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DEVELOPMENT AND EVALUATION OF MATRIX TABLETS-FILLED-CAPSULE SYSTEM FOR CHRONOTHERAPEUTIC DELIVERY OF TERBUTALINE SULPHATE

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ABSTRACT

Terbutaline sulphate is a β_2-adrenergic agonist bronchodilator and used to treat bronchospasm (wheezing, shortness of breath) associated with lung diseases such as asthma, bronchitis, and emphysema. Terbutaline sulphate elimination half life 3 to 4 hrs (oral), thereby decreasing bioavailability up to 14.8%. So in order to improve the bioavailability and efficacy we have designed tablets-filled-capsule system. The system comprises of different doses of immediate release tablets (IRT) and sustained release tablets (SRT) contained in a HPMC capsule. The drug-loaded core tablets were produced by wet granulation procedure using alcoholic solution of PVP K-30 as a binder. Different composition of IRT prepared with varying amount of sodium starch glycolate (as a superdisintegrant), and SRT was prepared with different ratios of ethyl cellulose to HPMC and number (5 of tablets in a HPMC capsule) were used to obtain different drug release rates. 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 dug and other excipients. All the pre and post-compressional parameter are evaluated were prescribed limits and results were within acceptable limits. The *in-vitro* performance of our best tablet-filled-capsule system showed the desired behavior, the drug contained in the IRT

(immediate release tablets) dissolved within the first 45 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, tablets-filled-capsule systems containing Terbutaline sulphate shows 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 tablet, hydroxy propyl methyl cellulose.

NTRODUCTION

Chronotherapeutic refers to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm. Asthma is a chronic obstructive lung disease characterized by airways, inflammation and hyperactivity. In most patients, the condition worsens at night with acute exacerbation being most common. Clinical and epidemiological studies verify that asthma is several hundred folds more likely at night than during the day with disturbance of sleep. The worsening of asthma at night commonly referred to as nocturnal asthma (NA). It is a variable exacerbation of the underlying asthma conditions associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. Generally a reduction in peak flow or forced expiratory volume in one second of at least 20% is implicit in this definition. Approximately two-thirds of asthmatics suffer from night time symptoms. In a large study involving 8,000 asthmatics it is observed that 70% awakened one night per week, 64% awakened 3 nights per week and 39% had their sleep disturbed on a nightly basis. The patients who self-characterized their asthma as mild, 26% has nightly awakenings and 53% of asthma deaths occurred during the night time hours. A drug delivery system administered at bed time but releasing drug during morning hours would be ideal in this case. The possibility of deferring the drug release for a programmed time interval after oral administration of the dosage form is to perform chronotherapy is quite appealing for those diseases the symptoms of which recur mainly at night times or in the early morning, such as asthma[1, 2].

Multi-particulate (MP) modified release drug delivery systems have several performance advantages vs. single unit dosage forms. After ingestion, MP units are released from the

capsule in the stomach, predictably transit to the small intestine and spread along the gastro-intestinal tract resulting in a consistent drug release with reduced risk of local irritation. MP formulations generally have a more reliable *in-vivo* dissolution performance when compared to a single unit dosage form, resulting in more uniform bioavailability and clinical effect[3].

Sustained-release preparations provide an immediate dose required for normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, it provides drug levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen. Sustained-release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action[4].

Terbutaline sulphate is a β_2-adrenergic agonist bronchodilator and used to treat bronchospasm (wheezing, shortness of breath) associated with lung diseases such as asthma, bronchitis, and emphysema. The main drawback of conventional Terbutaline sulphate formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half- life 3 to 4 hrs, thereby decreasing bioavailability up to 14.8%. The present work describes such delivery system, which will improve the biological half-life as well as bioavailability of Terbutaline sulphate. This makes Terbutaline sulphate a candidate for incorporation in sustained release dosage form and was used as a model drug[5-9].

