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FORMULATION AND EVALUATION OF BIPHASIC DRUG DELIVERY SYSTEM OF TERBUTALINE SULPHATE FOR CHRONOTHERAPY

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ABSTRACT

Terbutaline sulphate is a β_2-adrenergic agonist bronchodilator used to treat bronchospasm (wheezing, shortness of breath) associated with lung diseases such as asthma, bronchitis, and emphysema. Bioavailability of terbutaline sulphate about 14.8 %. The drug half life is 3-4 hrs.. So in order to improve the bioavailability and efficacy we have designed granules and tablets filled in HPMC capsule system, which is presented as a biphasic delivery system. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a sustain release. Fast releasing component comprises superdisintegrant croscarmellose sodium, while mini-tablet was formulated using different concentration of HPMC and Ethyl cellulose to obtain different drug release rates. The *In-vitro* performance of these systems showed the desired biphasic behaviour. The drug contained in the fast releasing phase (Granular powder) dissolved within the first 5 min, whereas the drug contained in the mini-tablets was released at different rates, depending upon composition of mini tablets. The prepared tablets were subjected for post-compression parameters. The compatibility of drug with other ingredients was checked by FTIR and DSC studies. FTIR and DSC results revealed that there was no interaction between drug and other excipients. All the pre and post-compressional Parameters were evaluated and the results were within acceptable limits. The *in-vitro* performance of our best tablet filled HPMC capsule system showed the desired behavior, the drug contained in the granules for immediate release dissolved within the first 5 min, whereas the drug contained in the sustained release tablets was released over a period of 10 to 12 hrs. Based on the release kinetic parameters calculated, it can be concluded that tablets containing HPMC and EC were particularly suitable approaching to sustain or prolong release over 10-12 hrs time periods. From this, study it can be concluded that, granules and tablets filled in HPMC capsule systems containing Terbutaline sulphate shows that both sustained release as well as immediate release may improve the bioavailability and efficacy.

KEYWORDS: Sustained release, Terbutaline sulphate, tablets filled capsule system, immediate release, hydroxy propyl methyl cellulose, ethyl cellulose, HPMC capsule.

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INTRODUCTION

Terbutaline sulphate is a β_2-adrenergic agonist bronchodilator used to treat bronchospasm (wheezing, shortness of breath) associated with lung diseases such as asthma, bronchitis, and emphysema. Bioavailability of terbutaline sulphate about 14.8 %. The drug half life is 3-4 hrs.So in order to improve the bioavailability and efficacy we have designed tablets filled HPMC capsule system[1-5]. Compressed mini-tablets systems are presented as a biphasic delivery system. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a sustained release. Fast releasing component comprises superdisintegrant croscarmellose sodium, while mini-tablet was formulated using different concentration of HPMC and Ethyl cellulose to obtain different drug release rates. The *In-vitro* performance of these systems showed the desired biphasic behaviour[6]. Prepared immediate release granules and sustained release mini tablets are filled in the HPMC capsule. The advantage of the HPMC capsule is that the HPMC capsules exhibited lower moisture contents compared to gelatin capsules (*e.g.* 6% and 14% respectively at 50% RH) that have shown to be more hygroscopic. The main advantage of HPMC capsules over gelatin capsules could be because of their vegetable source which has wider customer acceptance. Hindus or Buddhists for example rely on vegetable sources for their nutrition[7-11]. The drug contained in the fast releasing phase (Granular powder) dissolved within the first 5 min, whereas the drug contained in the mini-tablets was released at different rates, depending upon composition of mini tablets [12-13].

Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides release vice versa[14].

Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents[15]. Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. While immediate release granules give fast release to provide rapid onset of action, but fails to provide longer duration of action. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract[16]. On the basis of these considerations, we have proposed a new oral delivery device, in the form of a double-component tablet and granules, in which the one portion is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second portion is a sustain release matrix, which is designed to maintain an effective plasma level for a prolonged period of time[17]. This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipients powder that fills The void spaces between the mini-tablets incorporate a part of the total drug dose. This system can produce a rapid rise in the plasmatic concentrations for some drugs (such as analgesic, anti-inflammatory, anti hypertensive and antihistaminic agents) that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations[18]. Compressed mini-tablets systems are presented as a biphasic delivery system. Granules and tablet filled HPMC capsule system were shown in below Fig-1.

