Available online at www.pharmaresearchlibrary.com/ijcps ISSN: 2321-3132

Research Article

International Journal of Chemistry and Pharmaceutical Sciences
IJCPS, 2013: Vol.1(7): 450-461
www.pharmaresearchlibrary.com/ijcps

Formulation and Evaluation of Mucoadhesive Beads of Terbutaline Sulphate

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Available Online **27 November 2013**

Abstract
The objective of the present investigation was to formulate and evaluate mucoadhesive beads of Terbutaline sulphate to achieve substantial increase in length of stay of drug in GI tract for the treatment of asthma. Terbutaline sulphate is a β_2 adrenergic receptor against which produces bronchodilation. Its short biological half life (3-4hrs) necessitates the need to be administered in three to four doses of 5mg per day. Mucoadhesive beads exhibit a prolonged residence time at the site and facilitate an intimate contact with underlying absorption surface and contributes to improved therapeutic performance of drug. In the present research work, the adhesive polymers like sodium alginate, HPMC, SCMC has been used to prepare Terbutaline sulphate mucoadhesive beads using calcium chloride(2%w/v) and aluminium chloride (2%w/v) as cross linking agents. The incorporation efficiency of prepared beads ranged between 0.199 to o.386. The effect of Bioadhesive polymers, cross linking ions were evaluated with respect to entrapment efficiency, particle size, surface characteristics and in-vitro drug release studies. Among all the formulations TBS-2 (formulated using sodium alginate (2%w/v) and HPMC(0.5%w/v) using 2%w/v calcium chloride as gellant solution) and TBS-6 (formulated using sodium alginate (2%w/v) and HPMC(0.5%w/v) using 2%w/v aluminium chloride as gellant solution) showed optimum drug release profile. Between TBS-2 and TBS-6 retarded the drug release for 12hrs which may be due to the presence of aluminium chloride as cross linking agent. Drug release kinetics indicates that all the formulations showed linearity with respect to zero order (R2=0.990 to 0.99) as compared to first order (R2=0.751 to 0.828). The exact release mechanism was found to be super case 2 transport.
Key words: Mucoadhesive beads, bio adhesion, Terbutaline sulphate.

Introduction
Mucoadhesive drug delivery systems interact with the mucus layer covering mucosal epithelial surface, and mucin molecules which increase the residence time of the dosage form at site of absorption. The drug which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. Mucoadhesive drug delivery systems facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects**.** The muco adhesive beads were prepared for following drugs like glicazide, clarithromycin, timolol maleate done the work.[1-5]

Terbutaline sulphate is a β_2 adrenergic receptor agonist. Terbutaline sulphate produces bronchodilation within 5 minutes, and the action lasts for 2-4hrs. It also influences mucus transport by reducing mucus viscosity and terminates asthma. Terbutaline can also be utilized to relax the uterus, if necessary prior to uterine replacement.[6-8] The objective of the present research work was to develop Terbutaline sulphate mucoadhesive beads by using ionotropic external gelation technique. The drug suspension was added drop wise in to gellant solution using a peristaltic pump with a pumping rate of 1ml/min. After the formulation of mucoadhesive beads, the beads were separated, washed with distilled water and dried air for 48hrs and the formed beads were evaluated for various parameters and filled into capsules.

Materials and Methods

Materials

Terbutaline sulphate was obtained from Drugs India Pvt ltd (India). Sodium alginate was obtained from Himedia. Sodium carboxy methyl cellulose was obtained from Fischer scientific. Aluminum chloride was purchased from Drugs India Pvt ltd (India). All the remaining ingredients and chemicals utilized were of analytical grade.

Methods

Standard graph for Terbutaline sulphate:

Step-1: Preparation of standard stock solution[9]

An accurately weighed quantity of 100mg of terbutaline sulphate was taken in a 100ml standard flask. To this equal volume of distilled water was added to standard flask and made up to the volume.

Step-2: Preparation of sample solution:

From the standard stock 1,2,3,4,5,6,7,8,9,10ml was taken in a separate 100ml standard flask and the dilutions were made up to the volume using equal volume of distilled water to get 10,20,30,40,50,60,70,80,90,100µg/ml and these samples were analyzed by using UV spectroscopy at a wae length of 276nm.

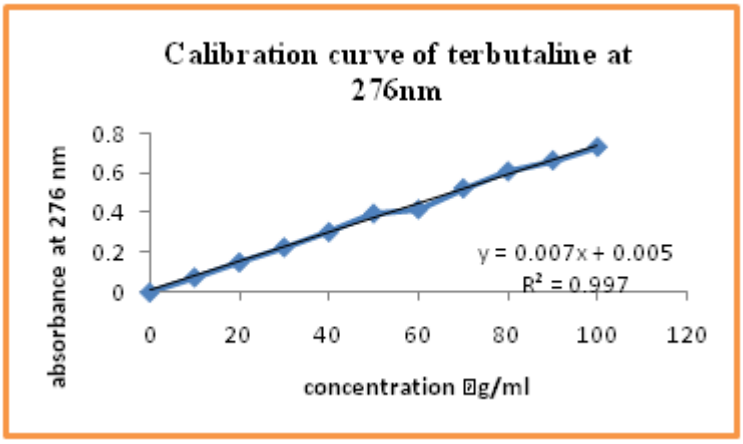

Fig-4: Calibration curve for terbutaline drug at 276 nm

Drug-Excipient compatibility study: FT-IR spectroscopy

FT-IR patterns were studied by Shimadzu 8400S, Japan FT-IR spectrometer. The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. The scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

