Formulation and evaluation of gastro retentive floating tablets of Terbutaline sulphate

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ABSTRACT

The purpose of this research was to develop a novel gastro retentive floating tablets of Terbutaline sulphate (TBS). Terbutaline sulphate has short half life (3-4 hrs) so an attempt has been made to Sustain the drug release by the incorporation of hydrophilic swellable polymer such as Hydroxy propyl methylcellulose (HPMC) and present it in the form of gastro retentive floating tablets, which after oral administration are designed to provide the desired controlled and complete release of drug for prolonged period of time in the treatment of Asthma. Floating effervescent tablets were formulated using various grades of hydroxy propyl methylcellulose (HPMC K4M, HPMC K15M and HPMC K100M), and gas generating agent like sodium bicarbonate. The concentration of this agent was also optimized to get desired controlled release of drug. The floating tablet formulations were evaluated for physical characterization, hardness, friability, weight variation, drug content uniformity, swelling index and buoyancy studies. The results indicated that the optimized intragastric floating (IGF) tablet (F9) composed of 50 mg HPMC K100M and 18 mg MCC, exhibited 95.28% drug release in 12 h, while the buoyancy lag time was 10.33 sec, and the intragastric floating tablet remained buoyant for 24 h. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or in vitro dissolution pattern after storage at 40°C/75% relative humidity for 1 month.

Keywords:

Terbutaline sulphate, gastro retentive, gastric floating tablet, floating drug delivery, controlled release.

INTRODUCTION

Terbutaline Sulphate is a short acting β adrenergic agonist, used for symptomatic relief and treatment of asthma. TBS is available in formulation for oral intake, inhalation and injection for treatment of bronchial asthma. In the treatment of bronchial asthma, it is given by mouth in an adult dose of 5 mg two or three times daily. The systemic mean residence time of the drug is about 3 hr. approximately 30-50% absorbed, if administered orally. i.e. Terbutaline Sulphate suffers from reduced bioavailability .

Terbutaline Sulphate needs to be administered frequently due to its short biological half life (3-4 hr). However, such a dosing schedule may be inconvenient for the patients. Therefore long acting Terbutaline Sulphate formulation is desirable to improve patient compliance.

To overcome the above problems we made an effort to develop the floating tablet of Terbutaline Sulphate to prolong the gastric residence time, after oral administration at a particular site, and controlling the release of drug especially useful for achieving controlled plasma level as well as for improving bioavailability and diminish the side effect of irritating drug.

In order to achieve the required release profile, various formulation of Terbutaline Sulphate were prepared using HPMC as a release retarding polymer and sodium bicarbonate as a gas forming agent to achieve the desired buoyancy. The polymer viscosity of HPMC may play an emerging role on drug release as well as on floating lag time.

The real issue in the development of oral controlled release dosage form is to extend the duration of action of drug from GIT.

So the main objective of this research is to optimize concentration of different grades of HPMC polymers with sodium bicarbonate to maintain the sustained effect of Terbutaline Sulphate for desired period of time to maximize its efficiency.

MATERIALS AND METHODS

Material: Terbutaline Sulphate was received as gift sample from Ranbaxy Laboratories Ltd. Dewas M.P. (India). Excipients such as HPMC K15M, HPMC K100M, HPMC K4M, Talc, Aerosil, microcrystalline cellulose, and Sodium bicarbonate were procured from SD Fine Chemicals, Mumbai.

Methods:

Preparation of standard curve of Terbutaline sulphate: The samples of different concentration were analyzed at 276 nm using UV-Spectrophotometer against 1.2 pH buffer as blank.

Compatibility Studies:[1,2] The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy.

Formulation design: [3-5] Floating tablets containing Terbutaline sulphate were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and microcrystalline cellulose. The compositions of all formulations are given in table no. 1.

EVALUATION PARAMETERS:

Precompression parameters:

Bulk density and tapped density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD was calculated using following formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder

Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

Compressibility index: Percentage compressibility of powder mix was determined by Carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is calculated by following formula.

Carr's index (%) = [(TBD -LBD) × 100]/TBD

Angle of repose (Θ): The frictional forces in a loose powder or granules can be measured by the angle of repose.

$\tan \theta = h / r$

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

Where, θ is the angle of repose

h is height of pile

r is radius of the base of pile

Post compression parameters:

Weight variation test: [6] Twenty tablets from each formulation were selected randomly and weighed individually average weight was determined. Individual tablets weighed were then was compared with average weight.