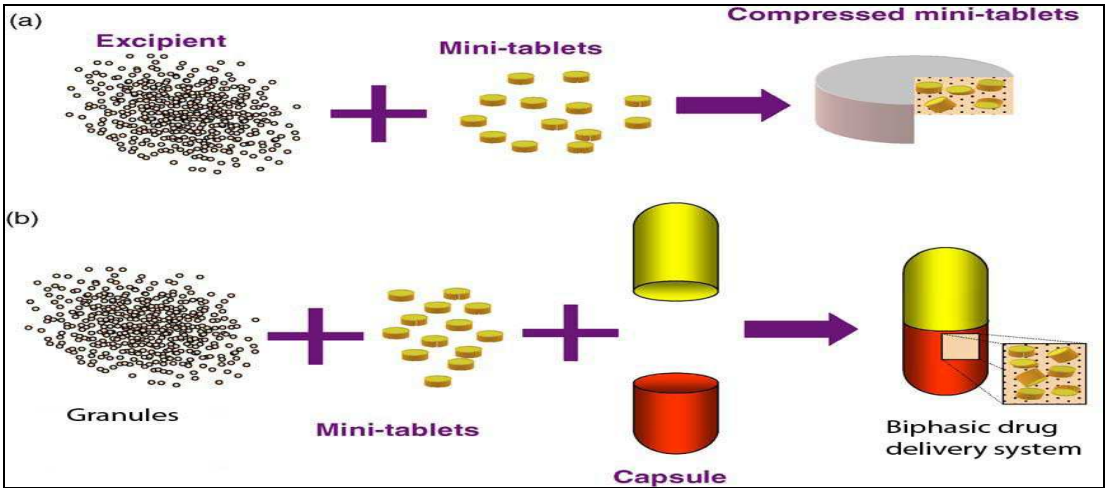

Figure 1
Granules and tablet filled HPMC capsule system

MATERIALS AND METHODS

Materials

Terbutaline sulphate (Gifted by Franco Indian Pharmaceuticals Ltd.) was incorporated in both components of the biphasic delivery system. For the preparation of the sustained release component (mini-tablets), Ethyl cellulose (EC, Ethocel,) and hydroxy propyl Methylcellulose (HPMC, Methocel) were considered, whereas for the fast release component, Microcrystalline Cellulose (Avicel PH 102) and sodium croscarmellose were used. Both components were encapsulated in the HPMC capsules (Gifted by Associated Capsule Limited).

Immediate release granules component (Granules): Microcrystalline cellulose (Avicel PH 102) was used because of its good compaction and disintegration properties. croscarmellose sodium was used as a super disintegrant to obtain an immediate release of the drug. The granules were prepared by wet granulation method. The composition of immediate release granules were mentioned in Table 1.

Table 1
Composition of immediate release granules (quantities in mg).

Ingredients	Quantity (mg)
Terbutaline sulphate	1.5
Croscarmellose sodium	12
Microcrystalline cellulose	50
Mannitol	46.5
HPMC (5 cps)	20
Mg. stearate	2
Total Weight	**120**

Sustained-release tablet component (SRT): The SRT contained various EC to HPMC ratio (60:40, 70:30, 75:25 80:20, 85:15) as controlling agents. The ingredients consisting of Terbutaline sulphate, lactose, HPMC (5 cps), ethyl cellulose were passed through 60 mesh (250 µm) separately and dry mixed. The dry mixing was carried at a slow speed for 10

min and the blend was granulated with 10% w/v alcoholic solution of PVP K-30 for 5 min. The resulting wet mass was immediately passed through a 16 mesh screen (1000 µm). The granules obtained were dried for 1 hrs in a thermostatic hot air oven maintained at 30-35° C to a moisture content of 2 to 3 %. The dried granules were passed through the same sieve (1000 µm) to break the lumps and blended with magnesium stearate and talc. The lubricated granules were compressed into tablets weighing 120mg using 6.3 mm round convex punches in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavati engineering, Ahmadabad) to a hardness of 3 kg/cm^2. The qualitative and quantitative composition of the different formulations of the sustain release tablet can be seen in Table 2.

