Research Article

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Formulation evaluation of terbutaline sulfate sublingual tablet by using natural superdisintegrants

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ABSTRACT

Terbutaline sulfate is a selective B2 bronchodilator which is used in the treatment of asthma. Conventional Terbutaline tablets available in the market are not suitable where quick onset of action is required. Terbutaline sulfate sublingual tablets were prepared by using mannitol, Aspartame, aerosil, magnesium steartate, talc and natural superdisintegrants like karaya gum, locust bean gum, gellan gum by direct compression method.F11 formulation of locust bean gum was selected as best formulation. It was shown less disintegration time of 17 seconds. It was observed that less disintegration time was observed when locust bean gum was used as natural superdisintegrant, may be due to swelling at faster rate upon contact with water and elimination of lump formation after disintegration when compared with gum karaya and gellan gum. F11 formulation was found to be the best as this formulation shown less disintegration time and possessing good tabletting properties. The bioavailability of terbutaline sulfate is 14.8%. Bioavailability also can be increased using natural superdisintegrants. Sublingual absorption avoids first pass metabolism.

Keywords: Terbutaline sulphate, Locust bean gum, Karaya gum, Gellan gum.

INTRODUCTION

Development of a formulation involves a great deal of study and experimental work to get optimum results. While doing so we have to keep in mind various, factors are considered like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects i.e. scale-up and last but not the least we have to consider the patients compliance and convenience. Now a day's formulation research is breaking barriers of conventional methods. Today, active ingredients can be delivered with a level of convenience, performance and bioavailability. First pass metabolism can be overcome by sublingual drug delivery, and quick drug delivery into the systemic circulation can be obtained. Sublingual administration can offer an attractive alternative route of administration [1]. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation by passing enzyme degradation in the gut and liver. These formulations are particularly beneficial to pediatric and geriatric patients. It also applies to

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people who are bedridden and to those active working patient, who are busy travelling, especially those who have no access to water. In addition, sublingual mucosa and abundance of blood supply at the sublingual region allow excellent drug penetration to achieve high plasma drug concentration with rapid onset of an action [2].

MATERIALS

Terbutaline sulfate, Gellan gum was purchased from Yarrow chemicals (Mumbai), Karaya gum, locust bean gum, Magnesium stearate, Talc, Mannitol, Aerosil and Aspartame were purchased from S.D Fine Chemicals Ltd., Mumbai (India) All other chemicals and reagents used were of analytical grade. Deionized distilled water was used throughout the study.

METHOD

All ingredients were triturated individually in a mortar and passed through #60 sieve. Then required quantity of all ingredients were weighed for a batch size of 30 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant this uniformly mixed blend was compressed in to tablets containing 2.5mg drug using 5mm flat face surface punches on a cemache rotary tablet machine by direct compression method. Total weight of tablet was kept 100mg [3]

Figure No: 1 Formulation of sublingual tablets

Table No. 1 Formulation table

S.no	Ingredients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1.	Terbutaline sulfate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	**2.5**	2.5	2.5
2.	Karaya powder	10	12	14	16	-	-	-	-	-	-	**-**	-	-
3.	Gellan powder	-	-	-	-	20	22	24	26	-	-	**-**	-	-
4.	Locust bean powder	-	-	-	-	-	-	-	-	10	15	**20**	25	-
5.	Cross povidone	-	-	-	-	-	-	-	-	-	-	**-**	-	5
5.	Mannitol	77.5	75.5	73.5	71.5	67.5	65.5	63.5	61.5	77.5	72.5	**67.5**	62.5	82.5
6.	Aspartame	4	4	4	4	4	4	4	4	4	4	**4**	4	4
7.	Magnesium	2	2	2	2	2	2	2	2	2	2	**2**	2	2

	stearate													
8.	Talc	2	2	2	2	2	2	2	2	2	2	**2**	2	2
9.	Aerosil	2	2	2	2	2	2	2	2	2	2	**2**	2	2
10.	Total Wt.	100	100	100	100	100	100	100	100	100	100	**100**	100	100

PRECOMPRESSION PARAMETERS OF THE POWDER BLEND

Preparation of mixed blend of drug and excipients [4, 5]

All the ingredients were passed through mesh no 60. Required quantity of each ingredient was taken for each specified formulation and all the ingredients were subjected to grinding to a required degree of fineness. The powder blend was subjected to pre compression parameters.

Angle of repose

Weigh accurately 100 g of the blend and are carefully poured through the funnel whose tip is secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The granules are poured until the apex of the conical pile just touches the tip of the funnel.

The interrelationship between the angle of repose and flow properties of powder are shown in the table. Angle of repose is calculated by the following formula.