Mini-tablets are good substitute for granules and pellets because they can be manufactured relatively easily. So the development of MT for controlling drug release is an important focus of research into oral-controlled release solid dosage forms. Several papers already been published describing matrix mini-tablets based on hydrophilic and as well as hydrophobic materials[10-20]. It has proven challenging to develop one dosage form with both sustained and immediate-release properties. However, production of a sustained dosage form that would maintain an effective plasma montelukast sodium concentration would improve patient compliance[21].

The purpose of this study was to develop a sustained-release Terbutaline sulphate dosage form using a matrix tablet-filled-capsule system (TFCS) to be administered in the evening hours to achieve an elevated Terbutaline sulphate level overnight when the risk of asthma was found to be maximum. Our TFCS comprises of immediate-release tablets (IRT) and

sustained-release tablets (SRT) in a capsule made from HPMC, a water soluble polymer. We aimed to reduce the size of the Terbutaline sulphate tablet such that it could be enclosed in a capsule, and then deploy tablets with different release properties, within the one TFCS. Inclusion of IRT permits the development of rapid acting TFCS dosage forms with optimal pharmacokinetic profiles for fast action. In this study, for the IRT we investigated the influence of superdisintegrant content on the immediate Terbutaline sulphate release profile, and for SRT we investigated the influence of different ratios of ethyl cellulose and HPMC on drug release. We thus aimed to develop a better understanding of the factors that can regulate Terbutaline sulphate release from IRT and SRT.

The major objectives of this study were:

I. To develop and to evaluate novel multifunctional matrix tablets-filled-capsule systems, in order to achieve a fast/slow drug release,
II. To investigate formulation parameters affecting in-vitro performance,
III. To obtain a matrix tablets-filled-capsule formulation, which has the ability to release the drug at a sustained or prolong release.

MATERIALS AND METHODS

Terbutaline sulphate was obtained as a gift sample by Franco Indian Pharmaceuticals Pvt Ltd., (Mumbai),. Sodium starch glycolate (SSG) was obtained from signet, Mumbai. HPMC (5 cps), magnesium stearate, potassium di-hydrogen o-phosphate, sodium hydroxide and lactose were purchased from S.D fine Chem. Lab, Mumbai, Ethyl cellulose, Talc was purchased from Loba Chemie Pvt. Ltd, Mumbai. PVP-K-30 was purchased from Himedia Chem. Lab, Mumbai. HPMC capsules were obtained as a gift samples from ACG Associated capsules Pvt Ltd, Mumbai.

Preparation of matrix TFCS sustained release dosage form: The qualitative and quantitative composition of the different formulations of the TFCS can be seen in **Table 1.**

Sustained-release component (SRT)

The SRT contained various ethyl cellulose to HPMC ratio (50:50, 60:40, 70:30, 80:20, 85:15) as controlling agents. The ingredients consisting of TBS, 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.

Immediate release component (IRT)

In this IRT various concentrations (0%, 2.5%, 5%, 7.5 and 10%) of SSG because of its disintegration properties was used to obtain an immediate release of the drug. The ingredients consisting of Terbutaline sulphate, HPMC (5cps), lactose and intra granular portion of SSG were passed through 60 mesh (250 µm) separately and dry mixed. The dry mixing was carried out at a slow speed (50 rpm) for 10 min and the blend was granulated with 10% w/v alcoholic solution of PVP K-30 at a high speed (150 rpm) for 5 min. The resulting wet mass was immediately passed through the 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 extra granular portion of SSG, required amount of fines, magnesium stearate and talc. The lubricated granules were compressed into tablets weighing 120 mg 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.

Matrix Tablets-filled-capsule system (TFCS): The tablets-filled-capsule system comprises of 2 immediate-release and 3 sustained-release tablets.

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.

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

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

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

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

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,

$$F= [(W_{initial}- W_{final})/ W_{initial}] \text{ X } 100$$

% 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 weights 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, weighted and finely grounded. An amount of powder equivalent to 5 mg of powder was accurately weighted and dissolved in 6.8 phosphate buffer. The resulting solution was suitably diluted and analysed on UV spectrophotometer Shimadzu 1601 at 278 nm.

Estimation of Terbutaline sulphate:

Preparation of standard calibration curve of TBS: The standard calibration curve for TBS was prepared using 6.8 phosphate buffer.

