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Design and *in-vitro* evaluation of multiparticulate drug delivery system of terbutaline sulphate for the treatment of nocturnal asthma

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ABSTRACT:

Terbutaline sulphate is a β2-adrenergic agonist bronchodilator and used to treat bronchospasm 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 bioavailability, half-life and efficacy we have designed sustained release film-coated pellets of terbutaline sulphate. The drug loaded pellets were prepared by using extrusion/spheronization method. Core pellets were coated with a combination of ethylcellulose and HPMC polymers by varying ratios in a coating pan to achieve a sustainable release. The drug excipient mixtures were subjected to pre-formulation studies. The pellets were subjected to in-vitro drug release studies, and stability studies. FTIR and DSC studies shown that there was no interaction between drug and polymers. The percentage of drug content from the core pellets was determined by UV-Spectroscopy and was found to be 98.86 ± 0.32 % indicating good content uniformity. Formulation F5 was considered as the best formulation as it released 96.83±1.64 % of drug at the end of 24 hrs. The opti mized formulation was also found to be stable.

Keywords: Terbutaline sulphate, Nocturnal asthma, sustained release, Film-coated pellets

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INTRODUCTION

One of the earliest references to coated solid dosage forms appears in early Islamic drug literature, where coated pills were mentioned by Rhazes (850-923). The use of coating on drugs was probably an adaptation from early food preservation methods, and French publications in the 1600s described coating as a means of masking the taste of medicines. Sugar coating of pills was developed to a considerable extent by the French in the mid-1800s, and patents issued in 1837 and 1840 utilized sugar compositions for coated pills of cubeb and copaiba. Subsequently there was rapid acceptance of sugar-coated pills as the preferred solid dosage form for both prescription and patent medicines in Europe and the United States. In 1953, a dramatic change was made in tablet coating when Abbott laboratories marketed the first film-coated pharmaceutical tablet. Concurrently, in the early 1950s Dr. Dale Wurster, a professor at the University of Wisconsin, patented an air suspension coater that efficiently applied film coating compositions. This stimulated renewed interest in tablet coating technology, and for the next 12 to 15 years, several hundred patents and research papers on the subject were published. [1]

For modified or extended release formulations, one method of obtaining reproducible control of drug release is the production of a system containing core particles or tablets surrounded by an inert polymeric coating. The release rates from these systems are generally controlled by the type and amount of polymer used and any defects i.e. pores,

which are intentionally or unintentionally found in the films[2]. Ethyl-cellulose (EC) is a water insoluble polymer, having a relatively small degree of swelling due to its hydrophobicity. [3] Incomplete drug release as well as a long lag time has been reported in some instances from EC coated MUDFs, even at low coating weight gains. [4] EC films can be applied by traditional solution techniques such as coacervation or spray coating. HPMC is a water soluble cellulose derivative that is compatible with EC and can be incorporated into EC films to alter permeability. [5,6]

Generally, there are two types of film coating: [7]

- **Immediate-release (non-functional) film coating:** They do not affect the biopharmaceutical properties of the tablet. They are readily soluble in water.
- **Modified-release (functional) film coating:** They allow the drug to be delivered in a specific manner; that is they affect drug release behavior.

Our formulation comprises of sustained-release pellets (SRP) in a capsule made from HPMC, a water soluble polymer. Several pellets can be placed into each HPMC capsule, which later disintegrates and releases these subunits. The SRP were coated with a mixture of ethyl cellulose (a water insoluble polymer) and HPMC (15cps). [8]

The production of Multiple unit dosage forms (MUDFs) is a common strategy to control the release of a drug, as shown by the reproducibility of the release profiles when compared to the ones obtained with Single unit dosage forms (SUDFs). These MUDFs is characterized by the fact that the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits. MUDFs may seem costlier than SUDFs in the short term; but causes significant savings, lower treatment failure rate, lower case-fatality ratios, reduction in development of resistance, higher colonic residence time, more predictable gastric emptying and consequently less money needed for the development of new products in long-term therapy. [9]

Terbutaline sulphate is a β2-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%. In nocturnal asthma, lung function is usually highest at 4 PM and lowest at 4 AM, the latter time is generally when asthma symptoms are most prevalent. Based on these findings drug delivery and therapy should be modified to achieve an effective drug level at the required time. This can be achieved by adapting a sustained drug delivery system of a suitable drug which when administered during night releases the drug till early morning hours. So in order to improve the bioavailability and efficacy we have designed pellets-filled-capsule system. 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. [10]

