockville, MD, Asian Edition. Printed in Canada by Webcome Ltd. Toronto, Ontorio; 2015.
12. Martin A. Physical Pharmacy Physical & Chemical Principles in the Pharmaceutical Sciences. Published by Lippincott Williams & Wilkins, Maryland USA. Fourth Edition; 2001: 443-448.
13. Joseph P Remington, Alfonso R Gennoro, Aro H Der Marderosien, Glen R Hanson DDS, Thomas Medwick, Nicholos G Popovich et al. Remington's pharmaceutical sciences. Published by Mack Publishing Company, Pennsylvania, Seventeenth edition, 1985; 1594-1596.
14. Sarkar, B. K., Jain, D. A., and Sharma, V. Formulation and Evaluation of Flurbiprofen Matrix Tablets for Colon Targeting. International Journal of Pharmaceutical and Chemical Science 2012; 477- 483.
15. Indian Pharmacopoeia. 2007, Volume I. Government of India, Ministry of health & family welfare, The Indian pharmacopoeia commission Ghaziabad. 183.
16. Pundlikrao, I. P., Patel, K. M. Design and Development of Floating Gastro Retentive Tablets for Mosapride Citrate Dihydrate: In vitro-in vivo Evaluation. Indian Journal of Novel Drug Delivery 2012. 295-305.
17. M. Harish, Charyana N. et al. Formulation design and optimization of sustained release tablet of terbutaline sulphate. Indian Journal of Pharmaceutical Education and Research 2011. 259-266.
18. A web Site of https://goodcalculators.com/one-way-anova-calculator/ assessed on 10.07.2019. assessed on dated 10.07.2019.

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