Standard solution: 200 mg of Terbutaline sulphate is dissolved in 100 ml of phosphate buffer (ph-6.8) to give a concentration of 2 mg/ml (2000µg/ml).

Stock solution: From the standard solution pipette out 10 ml of solution into 100ml volumetric flask and dilute it up to 100 ml with phosphate buffer (ph-6.8) to produce 200 µg/ml concentration. From this solution pipette out 1,2,3,4,5,6,7,and 8 ml into 10 ml volumetric flask and dilute them up to 10 ml with phosphate buffer (ph-6.8) to produce concentration as 20,40,60,80,100,120,140,and 160 µg/ml respectively. The absorbance of prepared solution of TBS is measured at 278 nm in Shimadzu UV/visible 1700 spectrophotometer against 6.8 phosphate buffer solution as blank.

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). Five 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.

Drug excipients interaction studies

FTIR Studies: IR spectra for pure drug Terbutaline Sulphate, Terbutaline Sulphate immediate release tablets IRT-1, IRT-5 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 tablets IRT-1, IRT-5 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

TBS is rapidly absorbed and excreted in the urine. In order to develop an optimized sustained release dosage forms, we tested TFCS comprising different release profile of tablets (IRT and SRT) in a HPMC capsule (size 0).

Evaluation of granules [Both IRT and SRT]

Granules of all the formulations [both IRT and SRT] were subjected for various pre-compressional evaluations such as LBD, TBD, and compressibility index, Angle of repose and hausner ratio. For IRT granules the LBD ranged from 0.51 to 0.52 and TBD ranged from 0.57 to 0.59 whereas for SRT granules LBD ranged from 0.52 to 0.55 and TBD ranged from 0.62 to 0.63. The LBD and TBD of IRT granules were found to be much lower than SRT granules which may be attributed to the absence of EC in the formulation. Granules prepared with HPMC alone showed compressibility index values ranging from 10.28 to 12.40 %, whereas granules prepared with HPMC and EC showed compressibility index values ranging from 10.60 to 15.4 %. Angle of repose of granules of all formulations ranged from 22.080 to 25.960. All these results were given in **Table 2** indicate that the formulated granules possessed satisfactory flow properties and compressibility.

The results of *in-vitro* drug release studies of IRT were given in **Table 6** and graphical representation was shown in **Fig 1**. These results demonstrate that the dissolution rate and extent of drug release increased with increasing SSG content in the tablets. The results reveal that IRT-1 releasing 94.50% Terbutaline sulphate within 105 min, IRT-2 releasing 94.68% of drug released in 90 min, IRT-3 releasing 93.18% released in 75 min, IRT-4 releasing 97.88% released in 60 min and IRT-5 releasing 98.82% of Terbutaline sulphate within 45 min. Hence, the most suitable immediate-release tablet seems to be IRT-5.

Influence of ethyl cellulose on release of Terbutaline sulphate from sustained release tablets

In order to evaluate the influence of ethyl cellulose content on the release of Terbutaline sulphate from SRT a separate *in-vitro* dissolution testing was carried out. The results of *in-vitro* drug release studies of SRT were given in **Table 7** and graphical representation was 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.

The IRT and SRT were filled into the 0 sized HPMC capsule [as TFCS]. Further, the *in-vitro* drug release study was carried out for these TFCS formulations. The results revealed that formulation TFCS-4 was releasing 26.45% of Terbutaline sulphate within 1 hrs as an immediate release phase and the sustained release phase was releasing 98.81% prolonged for a period of 12 hrs, and it was found to be the most suitable combination to have an immediate as well as sustained release of drug. The drug release results of TFCS were given in **Table 7** and graphical representation was shown in **Fig 3**. Hence, it was considered as the best formulation releasing Terbutaline sulphate both as an immediate and sustained-release phase.