Table 2
Composition of sustain release tablet (quantities in mg).

FC	SRT-1	SRT-2	SRT-3	SRT-4	SRT-5
TBS	2	2	2	2	2
HPMC(5 cps)	40	30	25	20	15
Ethyl Cellulose	60	70	75	80	85
Lactose	16	16	16	16	16
Magnesium stearate	2	2	2	2	2
Total weight (mg/tab)	120	120	120	120	120

Granules and Tablets filled HPMC capsule system (GTFCS): The tablets filled HPMC capsule system comprises immediate-release granules and 3 sustained-release tablets. The compositions of various GTFCS are mentioned in Table 3.

Table 3
Composition of Tablet Filled HPMC capsule Systems [GTFCS]

Formulation code	Composition
GTFCS- 1	**Granules : SRT-1:SRT-2:SRT-3**
GTFCS – 2	**Granules : SRT-1:SRT-3:SRT-4**
GTFCS – 3	**Granules : SRT-1:SRT-2:SRT-5**
GTFCS – 4	**Granules : SRT-1:SRT-4:SRT-5**

Evaluation of granules

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, which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:

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

Where, 'θ' is the angle of repose
'h' is the height of pile, 'r' is radius of base of pile.

Bulk density and tapped density:
Both loose bulk density and tapped bulk density were determined. A quantity of 2 gm of granules from each formula, previously light shaken for the break of any agglomerates formed, was introduced into the 10ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec intervals. The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas.

$$LBD = \frac{\text{Weight of the powder}}{\text{volume of the packing}}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

Compressibility index: The compressibility index of the granules was determined by carr's compressibility index.

$$\text{Carr's index} = \frac{(TBD-LBD)}{TBD} \times 100$$

Where, LBD= Weight of the powder/volume of the packing.
TBD= Weight of the powder/Tapped volume of the packing.

Hausner's ratio: Hausner's ratio can be determined by the following equation,

$$\text{Hausner's ratio} = \frac{TBD}{LBD}$$

Where, TBD= Tapped bulk densities and LBD= Loose bulk densities.

Evaluation of tablets
Hardness test: The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability: A friability test was conducted on the tablets using friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the mini-tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$F = [(W_{initial} - W_{final})/ W_{initial}] \times 100$
% Friability of tablets less than 1% is considered acceptable.

Weight variation: The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The specification of weight variation is 10%.
Uniformity of thickness: The tablet thickness was measured using screw gauge.

Estimation of drug content: Drug content of prepared tablet of each batch of the formulation was determined. From each batch 20 tablets were taken, weighed and finely grounded. An amount of powder equivalent to 5 mg of powder was accurately weighed and dissolved in 6.8 phosphate buffer. The resulting solution was suitably diluted and analysed on UV spectrophotometer Shimadzu 1601 at 278 nm[19].

Dissolution testing: Dissolution test of Terbutaline Sulphate was performed in 6.8 phosphate buffer at 50 rpm using USP

dissolution test apparatus type II (paddle type). 5 ml aliquots were withdrawn with a pipette and replaced with 5 ml fresh dissolution medium at different time intervals. The aliquots were passed through Whatman filter paper number 41 to remove any suspended impurity which may interfere during spectroscopic estimation. The absorbance of samples was taken on UV spectrophotometer (Shimadzu 1601) at 278 nm against blank and correspondingly concentration of the drug was determined at various time intervals[20].