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

Where, θ = angle of repose, r=radius of the pile, h=height of the pile,

Bulk density

Bulk density is defined as a mass of a powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

*b=M/V

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (V_1) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula.

$*t=M/V_t$

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which is calculated using the formula,

$$C.I\ (\%) = \frac{\text{Tapped density- Bulk density}\times 100}{\text{Tapped density}}$$

Hausner's ratio

Hausner ratio is an index of ease of powder flow. It is calculated by using the formula,

Hausner ratio = *dt/*db

Where *dt = tapped density. *db = bulk density.

EVALUATION OF SUBLINGUAL ANTIASTHMATIC TABLET [7, 8, 9]

- Weight variation
- Thickness
- Hardness
- Friability
- Content uniformity
- *In-vitro* disintegration time
- *In-vitro* release studies
- Fourier transform infrared spectroscopy

Weight variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness

Control of physical dimension of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier calipers scale.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$F\ \% = (1 - W_0/W) \times 100$

Where,

W_0 is weight of the tablets before the test and W is the weight of the tablets after test.

Content uniformity

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 1 mg was weighed and dissolved in 100ml of 6.8 pH buffer filtered and drug content analyzed spectrophotometrically at 276nm.

In-vitro disintegration time

The USP device to rest disintegration was six glass tubes are "3 long, open at the top, and held against 10" screen at the bottom and of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of buffer at 37±2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Invitro release studies

In-vitro drug release of Terbutaline sulfate sublingual anti-asthmatic tablets were determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 900ml 6.8 pH buffer at 37°C±0.5°C. The speed of rotation of paddle was set at 50rpm. 5ml samples were withdrawn at time points of 1,2,3,4,5,10,15,20,25, and 30 min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO-164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 276nm and drug release was determined from standard curve.

Dissolution study of Terbutaline sulfate of sublingual antiasthmatic tablets

Bath temperature : 37+0.5°C
Dissolution media : 6.8 pH buffer
Volume of dissolution media: 900 ml
Aliquot withdrawn : 5 ml
Dissolution apparatus : USP type II (paddle)
Revolution per minute (speed) : 50rpm

Accelerated stability studies

The optimized formulation was subjected to stability studies at 40°C±75%RH for period of three months. Each tablet was individually wrapped in aluminium foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for three months. For every one month tablets were analyzed for the hardness, friability disintegration time, drug content and *in-vitro* drug release. The results are obtained within the limits

RESULTS AND DISCUSSIONS

Preparation of standard calibration graph for Terbutaline sulfate

Standard solutions in the range of 120 to 220 mcg/ml were prepared and absorption values were recorded at 276nm against the reference. From this data, the standard curve of Terbutaline sulfate was obtained by plotting absorbance on Y-axis against concentration on X-axis.

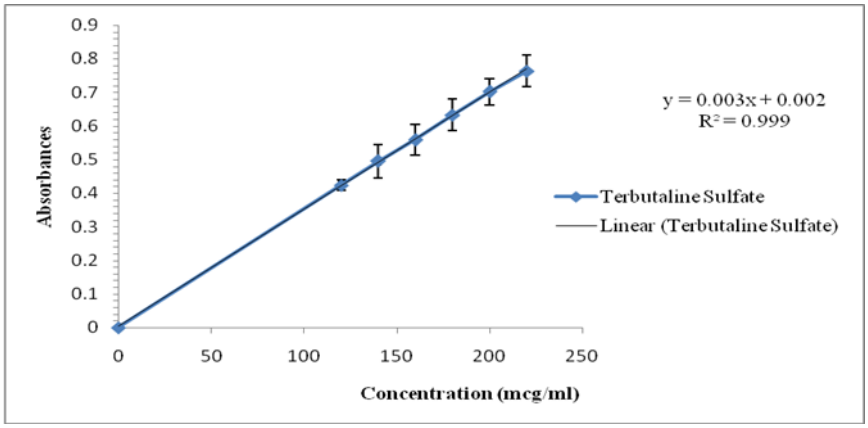

Figure No: 2 Standard graph of Terbutaline sulphate Evaluation tests

Pre-compression parameters of factorial formulations

Physical appearance: Tablets are white in color with good texture.