The *in-vitro* release profile of this TFCS coincided with the profile expected from the combination of two IRT and three SRT. The TFCS undergoes four processes as follows: (a) the HPMC capsule dissolves rapidly, and has no influence on the release rate of Terbutaline sulphate from the TFCS; (b) once dissolved, the HPMC capsule releases the IRT and SRT subunits; (c) Terbutaline sulphate is released rapidly from the IRT; and (d) Terbutaline sulphate is released from the SRT over 10 -12 hrs. Using different types of tablets, the TFCS can be designed to yield the desired stable drug release profiles, thereby improving patient compliance.

The IR spectrum of the pure drug TBS and IRT-1, IRT5, SRT-4 and SRT-5 formulations were shown in **Fig 4**. In the IR spectrum of the pure drug TBS showed characteristic absorption bends.

In the following IR region.

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.

IRT-1, IRT5, 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 as there is no change in the positions of the bends in the both drug and its formulations, suggest that the drug has remained in its normal form even in formulation without undergoing any type of change. This only suggest that there is no interaction of the drug with the various polymers used for the preparation of different formulations.

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 and also in the behavior of the drug in its pure form and also in the form of its various formulations. DSC thermo grams of pure drug TBS and its various formulations were shown in **Fig 5**.

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 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.

As 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 the possess its various formulations. Thus the DSC thermo grams study reveals that there is no any kind of interaction of the drug with different types of polymer and there excipients used during the study.

Table 1: Composition of Immediate Release Matrix Tablet (IRMT).

INGRADIENTS	IRT-1	IRT-2	IRT-3	IRT-4	IRT-5
Terbutaline sulphate	0.75	0.75	0.75	0.75	0.75
SSG	3				
		6			
			9		
				12	
					15
HPMC 5 CPS	20	20	20	20	20
Lactose	96.25	93.25	90.25	87.25	84.25
Total weight Mg/Tab	120	120	120	120	120

Table 2: Composition of Sustained Release Tablet (SRT).

FC	SRT-1	SRT-2	SRT-3	SRT-4	SRT-5
TBS	2	2	2	2	2
HPMC(5 cps)	50	40	30	20	15
Ethyl Cellulose	50	60	70	80	85
Lactose	18	18	18	18	18
Total weight (mg/tab)	120	120	120	120	120

Table 3: Composition of Tablet Filled Capsule Systems [TFCS]

Formulation code	Composition
TFCS-1	IRT-1:IRT-5:SRT-1:SRT-2:SRT-3
TFCS-2	IRT-2:IRT-5:SRT-1:SRT-3:SRT-4
TFCS-3	IRT-3:IRT-5:SRT-1:SRT-4:SRT-5
TFCS-4	IRT-1:IRT-5:SRT-2:SRT-4:SRT-5

Table 4: Pre-compressional of evaluation of immediate release and sustained release Tablets [IRT and SRT]

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
IRT-1	23.45 ± 0.03	0.49 ± 0.006	0.61 ± 0.006	19.67 ± 0.09	1.24 ± 0.007
SRT-1	24.12 ± 0.12	0.53 ± 0.006	0.65 ± 0.022	18.46 ± 0.12	1.23 ± 0.009
IRT-2	23.90 ± 0.04	0.50 ± 0.005	0.64 ± 0.007	21.88 ± 0.18	1.28 ± 0.007
SRT-2	22.72 ± 0.61	0.52 ± 0.006	0.67 ± 0.009	22.39 ± 0.10	1.29 ± 0.013
IRT-3	21.56 ± 0,02	0.53 ± 0.006	0.68 ± 0.013	22.06 ± 0.21	1.28 ± 0.006
SRT-3	25.43 ± 0.45	0.54 ± 0.005	0.65 ± 0.034	16.92 ± 0.11	1.20 ± 0.002
IRT-4	24.17 ± 0.06	0.50 ± 0.006	0.64 ± 0.008	21.88 ± 0.15	1.28 ± 0.008
SRT-4	23.49 ± 0.79	0.51 ± 0.006	0.60 ± 0.019	15.00 ± 0.30	1.18 ± 0.016
IRT-5	25.15 ± 0.69	0.50 ± 0,005	0.61 ± 0.027	18.03 ± 0.19	1.22 ± 0.009
SRT-5	26.23 ± 0.27	0.54 ± 0.005	0.65 ± 0.011	16.92 ± 0.08	1.20 ± 0.004