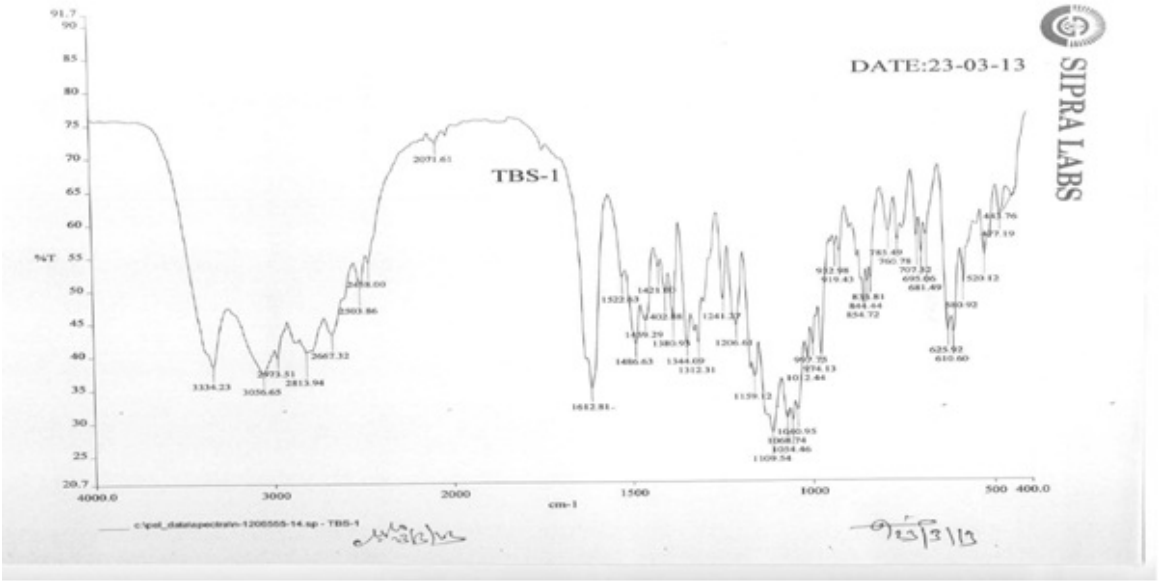

Fig-5: FT-IR Spectra of Terbutaline sulphate

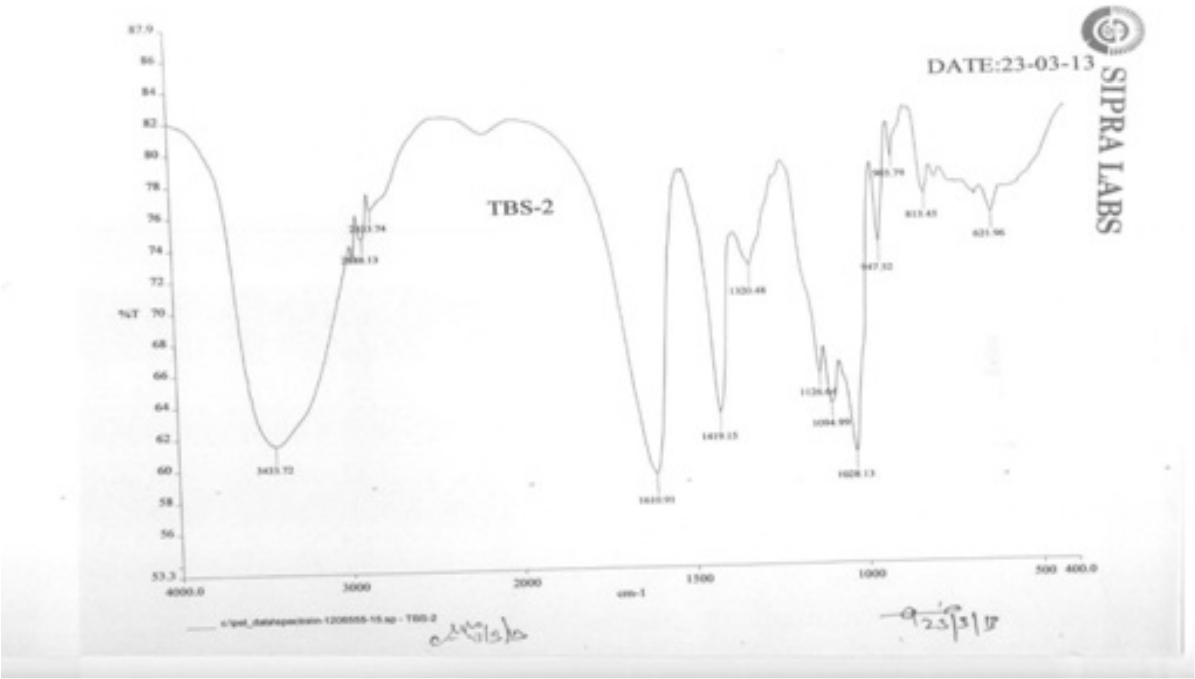

Fig-6: FT-IR Spectra of sodium alginate

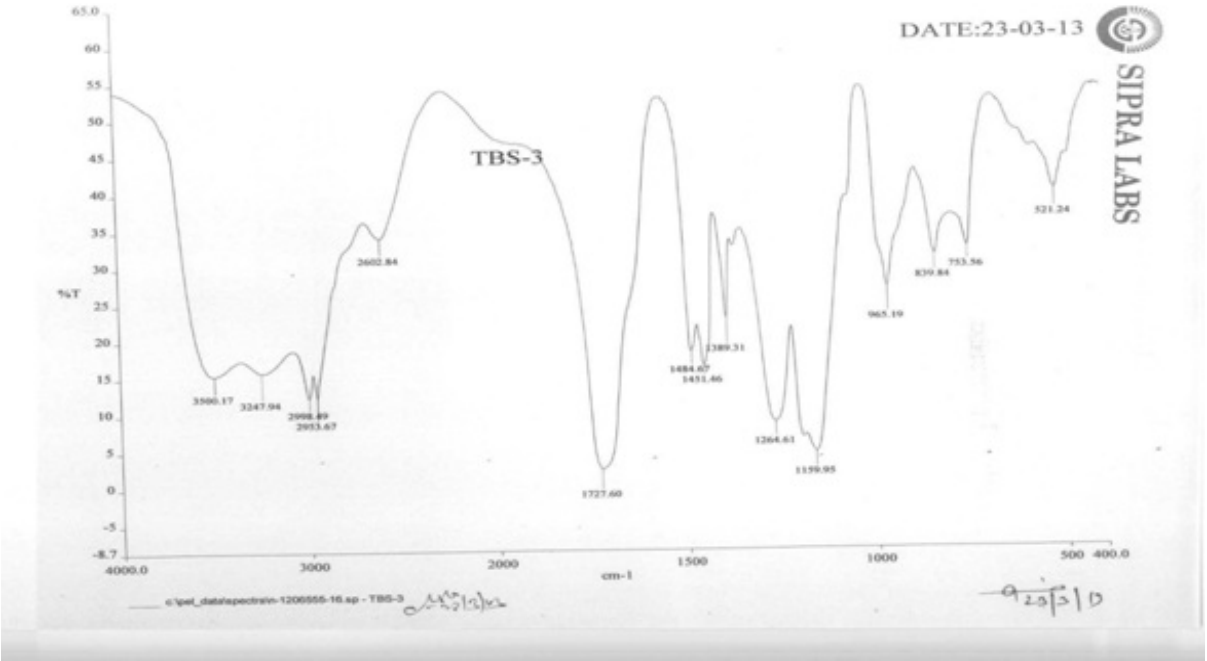

Fig-7: FT-IR Spectra of HPMC

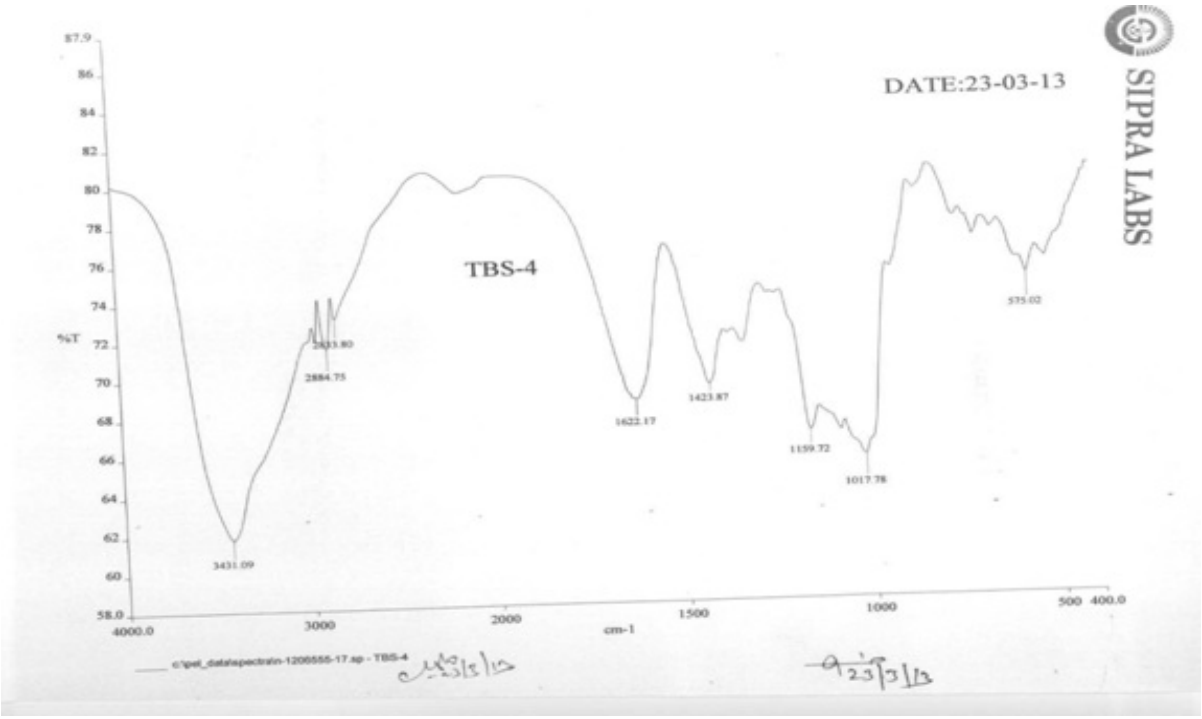

Fig-8 FT-IR Spectra of SCMC

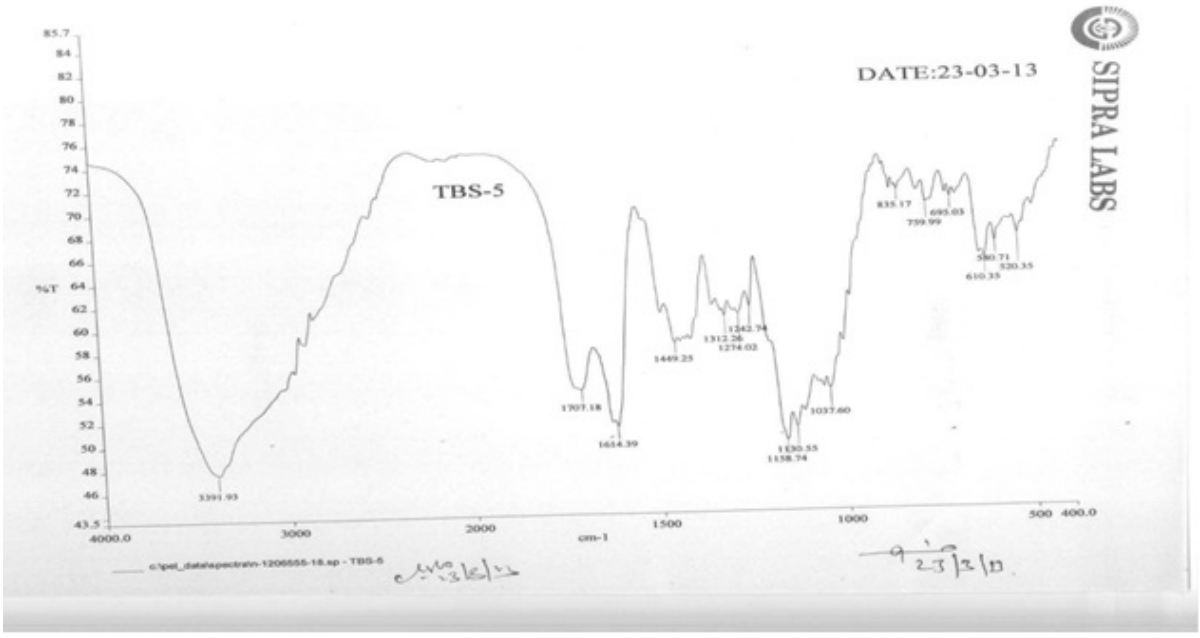

Fig-9: FT-IR Spectra of Terbutaline sulphate+ sodium alginate+ HPMC

Preparation of Terbutaline Sulphate Mucoadhesive Beads

Alginate beads were prepared by Ionotropic external gelation technique. In this process sodium alginate and HPMC, SCMC were dissolved in distilled water with agitation to have ratio of 1:0.5 & 2:0.5. The drug was added to this solution, then the drug suspension was added to solution contain $CaCl_2$ and $Alcl_3$ with different concentrations to cure for 15mins. The drug suspension was added drop wise into this solution using a syringe with neddle. The obtained beads were filtered using Whattman paper filters, washed twice by deionized water and dried at 450C for 48hrs.

Table-1: Formulation table for Terbutaline sulphate Extended Release Beads

S.No	Ingredients	TBS-1	TBS-2	TBS-3	TBS-4	TBS-5	TBS-6	TBS-7	TBS-8
1	Terbutaline	0.5g	0.5g	0.5g	0.5g	0.5g	0.5g	0.5g	0.5g
2	Sodium alginate	1g	2g	1g	2g	1g	2g	1g	2g
3	HPMC K15	0.5g	0.5g	-	-	0.5g	0.5g	-	-
4	SCMC	-	-	0.5g	0.5g	-	-	0.5g	0.5g
5	Calcium chloride	2%w/v	2%w/v	2%w/v	2%w/v	-	-	-	-
6	Aluminium chloride	-	-	-	-	2%w/v	2%w/v	2%w/v	2%w/v

Evaluation of terbutaline sulphate mucoadhesive beads:

Pre-Formulation Parameters:

Pre-compression parameters such as Bulk density, Tapped density, Angle of repose Carr's compressibility index, Hausner's ratio were performed for the powder mixture and the results were tabulated in table-14.

Bulk Density [10-11]

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measured was called as the bulk volume and the bulk density is calculated by following formula;

Bulk density = Weight of powder / Bulk volume

Tapped Density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (V_a) and again tapped for 750 times and volume was noted as (V_b). If the difference between V_a and V_b not greater than 2% then V_b is consider as final tapped volume. The tapped density is calculated by the following formula

Tapped density = Weight of powder / Tapped volume

Carr's Index (Compressibility Index) [12]

It is one of the most important parameter to characteristic the nature of powders and granules. It can be calculated from the following equation

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's Ratio

Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula

Hausner's ratio = Tapped density / Bulk density

HR<1.25-indicates good flow property

HR>1.25-indicates poor flow property

Post- Formulation Parameters[13]

After formulation of desired doses of drug and its excipients into suitable dosage form, each batch was subjected to the evaluation parameters such as drug content, drug loading, percentage encapsulation efficiency, microscopical characteristics of beads, swelling studies and was tabulated in table-15.

Drug Content

Beads were weighed after drying and process yield and desired yield (-22/+44 sieve fraction) were calculated. For determination of drug content, 100-mg beads were triturated and dissolved in 100mL of water. The solution was analyzed spectrophotometrically at 272 nm.