Hardness test: [6] The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Pfizer hardness tester. The hardness was measured in terms of Kg/cm^2

Friability: Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Content uniformity test:[6] Twenty tablets were finely powdered; quantities of the powder equivalent to 5mg of Terbutaline sulphate were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCl (pH 1.2 buffer) solution and mixed thoroughly. The solution was made up to volume 100ml and filtered. Dilute 1 ml of the resulting solution to 10 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 276 nm using a Shimadzu UV-visible spectrophotometer.

Swelling Study:[7] The floating tablets were weighed individually (designated as W_0) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1 -h time intervals until 24 h, the floating tablets were removed from beaker, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (W_t), and % swelling index SI was calculated by following formula

$SI (\%) = (W_t – W_0 / W_0). 100$

In vitro Dissolution Studies: [8-10] The In vitro dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at $37^oC \pm 0.5\ ^oC$.

Stability studies:[11] The optimized formulation of Terbutaline sulphate were packed in strips of 0.04mm thick aluminium foil laminated with poly vinyl chloride by strip packing and the packed formulations were stored in ICH certified stability chambers maintained at 40 ^oC and 75% RH for 1 month.

RESULTS AND DISCUSSION

Standard calibration curves of Terbutaline sulphate: Figure 1 shows the standard calibration curves for Terbutaline sulphate with slope, regression co-efficient and intercept.

Compatibility Studies: Compatibility studies of pure drug Terbutaline sulphate with all excipients were carried out prior to the preparation of floating tablets. I.R spectra of pure drug Terbutaline sulphate and combination of Terbutaline sulphate and excipients were obtained, which are shown in Figure 2.

Formulation development of floating tablets: The floating tablets of Terbutaline sulphate were prepared using direct compression method.

Precompression Parameters:

Angle of repose: The values were found to be in the range of 19^o 85' to 25^o 16'. All the formulation showed angle of repose below 30^o which indicates a good flow property of the granules.

Compressibility index: Carr's index lies within the range of 11.32 to 15.68 %. All formulations show good compressibility. The results are shown in Table 3.

Hausner ratio: Hausner ratio was found to be in the range of 1.1063 to 1.1860 as shown in Table 3.

Post compression Parameters:

Weight variation test: The values of tablets ranged from 98.6 ± 0.054 to 102.4 ± 0.096 mg. All the tablets passed weight variation test as the % weight variation was within the Pharmacopeial limits of ±10 % of the weight and is shown in table 4

Hardness test: The hardness of all formulations was in the range of 3.7±0.14 to 4.1±0.26 kg/cm^2.

Friability test: The friability values of prepared tablets are given in Table 6. The values ranged from 0.36 to 0.64%

Content uniformity test: The percent drug content of tablets was found to be in between 90.2 to 99.4% of Terbutaline sulphate and all results are shown in table 4.

In vitro Buoyancy Studies: The IGF tablets F1, F2 and F3 containing HPMC K4M in 25, 37 and 50 mg respectively. These three formulations exhibited short buoyancy lag time of 10.56, 12.52 and 13.71 sec respectively. The IGF tablets F4, F5 and F6 containing HPMC K15M showed floating lag time of 10.47, 10.57 and 10.67 sec respectively and showed. The formulation F7 and F8 and F9 showed the FLT of 10.35, 10.36 and 10.33 sec respectively with total floating time of 18, 20 and 24 hrs. Among IGF tablets F1 to F9, the formulation F9 except formulation F8 showed shortest buoyancy lag time (10.34 sec) with more total buoyancy time (24 hrs).

Swelling Study: Swelling study was performed on all the batches for 7 hrs. and the results of swelling index is given in Table 5.

In vitro Dissolution Studies: The IGF tablets F1, F2 and F3 showed the release of 98.21%, 97.91% and 97.11% at the end of 12 hours respectively. So as the concentration of the HPMC K4M is increased the initial drug concentration in the dissolution medium is decreased as well as shows sustained release of drug. So varying the amount of HPMC K4M affects the drug release.

The IGF tablets containing HPMC K15M, (F4, F5 and F6) showed release of 97.81%, 97.13% and 96.97% respectively at the end of 12 hrs. It was observed that as the concentration of polymer (HPMC K15M) was increased in formulations (F1, F2 and F3) the extent of drug release was decreased.