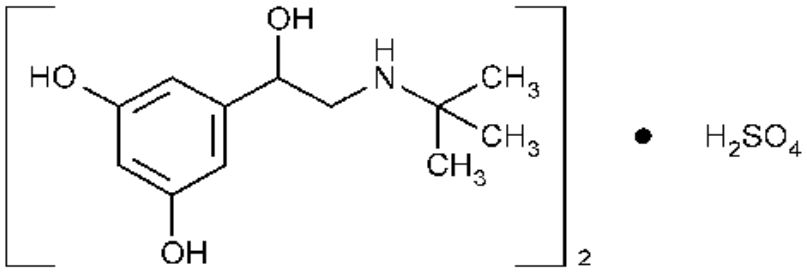

Figure 1: Structure of Terbutaline sulphate

The major objectives of this study were:
I. To develop and to evaluate novel multifunctional coated pellets, in order to achieve sustained release drug profile.
II. To investigate formulation parameters affecting in-vitro performance,

MATERIALS AND METHODS

Materials used

Terbutaline sulphate was obtained as a gift sample by Franco Indian Pharmaceuticals Pvt Ltd., (Mumbai), Avicel pH 101 (microcrystalline cellulose) as spheronizing agent, Ac-di-sol (croscarmellose sodium) as swellable superdisintegrant, PVPK-30 (polyvinylpyrrolidone) as binder, Pharmatose (lactose monohydrate) were purchased from Rajesh chemicals, Mumbai. HPMC (5 cps), Ethyl cellulose (18-22cps) and sodium lauryl sulphate were purchased from S.D fine Chem Lab, Mumbai. Magnesium stearate was purchased from Himedia Chem Lab, Mumbai. HPMC capsules were obtained as a gift samples from ACG Associated capsules Pvt Ltd, Mumbai.

Experimental Methods

Drug-excipient compatibility studies: Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers were subjected to infra-red (IR) and Differential Scanning Calorimeter (DSC) studies. The pure drug and formulations mixed with polymers were separately mixed with IR grade potassium bromide in a ratio (1:100) and pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over range of 4000-400cm-1 in FTIR instrument. Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and final tablet were also recorded. The thermal analysis was performed over a temperature range of 30°C to 250°C. [11]

Preparation of Terbutaline sulphate core pellets: Drug containing core pellets were prepared by extruder-spheronizer (NAOMI, Mumbai, India). The Terbutaline sulphate, spheronizing agents Avicel pH 101, lactose (filler), superdisintigrant croscarmellose sodium were mixed to form a uniform blend. The binder solution PVPK-30 (2.5% in 50:50 alcohol/ water) was slowly added in the powder mixture to achieve a consistency of the damp mass suitable for further extrusion-spheronization process. The composition of core pellets is given in **Table 1**. The prepared mass was immediately passed through a screw type extruder using 1mm diameter screen with the speed set at 15 rpm. The extrudes were then transferred to spheronizer for 15-20 min at a rotation speed of 700 rpm. The resultant pellets were dried at 50^0C in oven for 30 min. [12]

Table 1: Composition of core pellets

Ingredients	Quantity (mg)
Terbutaline sulphate	15
Pharmatose	60
Croscarmellose sodium	10
Polyvinyl pyrollidone (PVPK-30)	2.5
Avicel q.s to make	200

Preparation of coating solution: A coating suspension for SRP was prepared from HPMC (5cps), ethyl cellulose, magnesium stearate, ethyl alcohol and water. We used magnesium stearate in the coating preparation to minimize friction between the surfaces of pellets, the pellets-filling system and the HPMC capsules. HPMC, ethyl cellulose and magnesium stearate were dispersed in an ethanol/water mixture. Aqueous ethanol solutions of HPMC and ethyl cellulose were mixed at the desired ratios (00:100, 100:00, 75:25, 70:30, 65:35) based on the experimental design **Table 2**. The core pellets were coated using using an aqueous ethanolic solution of HPMC and ethyl cellulose to yield 5 % increase in weight. A coating load of 5% was used to test the effect of the various ratios of HPMC and ethyl cellulose. [13]

Table 2: Composition of coating solution for core pellets

Ingredients	SRP-A	SRP-B	SRP-C	SRP-D	SRP-E
Ethyl cellulose (18-22CPS)	--	96.2	72.2	67.3	62.5
Hydroxy propyl methyl cellulose (5cps)	96.2	--	24.0	28.9	33.7
Magnesium stearate	3.8	3.8	3.8	3.8	3.8
% Coating load	5	5	5	5	5