Drug excipients interaction studies:

FTIR Studies: IR spectra for pure drug Terbutaline Sulphate, Terbutaline Sulphate immediate release granules and sustained release tablets SRT-4, SRT-5 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC Studies: 5 mg of pure Terbutaline Sulphate, Terbutaline Sulphate immediate release granules and sustained release tablets SRT-4, SRT-5 were sealed in perforated aluminium pans for DSC scanning using an automatic thermal analyzer system (Mettler Toledo, USA). Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10^0 C/min from 50-300^{0}C.

RESULTS AND DISCUSSION

Evaluation of sustained release granules

The prepared sustain release granules were subjected for various pre-compressional evaluations such as LBD, TBD, and compressibility index, Angle of repose and hausner's ratio. For SRT granules LBD ranged from 0.51 to 0.54 and TBD ranged from 0.60 to 0.67. Compressibility index values ranges from 15.00 to 22.39 %. Angle of repose of granules of all formulations ranged from 22.72 to 26.23. All these results are given in Table 4 and Table 5 indicates that the formulated granules possessed satisfactory flow properties and compressibility.

Table 4
Evaluation of SRT Granules

Tablet code	Angle of repose (degree) ± SD, n=3	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	carr's index (%), n=3	Hausner's ratio ± SD, n=3
SRT-1 Granules	24.12±0.12	0.53±0.006	0.65±0.022	18.46±0.12	1.23±0.009
SRT-2 Granules	22.72±0.61	0.52±0.006	0.67±0.009	22.39±0.10	1.29±0.013
SRT-3 Granules	25.43±0.45	0.54±0.005	0.65±0.034	16.92±0.11	1.20±0.002
SRT-4 Granules	23.49±0.79	0.51±0.006	0.60±0.019	15.00±0.30	1.18±0.016
SRT-5 Granules	26.23±0.27	0.54±0.005	0.65±0.011	16.92±0.08	1.20±0.004

Table 5
Evaluation of SRT

Tablet code	Thickness (±SD), n=6	Diameter (mm) (±SD), n=6	Hardness (kg/cm^2) (±SD), n=6	Friability (%)	Average weight (mg) (±SD), n=20	Drug Content (%) (±SD), n=6
SRT-1	3.01 ± 0.76	6.3 ± 0.01	3.02 ± 0.07	0.46	120 ± 0.78	97.22 ± 0.59
SRT-2	2.92 ± 0.078	6.3 ± 0.03	3.11 ± 0.08	0.58	120 ± 1.03	97.01 ± 0.49
SRT-3	2.67 ± 0.048	6.3 ± 0.05	3.07 ± 0.61	0.48	120 ± 0.79	96.90 ± 0.82
SRT-4	2.67 ± 0.098	6.3 ± 0.07	2.85 ± 0.10	0.49	120 ± 0.83	99.02 ± 0.73
SRT-5	2.97 ± 0.062	6.3 ± 0.09	2.80 ± 0.13	0.53	120 ± 0.84	99.97 ± 0.66

Evaluation of sustained release tablet (SRT)

A separate *in-vitro* dissolution testing was performed for only IRT tablets. The results of *in-vitro* drug release studies of SRT are given in Table 6 and graphical representation is shown in Fig 2. These results demonstrate that the dissolution rate and extent of drug release decreased with increasing ethyl cellulose content in the tablets. Hence, the most suitable sustained-release tablet seems to be SRT-5 releasing 99.97% of Terbutaline sulphate within 12 hrs.

Table 6
In-vitro release study of sustained-release tablets (SRT).