Table No.2 Post-compression parameters

S.No.	Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Assay (%)	Weight Variation (mg)
1	**F1**	3.1±0.1	2.1±0.3	0.54±0.4	40±0.5	97.54±0.5	101±0.54
2	**F2**	3.2±0.4	2.2±0.4	0.56±0.2	39±0.2	97.32±0.4	98±0.45
3	**F3**	3.4±0.3	2.1±0.5	0.65±0.1	48±0.3	96.21±0.1	97±0.65
4	**F4**	3.1±0.2	2.4±0.3	0.71±0.5	45±0.1	98.11±0.4	96±0.32
5	**F5**	3.6±0.3	2.5±0.2	0.83±0.6	32±0.4	98.21±0.5	94±0.65
6	**F6**	3.2±0.5	2.3±0.3	0.72±0.7	34±0.7	98.65±0.2	95±0.54
7	**F7**	3.3±0.8	2.4±0.5	0.63±0.8	47±0.2	97.42±0.5	98±0.64
8	**F8**	3.5±0.7	2.2±0.6	0.65±0.9	45±0.4	97.54±0.8	99±0.62
9	**F9**	3.6±0.5	2.6±0.2	0.71±0.4	49±0.1	98.43±0.9	95±0.54
10	**F10**	3.7±0.4	2.7±0.3	0.81±0.2	30±0.4	98.42±0.3	94±0.76
11	**F11**	**3.3±0.6**	**2.0±0.1**	**0.46±0.5**	**17±0.5**	**99.67±0.7**	**100±0.65**
12	**F12**	3.5±0.9	2.4±0.4	0.70±0.3	28±0.1	97.34±0.5	96±0.65
13	**F13**	3.2±0.5	1.9±0.1	0.43±0.6	17±0.4	97±0.6	99±0.61

All the prepared value as mean (n=3) (±SD)

Precompression parameters

Precompression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The two most important attributes for the direct compression formula are good flow and good compressibility. Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder, such a comparison is often used as an index of the ability of the powder to flow. The angle of repose gives important information about the flow characteristics of the powder mixture. The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, compressibility), the bulk powder properties (e.g., size distribution, compaction), and the processing environment (e.g., storage, humidity).

In the present study Terbutaline sulfate sublingual tablets were prepared by using natural superdisintegrants namely, karaya powder, gellan powder, locust bean powder. All the formulations were evaluated for various parameters like hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and *In-vitro* drug release values are given in Table

The hardness of the tablets was found to be 3.1±0.1-3.7±0.4 (kg/cm²) and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 2.7±0.3-2.0±0.1 (mm). All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e.±7.5% and the values were found to be in the range of 101±0.54-94±0.65 (mg). The drug content was found to be 96.21±0.1-99.67±0.7 (%), indicating uniform distribution of drug in the tablets & *in-vitro* drug release was found to be 13.01±1.25-98.61±1.62.

The most important parameter that needs to be optimized in the development of sublingual tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 17±0.59-49±0.1 (sec) fulfilling the official requirements (less than 1 min) for disintegrating tablets. It was observed that the disintegration time of the tablets increased with increasing concentration of karaya powder, gellan powder, locust bean powder.

F11 formulation of locust bean powder was selected as best formulation. It was shown less disintegration time of 17 seconds. It was observed that less disintegration time was observed when locust bean powder was used as natural superdisintegrant, may be due to swelling at faster rate upon contact with water and elimination of lump formation after disintegration when compared with karaya powder and gellan powder. F11 formulation was found to be the best as this formulation shown less disintegration time and possessing good tabletting properties.

Invitro dissolution study

The dissolution study on formulation no : F1 to F13 were carried out using 900ml of respective dissolution medium at 50rpm using USP. The formulations F1 to F13 shown 13.01±1.25-98.61±1.62 in 10min respectively. The rapid *In-vitro* dissolution was shown in the F11 formulation containing locust bean powder as natural superdisintegrant. High dissolution resulted due to faster break down & rapid disintegration of tablet.

The dissolution graphs are shown in fig. by this study an important conclusion can be drawn that addition of natural superdisintegrants technique has improved the dissolution profile of the water soluble drugs besides the disintegration time.

Sublingual tablets of terbutaline sulfate tablets were prepared using either terbutaline sulfate with various amounts of natural superdisintegrants by direct compression. The physical characteristics of the tablets were as follows: hardness measured using Monsanto hardness tester), 2.8 kg/cm² and 2.6kg/cm²; friability (determined using a friabilator, Electronics India Ltd., Mumbai), 0.63%;

Formulations of rapidly disintegrating sublingual tablets using natural superdisintegrants is based on two principal criteria: the tablets should disintegrate in less than 1 min and 95% of drug should dissolve in less than 10 min.