Drug loading

Drug loading was determined by dissolving 25mg of muco adhesive beads in 100 mL of water. The prepared solution was filtered through 45 µm filter paper and assayed spectrophotometrically at 272nm. The drug loading was calculated according to formula;

% drug loading = (Amount of drug in beads/Amount of beads) × 100

Percentage encapsulation efficiency

Percentage encapsulation efficiency was calculated using following formula,

Percentage encapsulation efficiency= AQ / TQ × 1OO

Where AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads.

Microscopical characteristics of beads [14-16]

Mucoadhesive beads of terbutaline were evaluated for particle size by taking 50 beads by using Motic microscope. The average particle size was calculated.

Swelling studies

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug-loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of phosphate buffer (pH 7.2) maintained at 37^0C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

Swelling ratio = weight of wet beads/weight of dried beads

In-vitro dissolution studies

The dissolution of Terbutaline sulphate mucoadhesive beads was studied using USP Type II dissolution apparatus containing 900 ml of phosphate buffer (pH 7.2) maintained at 37 ± 0.5^0C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. These samples were analyzed for the drug present in them with help of UV spectrophotometer (UV- 1700, Pharmaspace and Shimadzu). Only those batches were selected for the release study, which have good drug content and drug entrapment efficiency more than 50%.