Time (hrs)	SRT-1	SRT-2	SRT-3	SRT-4	SRT-5
0	0	0	0	0	0
1	27.16	20.71	17.86	12.15	7.40
2	59.92	37.94	34.13	25.47	16.17
3	81.58	62.45	51.04	37.41	24.09
4	98.38	76.83	67.21	49.88	30.54
5	--	89.72	78.52	61.29	39.10
6	--	97.01	87.82	73.97	46.50
7	--	--	96.90	88.98	51.99
8	--	--	--	99.02	65.10
9	--	--	--	--	73.23
10	--	--	--	--	82.32
11	--	--	--	--	90.14
12	--	--	--	--	99.97

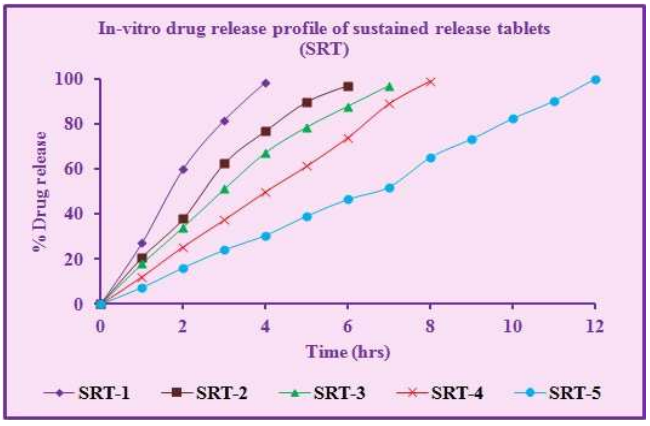

Figure. 2
In-vitro drug release profile of sustained release tablets (SRT)

A biphasic oral delivery system was developed by compressing granules and mini-tablets into a HPMC capsules. The compressed mini-tablets showed slight deformation and no fragmentation. Because of their physical characteristics, mini-tablets tend to keep their integrity after compression, making more difficult the fracturing process of

these subunits. This technology may be achieved by fast/slow delivery system. This is characterized by an initial rapid release phase, corresponding to the drug release contained in the powder layer filled between mini-tablets, followed by a period of slow release, corresponding to the drug release of mini-tablets. The proposed fast/slow delivery devices show a wide flexibility in the modulation of the delivery program.

TBS is rapidly absorbed and excreted in the urine. In order to develop an optimized sustained release dosage forms, we tested GTFCS comprising different release profile of granules and tablets (SRT) in a HPMC capsule (size 0). The results revealed that formulation GTFCS-4 was releasing 31.51% of Terbutaline sulphate within an hour as an immediate release phase and the sustained release phase was prolonged for a period of 12 hrs, and it is found to be the most suitable combination to have an immediate as well as sustained release of drug. The drug release results of GTFCS are given in Table 7 and the graphical representation is shown in Fig 3. Hence, it was considered as the best formulation releasing Terbutaline sulphate both as an immediate and sustained-release phase.

Table 7
In-vitro release study of Granules and tablet filled HPMC capsule system (GTFCS).

Time (In Hours)	GTFCS - 1	GTFCS - 2	GTFCS - 3	GTFCS - 4
0	0	0	0	0
1	38.75	35.23	31.72	31.51
2	54.56	51.25	46.29	39.68
3	71.40	64.68	56.93	50.73
4	84.00	76.77	68.30	60.14
5	90.41	82.56	75.95	69.54
6	95.16	88.34	80.18	75.22
7	98.47	94.23	85.45	80.70
8	--	99.09	90.10	87.10
9	--	--	94.13	91.13
10	--	--	96.92	93.51
11	--	--	99.50	95.68
12	--	--	--	99.09

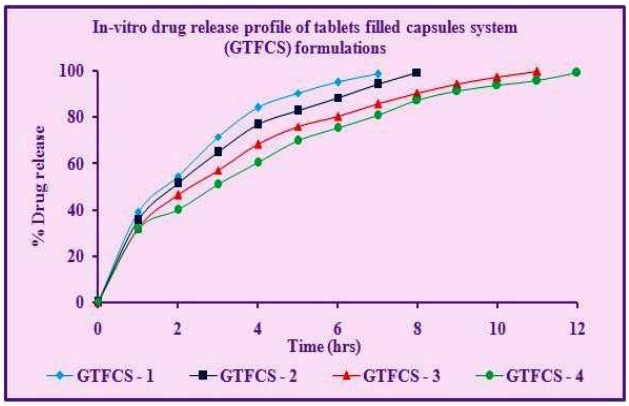

Figure 3
In-vitro drug release profile of Granules and tablet filled HPMC capsule system

The IR spectrum of the pure drug TBS and immediate release granules, SRT-4 and SRT-5 formulations were shown in Fig 4. In the IR spectrum of the pure drug TBS showed characteristic absorption bends The spectrums are in the following IR region..