Table 5: Post-compressional evaluation of immediate release and sustained release Tablets [IRT and 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
IRT-1	2.80 ± 0.081	6.3 ± 0.00	2.23 ± 0.22	0.55	120.5 ± 0.90	94.5 ± 0.46
SRT-1	3.01 ± 0.76	6.3 ± 0.01	3.02 ± 0.07	0.46	120 ± 0.78	97.22 ± 0.59
IRT-2	2.82 ± 0.163	6.3 ± 0.02	2.39 ± 0.10	0.61	120 ± 0.91	98.38 ± 0.70
SRT-2	2.92 ± 0.078	6.3 ± 0.03	3.11 ± 0.08	0.58	120 ± 1.03	97.01 ± 0.49
IRT-3	2.77 ± 0.119	6.3 ± 0.04	2.51 ± 0.45	0.51	120 ± 0.87	93.18 ± 0.68
SRT-3	2.67 ± 0.048	6.3 ± 0.05	3.07 ± 0.61	0.48	120 ± 0.79	96.90 ± 0.82
IRT-4	2.81 ± 0.022	6.3 ± 0.06	2.99 ± 0.09	0.55	120 ± 0.98	97.88 ± 0.96
SRT-4	2.67 ± 0.098	6.3 ± 0.07	2.85 ± 0.10	0.49	120 ± 0.83	99.02 ± 0.73
IRT-5	2.83 ± 0.103	6.3 ± 0.08	3.05 ± 0.24	0.54	120 ± 0.95	98.82 ± 0.87
SRT-5	2.97 ± 0.062	6.3 ± 0.09	2.80 ± 0.13	0.53	120 ± 0.84	99.97 ± 0.66

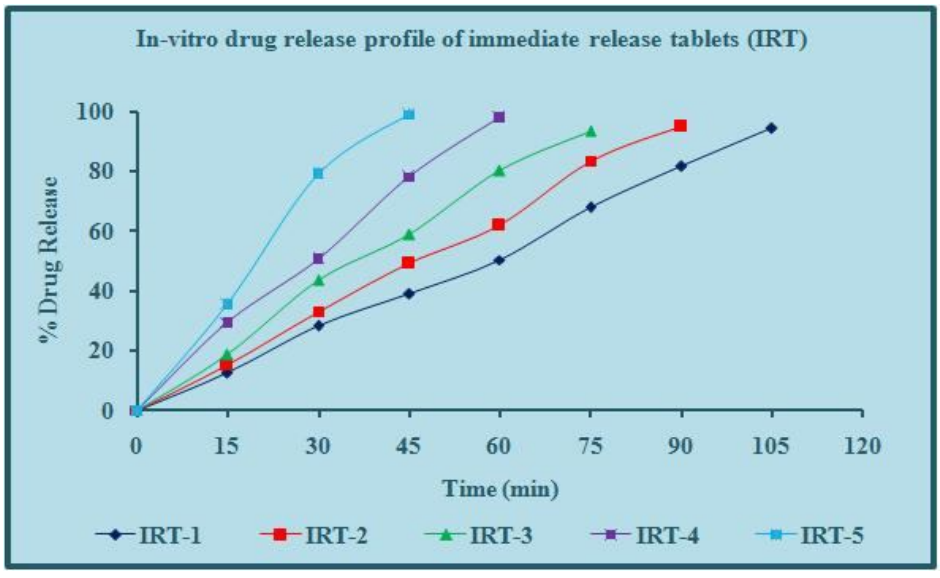

Fig 1: *In-vitro* drug release profile of immediate-release tablets (IRT).

Table 6: *In-vitro* release study of Immediate-release tablets (IRT).