Mathematical modeling for drug release profile[17-18]

The cumulative amount of Levamisole released from the formulated tablets at different time intervals were fitted in to several kinetic models such as Zero order kinetics, first order kinetics, Higuchi model and Korsemayer-peppas model to characterize mechanism of drug release. [S.S. Davis et al (1986)]

Results and Discussion

Results:

Table-2: Pre-formulation studies for Terbutaline sulphate

S.No	Testing	Terbutaline sulphate
1	Organoleptic properties	white, odourless, crystalline powder, tasteless
2	Solubility	Slightly soluble in ethanol and methanol, Insoluble in chloroform,
3	Bulk density	0.48gm/cm^3
4	Tapped density	0.62gm/cm^3
5	Compressibility index	22.5 %
6	Hausner's ratio	1.29
7	Angle of repose	$26^0.5^1$

Table- 3: Post formulation studies Terbutaline sulphate mucoadhesive beads

Formulations	Bulk density(g/ml)	Tapped density(g/ml)	Haussner's ratio (%)	Carr's index (%)	Angle of repose (^{0})
TBS-1	0.715	0.740	1.034	3.38	21.80
TBS-2	0.849	0.867	1.02	2.04	18.77
TBS-3	0.788	0.808	1.025	2.5	20.30
TBS-4	0.821	0.884	1.07	7.14	18.26
TBS-5	0.583	0.608	1.043	4.08	22.29
TBS-6	0.565	0.633	1.12	10.75	24.70
TBS-7	0.628	0.668	1.06	5.88	19.29
TBS-8	0.628	0.665	1.06	5.55	27.02

Formulations	Percentage yield (%)	Drug entrapment efficiency (%)	Swelling index(%)
TBS-1	77.9	58.24	56
TBS-2	99.5	75.12	62
TBS-3	87.9	64.26	52
TBS-4	82.5	70.35	59
TBS-5	76.1	76.28	42
TBS-6	90.3	98.25	34
TBS-7	71.6	82.54	22
TBS-8	99.6	90.72	20

Table- 4: Microscopical Studies

Formulations	Particle size(mm)
TBS-1	0.199
TBS-2	0.282
TBS-3	0.277
TBS-4	0.322
TBS-5	0.296
TBS-6	0.320
TBS-7	0.314
TBS-8	0.386

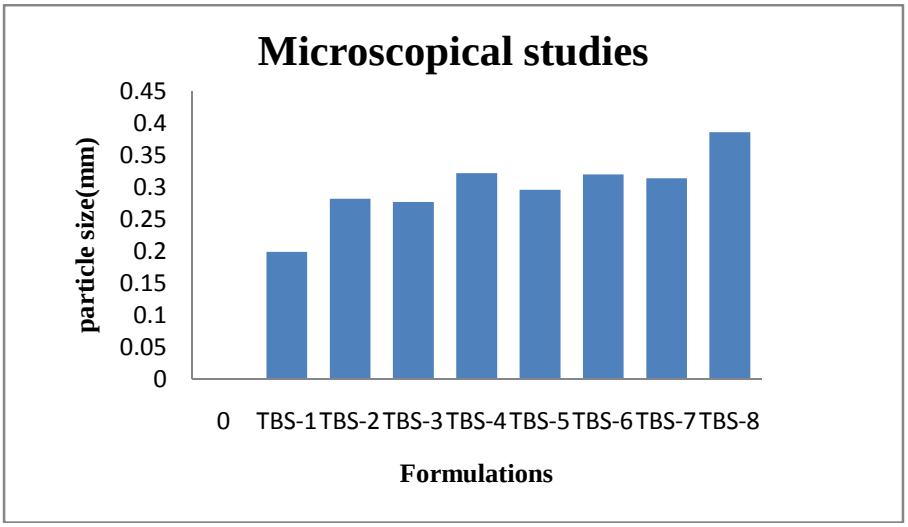

Fig-10: Microscopical studies

Table- 5: In-vitro drug release data for Terbutaline sulphate mucoadhesive beads

S.No	Medium	Time (Hrs)	TBS-1	TBS-2	TBS-3	TBS-4	TBS-5	TBS-6	TBS-7	TBS-8
1	7.2 phosphate buffer	1	9.7	9.5	10.8	9.9	9.2	8.2	9.5	8.2
2		2	20.4	17.9	23.7	20.5	15.8	20.2	16.5	20.4
3		3	29.2	24.8	38.4	28.2	22.4	25.8	24.8	28.6
4		4	38.5	35.8	44.5	36.5	30.8	32.5	38.4	33.8
5		5	48.7	46.8	52.6	42.7	42.4	47.8	48.9	41.8
6		6	52.4	58.7	68.7	56.9	55.8	53.6	56.3	58.5
7		7	65.1	66.5	73.4	63.2	64.7	60.2	62.5	68.2
8		8	77.9	75.6	84.3	75.6	72.3	66.4	69.4	74.8
9		9	85.6	84.6	98.0	84.7	85.4	76.9	89.8	80.5
10		10	97.4	89.5	-	97.5	92.5	80.3	97.4	92.8
11		11	-	98.6	-	-	98.2	92.4	-	97.8
12		12	-	-	-	-	-	98.8	-	-

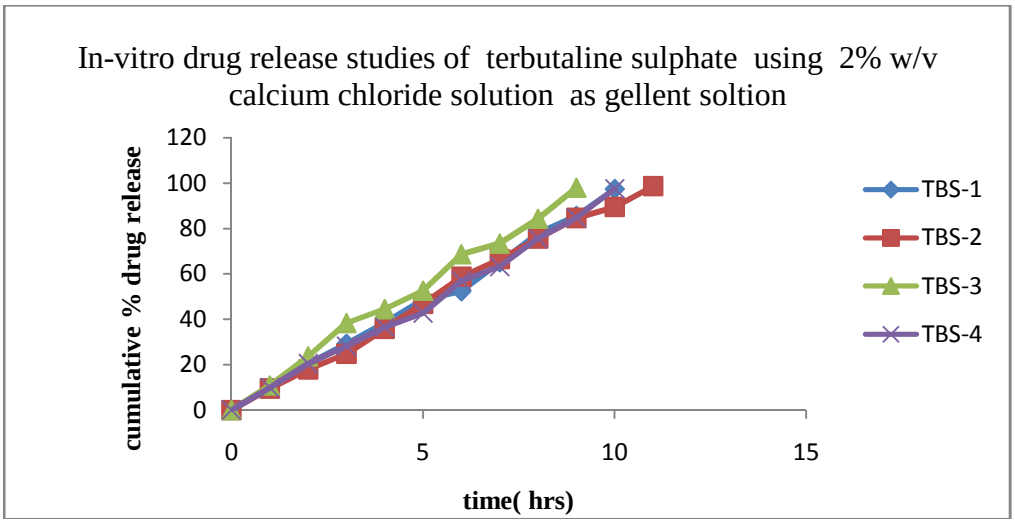

Fig-11 Cumulative % drug release data for TBS-1, TBS-2, TBS-3, TBS-4 formulations