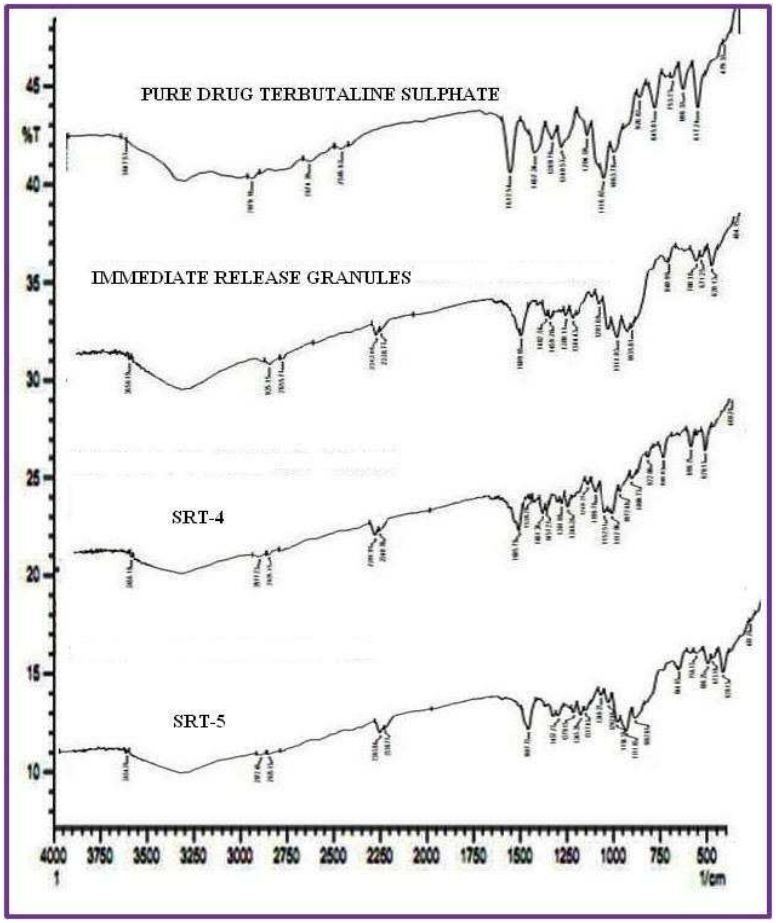

Figure 4
IR Spectra of pure Terbutaline sulphate, Immediate release granules, SRT-4 and SRT-5 formulations.

TBS: **3300-3400** a broad peak of OH and NH hydrogen bond
3070 aromatic C-H stretching
2979-2858 C-H stretching of CH3 and CH2 group
1612 C=C ring stretching
1612 and **1482** C-H bending of CH_3 and CH_2 group
1389 and **1340** CH bending of CH_2 and CH_3 group
1205 O-H bending
846 substituted phenyl ring.

SRT-4 and SRT-5 formulations*:* Shows a broad peak at 3300 is due to OH and NH group H bonded of the drug and the polymer
2926-2856 CH bending of CH_2 and CH_3 groups
1610-1459 stretching of c=c
1362-1348 CH bending of CH_2 and CH_3 groups
1201 O-H bending
849 substituted phenyl ring.

In the present study the IR spectra of the pure drug and formulation indicate that the characteristic absorption bends of the various functional groups and bends present in the spectrum of the drug also appeared in the IR spectra of the formulations involving the drug with different polymers used for the preparation of formulations.