The IGF tablets Containing HPMC K100M (F7, F8 and F9) showed drug release of 97.12%, 96.34% and 95.28% respectively at the end of 12 hrs. This might be due to the fact that HPMC K100M is a polymer with high molecular weight and viscosity, and, when contacted with water, it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded release of Terbutaline sulphate from the GFDDS.

Stability studies: The formulation batch showed circular shape with no cracks. The drug content of the formulation was found to be 98.60% which shows there was slight decrease in drug content but difference is insignificant. In vitro dissolution data of optimized formulation F9 during stability studies at 40^oC and 75% RH for one month is tabulated in table 7.

CONCLUSION

By incorporating alkalizing agents into a hydrophilic matrix formulation, it is possible to effectively control the pH within the matrix surrounding the Terbutaline sulphate molecules and thereby enhance the drug's solubility in the body. This has been accomplished by incorporating electrolyte sodium bicarbonate with a HPMC gel matrix, so that as the dosage form hydrates, a pH is induced that allows Terbutaline sulphate to solubilise within the hydrated gel region prior to release. The IGF tablets (F9) showed satisfactory results with short buoyancy lag time, long total buoyancy time and controlled drug released up to 12 hrs.

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Table 1: Composition of Gastroretentive Floating Tablets of Terbutaline sulphate (F1 to F9)

	Formulation Code								
Ingredients*(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Terbutaline sulphate	5	5	5	5	5	5	5	5	5
HPMC K4M	25	37	50	-	-	-	-	-	-
HPMC K15M	-	-	-	25	37	50	-	-	-
HPMC K100M	-	-	-	-	-	-	25	37	50
Microcrystalline cellulose	43	31	18	43	31	18	43	31	18
Sodium Bicarbonate	25	25	25	25	25	25	25	25	25
Aerosil	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total Weight (mg)	100	100	100	100	100	100	100	100	100

Table 2: Standard Calibration curve of Terbutaline sulphate at 276 nm in pH 1.2 Buffer.

S. N.	**Concentration µg/ml**	**Absorbance**
1	0	0
2	2	0.015
3	4	0.029
4	6	0.043
5	8	0.058
6	10	0.072

Table 3: Pre-compression Parameters of Designed Formulations (F1 to F9)

Formulation Code	Bulk density	Tapped density	Carr's index(%)	Hausner ratio	Angle of repose(θ)
F1	0.46	0.52	11.54	1.1304	22^o 07’
F2	0.43	0.51	15.68	1.186	24^o 56’
F3	0.44	0.51	13.72	1.159	22^o 77’
F4	0.47	0.53	11.32	1.1276	24^o 56’
F5	0.5	0.58	13.79	1.16	25^o 16’
F6	0.45	0.51	11.76	1.1333	24^o 27’
F7	0.52	0.61	14.75	1.173	23^o 12’
F8	0.48	0.55	12.72	1.1458	23^o 68’
F9	0.47	0.52	11.53	1.1063	19^o 85’

Table 4: Physical Characterization of Gastroretentive Floating Tablets of Terbutaline Sulphate (F1 to F9)

Formulation Code	Thickness (mm)	Hardness Kg/cm2	Friability (%)	Weight variation	Drug content (%)	Floating lag time (Sec)	Total Floating Time (hrs.)
F1	2.8 ± 0.13	3.8 ±0.13	0.64	100.1 ± 0.117	90.2	10.56	13
F2	2.8 ± 0.109	3.9 ±0.17	0.52	99.5 ± 0.147	91.2	12.52	14
F3	2.8 ± 0.192	4.0 ±0.17	0.49	101.7 ± 0.273	92.2	13.71	16
F4	2.8 ± 0.18	3.7 ±0.17	0.58	102.4 ± 0.138	95	10.47	15
F5	2.8± 0.168	3.9 ±0.18	0.37	98.9 ± 0.178	93.8	10.57	17
F6	2.8 ± 0.156	4.1 ±0.26	0.39	98.6 ± 0.054	97.8	10.67	19
F7	2.8 ± 0.178	3.7 ±0.14	0.48	102.4 ± 0.096	97.5	10.35	18
F8	2.8 ± 0.173	4.0 ±0.12	0.47	101.4 ± 0.092	96.6	10.36	20
F9	2.8 ± 0.17	4.1±0.15	0.36	100.4 ± 0.054	99.4	10.33	24