Time (min)	IRT-1	IRT-2	IRT-3	IRT-4	IRT-5
0	0	0	0	0	0
15	12.40	15.03	18.41	29.50	35.51
30	28.18	33.06	43.40	50.72	79.09
45	39.08	49.03	58.80	77.96	98.82
60	50.35	61.81	80.03	97.88	--
75	67.82	83.41	93.18	--	--
90	81.53	94.68	--	--	--
105	94.50	--	--	--	--

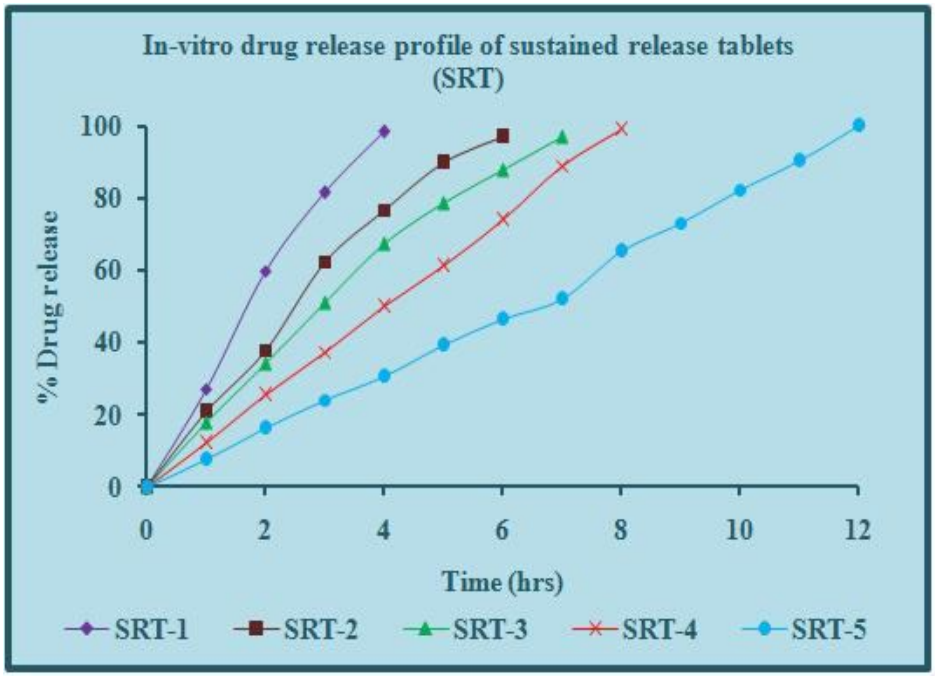

Fig 2: *In-vitro* drug release profile of sustained-release tablets (SRT).

Table 5: *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

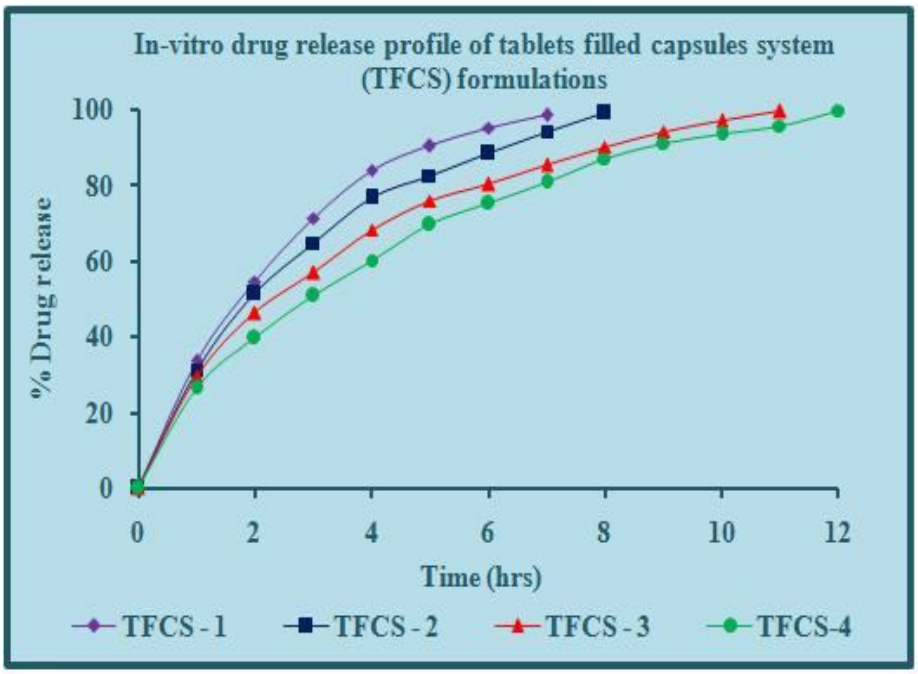

Fig 3: *In-vitro* drug release profile of tablets-filled-capsule system formulations (TFCS).