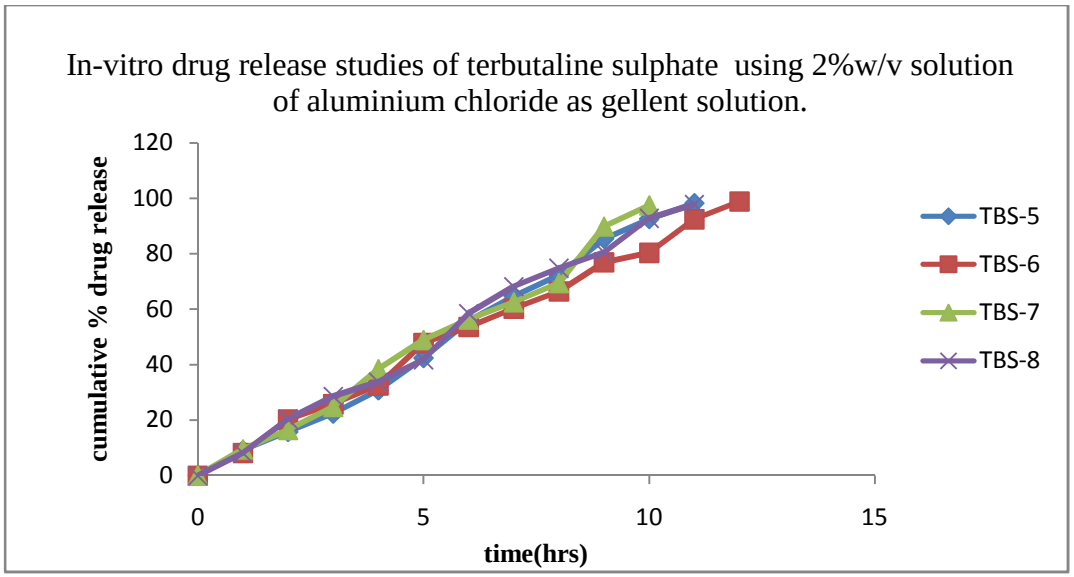

Fig-12 Cumulative % drug release data for TBS-5, TBS-6, TBS-7, TBS-8 formulations

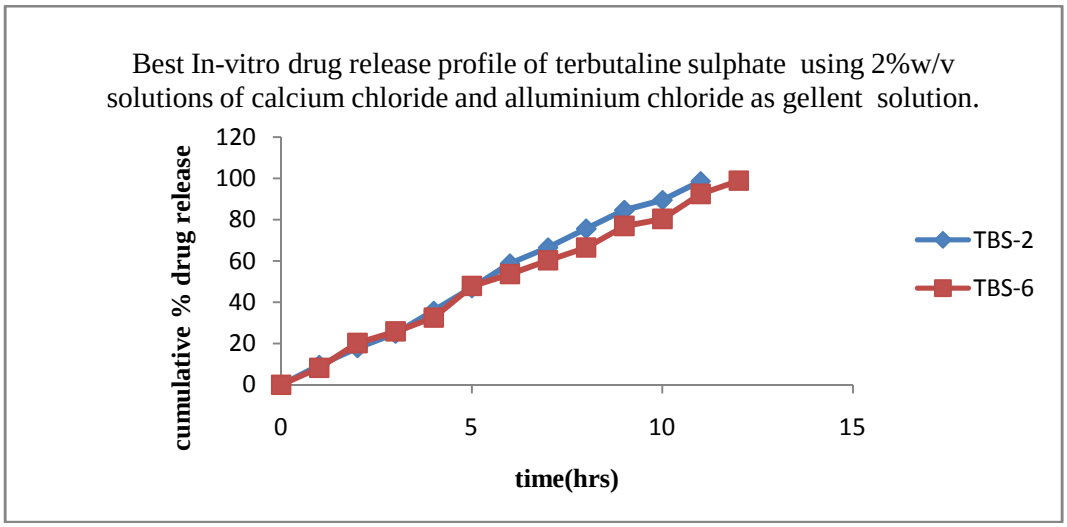

Fig-13: Cumulative % drug release data for TBS-2, TBS-6 formulations

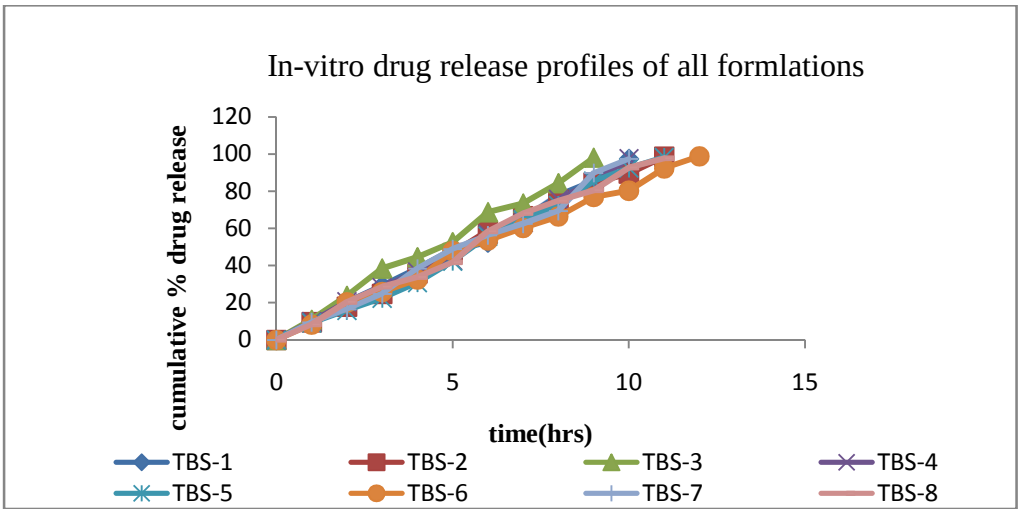

Fig-14 Cumulative % drug release data for all TBS formulations

Table-6: Parameters and determination coefficients of release profile from Terbutaline sulphate mucoadhesive beads