Table 5: Swelling index of Gastroretentive Floating Tablets of Terbutaline sulphate (F1 to F9)

Time (hrs)	**Swelling Index (%)**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	35	42	78.2	45	52	88.1	60	82	98.03
2	44	55	102.9	57	64	117.8	66	95	135.29
3	52	66	115.8	69	73	129.7	76	118	150.09
4	59	74	117.8	79	87	149.5	82	126	164.7
5	68	82	146.5	86	96	157.4	93	139	176.47
6	78	85	157.4	92	103	179.2	102	146	187.25
7	81	89	159.4	96	108	193.06	113	152	198.03

Table 6: In vitro Dissolution Data for Formulation F1 to F9

Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	19.92	16.92	13.92	17.98	15.96	14.23	14.979	13.47	12.34
2	39.29	32.29	29.29	36.26	34.96	31.16	35.756	32.22	30.993
3	54.76	47.76	46.76	50.77	49.97	46.99	48.87	46.23	39.32
4	70.92	63.22	57.22	68.22	61.22	56.92	65.678	57.832	47.42
6	79.02	73.02	70.02	78.02	75.72	70.02	74.739	68.73	60.13
8	81.2	77.2	78.22	80.2	80.2	77.94	78.66	79.678	70.691
10	89.71	87.31	86.91	86.31	85.33	83.332	85.97	84.23	82.943
12	98.21	97.91	97.11	97.811	97.132	96.97	97.121	96.34	95.285

Table 7: Stability Studies of Optimized IGF Tablet (F9) of Terbutaline sulphate

Evaluation Parameters	**Initial**	**After 1 month**
Physical Appearance	Off white, smooth, flat faced	Off white, smooth, flat faced
Hardness (kg/cm2)	4.1 ± 0.15	3.9 ± 0.16
Drug content %	99.4	98.6
Floating Lag Time (Sec)	10.33	11.57
Total Floating Time (hrs)	24	22
In vitro Drug Release at 12 hr (%)	95.285	93.103

Figure 1: Standard Calibration Curve of Terbutaline sulphate in pH 1.2 Buffer

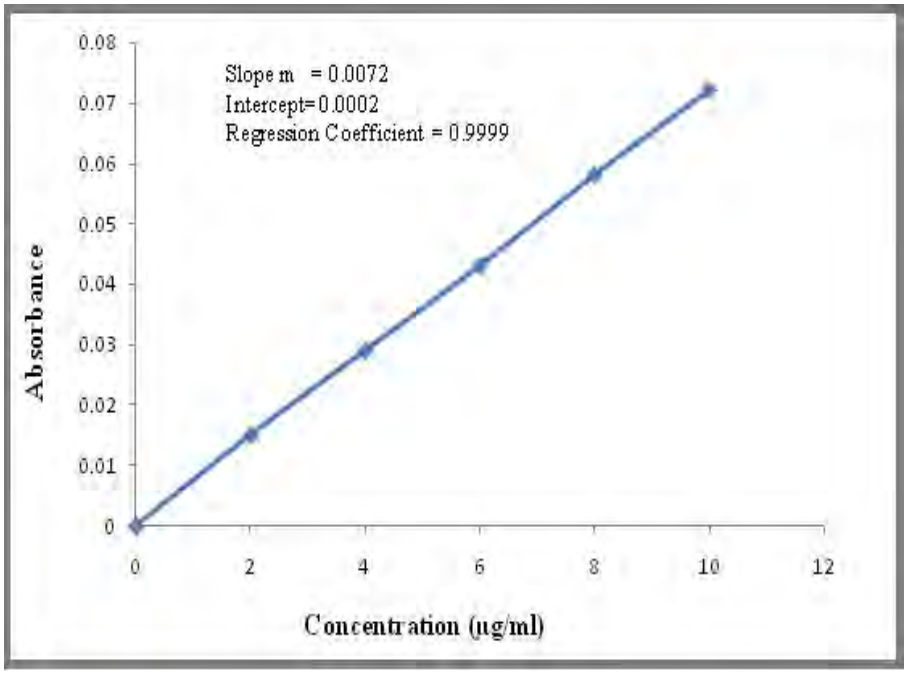

Figure 2: IR Spectra of Terbutaline sulphate, drug excipient mixture and excipient.