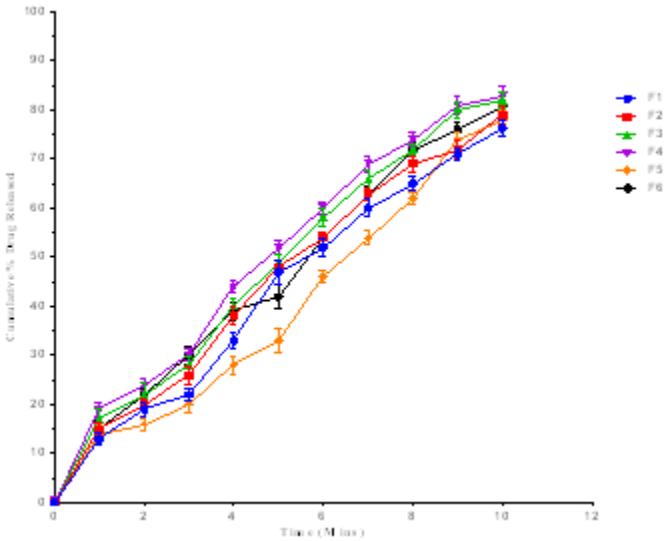

Figure No:3 Comparision of cumulative drug release profiles of Terbutaline sulfate Sublingual tablets: F1-F6

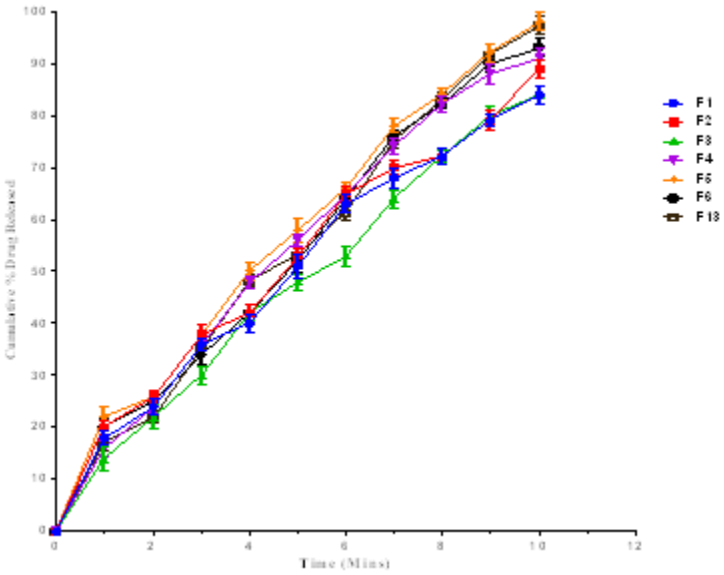

Figure No:4 Comparision of cumulative drug release profiles of Terbutaline sulfate Sublingual tablets:F7-F13

Accelerated stability studies

Table No: 3 Accelerated stability studies

Parameters	Time in months			
	0(Initial)	1st month	2nd month	3rd month
Hardness(kg/cm²)	3.3±0.057	3.3±0.029	3.3±0.046	3.3±0.019
Friability(%)	0.46±0.05	0.46±0.06	0.46±0.029	0.46±0.069

Disintegration time(sec)	17±0.577	17±0.739	17±0.628	17±0.834
Drug content(%)	99.89±0.085	99.89±0.059	98.89±0.039	98.89±0.019
***In-vitro* drug release (%)**	98.6±0.065	98.6±0.058	98.5±0.049	98.5±0.038

All the prepared value as mean (n=3) (±SD)

The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40°C±75% RH on optimized formulation (F11). The formulation was found to be stable, because there was no change in the hardness, disintegration time, drug content and *in-vitro* drug release pattern.

CONCLUSION

- The concept of sublingual tablets containing terbutaline sulfate offers a suitable and practical approach in serving the desired objective of asthma.
- The excipients used in the formulation were inexpensive and are easily available.
- Most of the excipients used in formulation are water-soluble and hence have better-patient acceptability.
- The present work of optimized formulation of a sublingual tablet containing terbutaline was successful in terms of reducing manufacturing difficulties, cost and providing a better patient compliance with effective medication.
- It has been observed from the above study that excipients like mannitol, aspartame, aerosil etc. were ideal excipients and effective for formulating sublingual tablets.
- F11 formulation was considered to be the best among all other batches since it exhibited a good dissolution profile, disintegration time, uniformity of drug content and further good stability and In vitro absorption profile.
- Disintegration time of F11 formulation was found to be 17sec.
- In the present study, it was revealed that use of natural superdisintegrates can produce tablets that provide less than 1min Disintegration Time
- Formulation F11 was subjected to further stability studies. Stability study was carried out at 45°C and 75% RH according to the ICH guidelines.
- The samples were analyzed at intervals of first month for the drug content and dissolution profile and disintegration time.
- The results indicated that there was no significant variation in the formulations.

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