It is clear from the study that there is no significant change in the positions of the characteristic absorption bends in the spectra of the drug and its various formulations, This results suggests that there is no interaction of the drug with the various polymers used for the preparation of different formulations.

Generally, IR and DSC spectra studies are used to establish physical characteristic of the drug, so as to know whether it interacts with the polymers or undergoes any type of change during the process of formulation. DSC thermo grams are taken for pure drug TBS and its various formulations to know the thermal behavior of the drug in its pure form, in the behavior of the drug in its pure form and also in the form of its various formulations. The DSC thermograms of the pure drug TBS and immediate release granules, SRT-4 and SRT-5 formulations are shown in Fig 5.

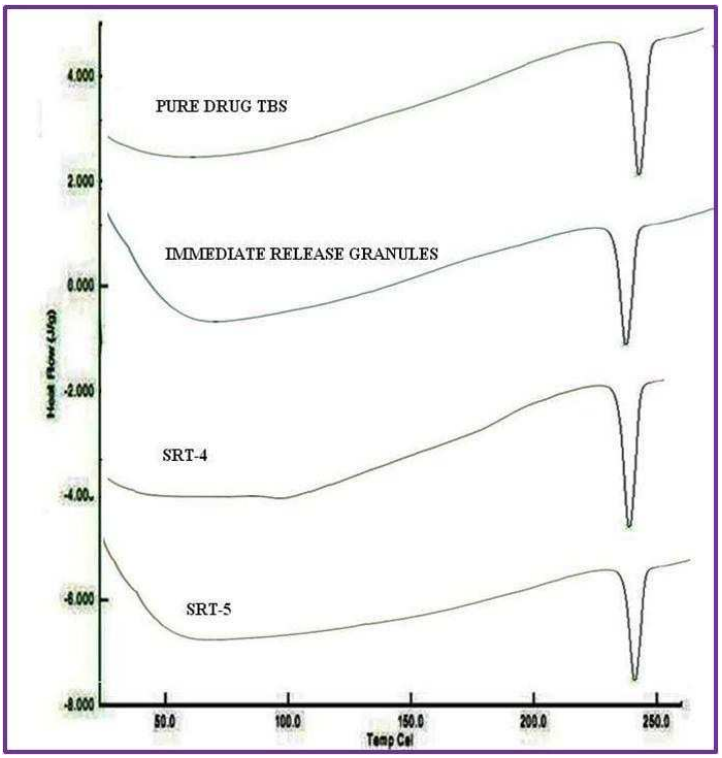

Figure 5
DSC thermograms of pure Terbutaline sulphate, immediate release granules, SRT-4 and SRT-5 formulations.

The study revealed that the thermo gram of the pure drug shows an endothermic peak in the range of 246-250^{o}C and the value approaches 248^{o}C. The endothermic peak clearly establishes the fact that the melting point observe with the DSC thermo gram is in agreement with reported literature value. It is also confirmed that the drug used is in its pure form. These thermo grams of all formulations with the polymers were also taken for this study.

It is quite interesting to note that irrespective of the polymer used the thermo grams exhibit the sharp endothermic peak with negligible change in the same range of 246-250^{0}C.

There is appreciable change in the melting point range of the formulations in comparison with the pure drug. It establishes the fact that the drug remains in the same normal state even in various formulations. Thus the DSC thermo grams study reveals that there is no kind of interaction of the drug with different types of polymer and thier excipients used during the study.

CONCLUSION

A novel biphasic granules and tablets filled in HPMC capsule system was developed by filling granules and mini-tablets into an empty HPMC capsule shell which releases 31 to 38% of the total dose within 60 min. Formulations GTFCS-1 to GTFCS-4 releases the drug up to 7 hrs, 8 hrs, 11 hrs, and 12 hrs respectively. Among all the formulations GTFCS-4 can be stated as the best formulation as it releases the initial dose i.e.; 31.51 % within first hours and then sustain the release up to 12 hrs, which would permit a treatment regimen of two doses per day.

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