Table 6: *In-vitro* release study of tablets-filled-capsule system formulations (TFCS).

Percentage amount of drug release				
Time (hrs)	**TFCS-1**	**TFCS-2**	**TFCS-3**	**TFCS-4**
0	0	0	0	0
1	33.68	31.31	29.65	26.45
2	54.56	51.25	46.29	39.68
3	71.40	64.68	56.93	50.73
4	84.00	76.77	68.3	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	80.7
8	--	99.09	90.1	87.1
9	--	--	94.13	91.13
10	--	--	96.92	93.51
11	--	--	99.5	95.68
12	--	--	--	99.81

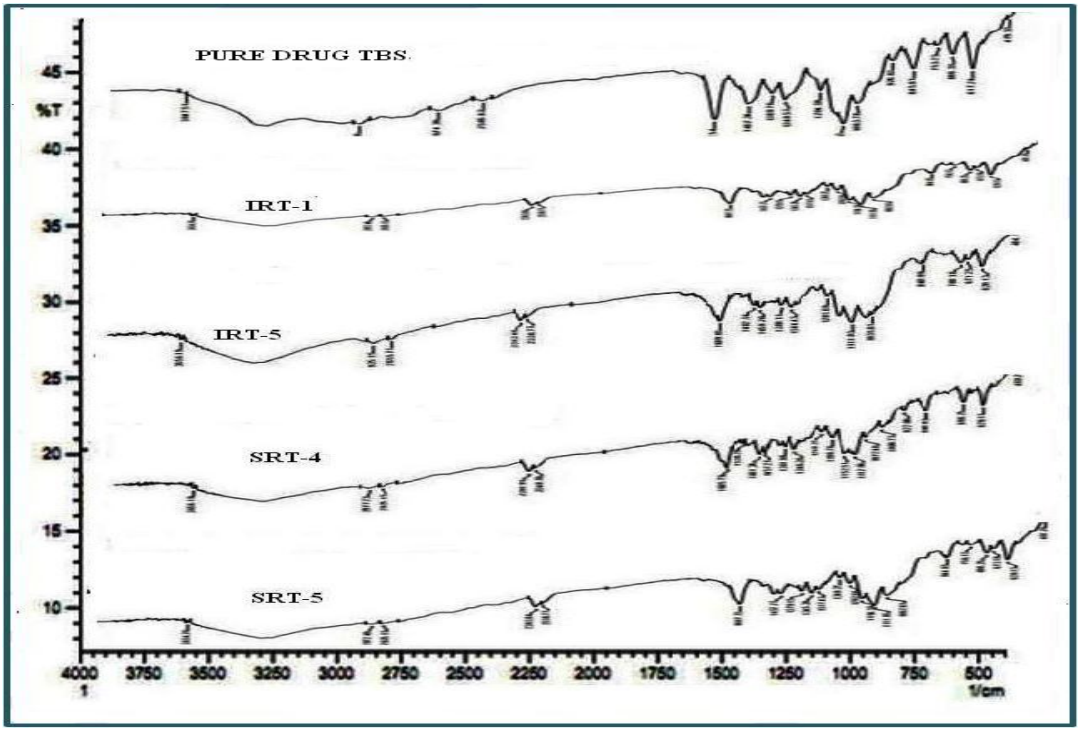

Fig 4: IR Spectra of pure Terbutaline sulphate, Formulations IRT-1, IRT-5, SRT-4 and SRT-5.