Formulation code	Correlation Coefficient values (R^2)				Diffusion Exponent value(n)
	Zero Order	First order	Higuchi	Korsemayer-peppas	
TBS-1	0.996	0.773	0.911	0.907	0.098
TBS-2	0.996	0.791	0.922	0.833	1.415
TBS-3	0.993	0.751	0.927	0.992	0.967
TBS-4	0.995	0.753	0.903	0.807	1.425
TBS-5	0.994	0.820	0.898	0.849	1.434
TBS-6	0.994	0.753	1	0.991	0.971
TBS-7	0.990	0.764	0.895	0.992	1.03
TBS-8	0.993	0.828	0.918	0.991	1.016

Table-7: Stability results of Terbutaline sulphate mucoadhesive beads (organoleptic properties)

(Batch -1) Week	Temperature and relative humidity (25°C/60%RH)		
	Size and shape of capsules	Goss nature of capsules	Colour of capsules
0	Regular ‘00	Smooth	Reddish brown
2	No change	Smooth	Reddish brown
4	No change	Smooth	Reddish brown
6	No change	Smooth	Reddish brown
8	No change	Smooth	Reddish brown
10	No change	Smooth	Reddish brown
12	No change	Smooth	Reddish brown

Table-8 Stability results of Terbutaline sulphate mucoadhesive beads (Batch-2)

(Batch -2) Week	Temperature and relative humidity (40°C/70%RH)		
	Size and shape of capsules	Goss nature of capsules	Colour of capsules
0	Regular ‘00	Smooth	Reddish brown
2	No change	Smooth	Reddish brown
4	No change	Smooth	Reddish brown
6	No change	Smooth	Reddish brown
8	No change	Smooth	Reddish brown
10	No change	Smooth	Reddish brown
12	No change	Smooth	Reddish brown

Table-9 Stability results of Terbutaline sulphate mucoadhesive beads (Batch-3)

(Batch -3) Week	Temperature and relative humidity (60°C/80%RH)		
0	**Size and shape of capsules**	**Goss nature of capsules**	**Colour of capsules**
2	Regular '00	Smooth	Reddish brown
4	No change	Smooth	Reddish brown
6	No change	Smooth	Soft spot
8	No change	Smooth	Soft spot
10	No change	Sticky Beads	Discoloration
12	No change	Sticky Beads	Discoloration

Table-10 Stability studies In-vitro dissolution profile of TBS –6

S.No	Medium	Time(hrs)	% drug release of TBS		
			Batch-1 (25°C/60%RH)	**Batch-2 (40°C/70%RH)**	**Batch-3 (60°C/80%RH)**
1	7.4 pH phosphate buffer	1	8.4	9.2	10.4
2		2	19.4	22.3	19.9
3		3	23.8	29.9	28.7
4		4	30.5	34.3	40.4
5		5	45.3	50.4	49.9
6		6	52.1	59.9	63.2
7		7	60.2	65.2	67.8
8		8	64.7	71.1	79.9
9		9	74.8	77.8	80.8
10		10	84.2	89.9	90.1
11		11	90.2	97.3	97.5
12		12	97.9		

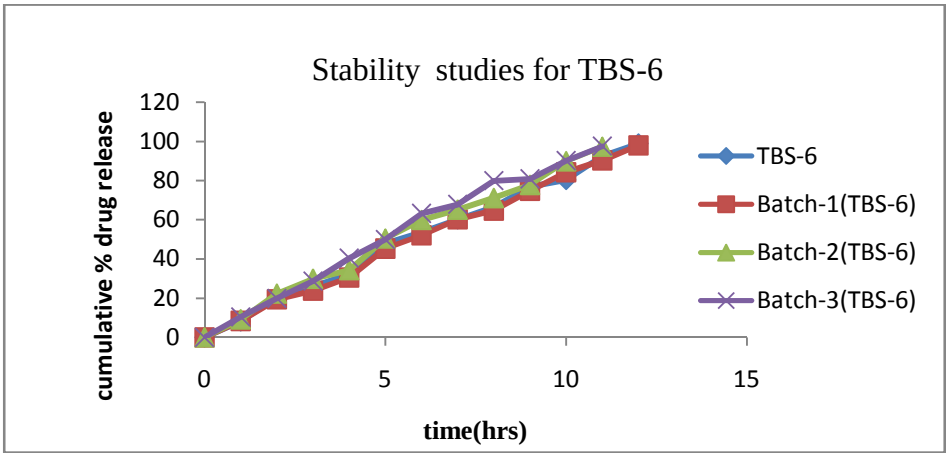

Fig-15 Stability studies for TBS-6

Discussion

The mucoadhesive beads of Terbutaline sulphate were prepared by using ionotropic external gelation technique. In this technique sodium alginate has been used in various proportions viz 1, 2% w/v, 0.5%w/v of HPMC, 0.5%w/v SCMC and calcium chloride (2%w/v), aluminium chloride (2%w/v) as gellant solutions. A total number of eight formulations were prepared by using the same technique and the following results have been obtained.