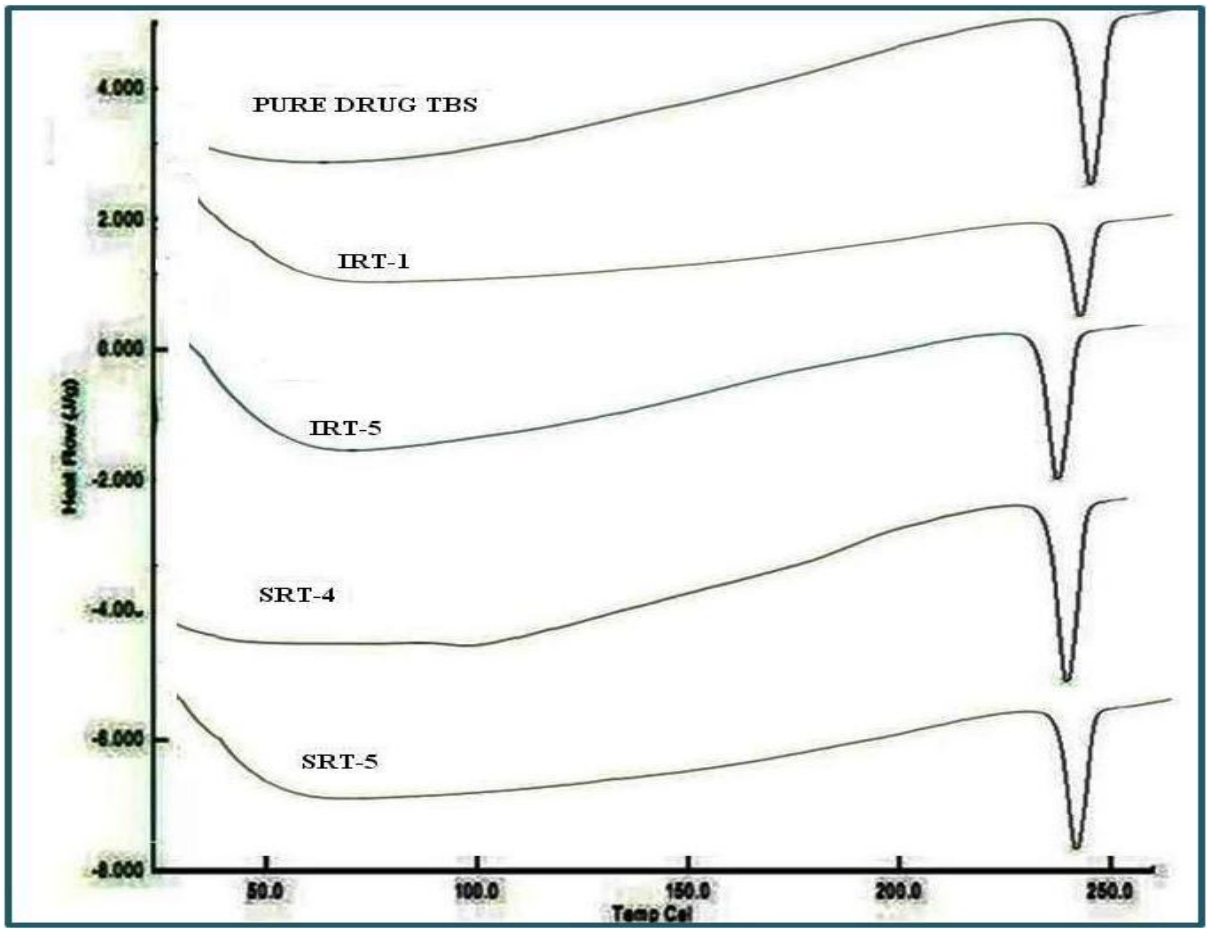

Fig 5: DSC of pure Terbutaline sulphate, Formulations IRT-1, IRT-5, SRT-4 and SRT-5.

CONCLUSION

From this, study it can be concluded that, tablets-filled-capsule systems containing Terbutaline sulphate shows both sustained release as well as immediate release may improve the bioavailability and efficacy. The formulation TFCS-4 will be the best formulation shows sustained release for 12 hrs.

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