Compatibility studies:

The drug polymer interaction was studied by infrared spectroscopy. The IR spectra were recorded between 500 to 3100 cm^{-1} for pure Terbutaline sulphate,1020 to 3500cm^{-1} pure alginate ,650 to 3000cm^{-1}pure HPMC ,1000 to 3500cm^{-1}pure SCMC, 500 to 1760 cm^{-1}mixture of Terbutaline and sodium alginate ,HPMC,SCMC in KBr pellets, using perkin Elmer-883 IR spectroscopy. From the results, it was found that there is no incompatibility between the Terbutaline sulphate and other excipients by observing the characteristic peaks. The characteristic peaks were given in the table .The results are given in spectrum 5 to 9.

Density and flow properties:

The results of pre compression and post compression parameters like bulk density, tapped density, carr's index, and porosity has been listed in table no-2. From the results it has been found that the flow property of beads has been increased when compared to pure Terbutaline sulphate. The increase in flow property may be due to decrease in cohesiveness between the particles.

Morphology and particle size:

Morphology of various formulations of alginate beads prepared was found to be discrete and spherical in shape. The SEM photographs of the dried alginate beads was shown in fig-18-21.The surface of the alginate beads when prepared with calcium chloride as a gellant solution was found to have rough surface. It may be due to higher concentration of drug ununiformly dispersed in alginate matrices. In the same way when the beads were prepared with aluminum chloride as a gellant solution, the surface of beads have found to be smooth when compared to the beads prepared with calcium chloride as a gellant solution. This may be due to more incorporation efficiency of Terbutaline. The mean particle size of various formulations of alginate beads was found to be 0.199 to 0.386mm. It was found that the particle size distribution of each formulation was within a narrow range, but the mean particle size was different among the formulation which was given in table no-4 and fig no.10. The results indicated the proportional increase in mean particle size of the beads with increasing amount of sodium alginate in the formulations TBS-1 to TBS-8. This could be attributed to an increase in relative viscosity at higher concentration of sodium alginate and formation of large droplets during addition of the polymer solution to gelling agents.

Incorporation effeciency:

The incorporation efficiency increased progressively with increase in sodium alginate concentration and results were tabulated in table no-3. The incorporation efficiencies were generally higher for the formulations crosslinked with $Al^{3+,}$, this may be due to formation of larger beads with formulation crosslinked with $Al^{3+,}$ entrapping greater amount of drug.

***In-vitro* dissolution:**

To study the effect of polymers on terbutaline sulphate, various concentrations of sodium alginate viz 1, 2% w/v, 0.5% of HPMC, 0.5% SCMC has been with calcium chloride (2%w/v) and aluminium chloride (2%w/v) as gellant solutions. The release profiles for these formulations were shown in Table no-5 and fig 11-14. The results indicated that the release has been retarded with increase in concentration of sodium alginate with alminium chloride as gellant solution. The release behavior of sodium alginate beads produced by ionotropic external gelation technique with different gelling agents depend upon valence and size of cations of respective cross linking agent. The results obtained can be explained on the basis of the extent of cross linking in the beads. Ca^{2+} being a divalent, it forms two dimensional bonding structures with sodium alginate inside the alginate matrices. This leads to faster release of Terbutaline from the beads and this may be due rapid removal of Ca^{2+} as calcium phosphate from the beads due to ion exchange process with Na^{2+} of phosphate buffer medium of and thus leading to greater uptake of buffer and fast release. But in case of Al^3 alginate beads, the delay in release due to the ability of Al^{3+} to form three dimensional bonding structures with sodium alginate inside the beads. This three dimensional bonding results in an extended cross linking through the whole bead producing hard alginate beads and thus leading to slow removal of Al^{3+} due to ion exchange with Na^{2+} in phosphate buffer. As a result the swelling of beads are delayed leading to slow disintegration. Moreover the formulations prepared by using sodium alginate and SCMC released the drug at a faster rate than the formulations prepared by using sodium alginate and HPMC. Hence TBS-6 (Sodium alginate 2%w/v, HPMC 0.5%w/v with aluminium chloride (2%w/v) as gellant solutions) was found to be the best formulation which retarded the drug release for 12 Hrs.

***In -Vitro* Drug Release Kinetics**

Hence different model dependent approaches (Zero order, First order, Higuchi, Korsemayer- Peppas plots) were performed for dissolution profile comparison of all formulations (Tables-6) (fig 26-57). The results of these models indicate all mucoadhesive beads filled in capsules follows zero order as "best fit model". This is due to previously proved fact depending on R^2 value obtained from model fitting. From the results TBS-6 showed more release retarding effect. Korsemayer - Peppas release exponent (n) values of Terbutaline sulphate mucoadhesive beads are greater than 0.85 indicating Super case 2 transport.

Stability studies

The stability tests were conducted on TBS-6 which is considered to be the best. The formulation was analyzed for its organoleptic properties and dissolution profile for a period of 12 weeks. The results showed that the colour of capsules and gross nature of beads were slightly changed for batch -3 (which is kept at 60^0c/80 % RH). No change was found for batch -1 (which is kept at 25^0c / 60 % RH) and batch -2(which is kept at 40^0c / 70 %RH). The percentage drug release was found to be faster after twelve weeks for batch -3(which is kept at 60^0c/80 % RH), shown in fig: 15. The results are tabulated in table no: 7-10.

Conclusion

From the research, it was concluded that the proper selection of formulation conditions is very important to achieve high encapsulation efficiency and to control the release of Terbutaline from alginate beads. From in-vitro dissolution

studies it was observed that with increase in concentration of sodium alginate with SCMC released the drug at a faster rate than the formulations prepared with increasing in concentration of sodium alginate with HPMC. Moreover the beads prepared with the help of aluminium chloride 2%w/v as gellant solution formed harder beads. When compared with the beads prepared with the help of calcium chloride 2%w/v as gellant solution. More investigations has to be employed further to prepare most successful formulations of Terbutaline sulphate.

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