NOTE:

- *The solvent used for coating is ethanol: water at 90:10 ratios.*
- *Values for coating load are percentages relative to the total weight of the core tablet.*
- *Values for ingredients are percentages relative to the total volume of each coating preparation.*

Coating: The 200gm core pellets containing 15mg drug per 200mg of pellets were coated using a pan- coating system, United technologies, Mumbai **(see Figure 2)** to yield a 5 % increase in weight. Percentage weight gain was calculated by following equation: [12,13]

$$\text{Percentage weight gain} = [(Wt - Wo)/Wo]*100$$

Where Wt = Weight of tablet after coating and Wo= Initial weight of tablet

Fig 2: Coating pan (6 inches), United Technologies, Mumbai.

Table 3: Coating parameters

Atomization Air	2 kg/cm²
Inlet temperature	65 ºC
Exhaust temperature	48-50 ºC

Preparation of pellets-filled-capsule system: To prepare pellets-filled-capsule system (PFCS), polymer coated pellets equivalent to 10mg of drug were placed in HPMC capsule (size 1) to achieve sustained release profiles of the (PFCS). [13]

Evaluation methods:

Pellets characterization:

The pellets were characterized for the size, shape using vernier caliper. The diameter of the core pellets, Film coated pellets were measured to assess the parameters like size and shape uniformity.

Micromeritic Properties:

The bulk density and tapped density of drug powder and pellets were evaluated to assess the packing ability due to tapping. The Carr's compressibility index and hausner's ratio was computed. [12,13]

Friability:

Friability studies on core pellets were performed by placing 5g in a friabilator (Veego, Mumbai) and tumbled for 200 revolutions at 25rpm. Twelve steel balls (diameter 6.3mm, weighing 1.028g each) were used as attrition agents.

After friability testing, the pellets were sieved through a sieve of 16# size. The weight loss (% F) after friability testing was calculated. [12,13]

Drug content uniformity:
Pellets were crushed in a mortar then weighed powder contained equivalent to 15 mg of drug transferred in 6.8 phosphate buffer. The resulting solution was suitably diluted and analysed on UV spectrophotometer Shimadzu 1601 at 278 nm. [10]

***In-Vitro* Release testing:**
Dissolution test of Terbutaline Sulphate PFC system 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. [10]

Stability studies:
The optimized formulations were evaluated for accelerated stability studies at 40°C and 75% RH for three months as per ICH guidelines. [14]

RESULTS AND DISCUSSION

Terbutaline sulphate is rapidly absorbed and excreted in the urine. In order to develop an optimized sustained release dosage forms, we tested pellets-filled-capsule system (PFCS).

The system consisting of drug containing core pellets prepared by extrusion/ spheronization process. The drug loaded core pellets were prepared by using combination of superdisintegrant and spheronizing agent. Superdisintegrant croscarmellose sodium acts by swelling mechanism while polyvinypyrrolidone PVPK-30 incorporates binding properties to pellets for sufficient hardness to withstand mechanical tension in coating pan. Further, the drug loaded core pellets were coated with different combination ratios of ethylcellulose and HPMC.

Drug excipients interaction studies: In FTIR spectral analysis, the pure drug terbutaline sulphate characteristic absorption bands and optimized formulations absorption bands have shown all most in same range **(see Tables 4,5 and Figure 3)**. As there is no variation and shift in the position of characteristic absorption bands it can be justified there is no interaction between drug and polymer.

Table 4: FTIR studies of pure drug Terbutaline sulphate

Peak in pure drug and Functional group	
2974-2849	C-H stretching of CH3 and CH2 group
1610	C=C ring stretching
1610 and 1478	C-H bending of CH3 and CH2 group
1389 and 1340	CH bending of CH2 and CH3 group
1205	O-H bending
846	substituted phenyl ring
3300-3400	A broad peak of OH and NH hydrogen bond.
3068	Aromatic C-H stretching

Table 5: FTIR studies of optimized formulation

Peak in physical mixture and Functional group	
844	Substituted phenyl ring.
1998	O-H bending
1358-1350	CH bending of CH2 and CH3 groups
1606-1454	Stretching of c=c
2925-2854	CH bending of CH2 and CH3 groups
3300	Broad peak at 3300 is due to OH and NH group

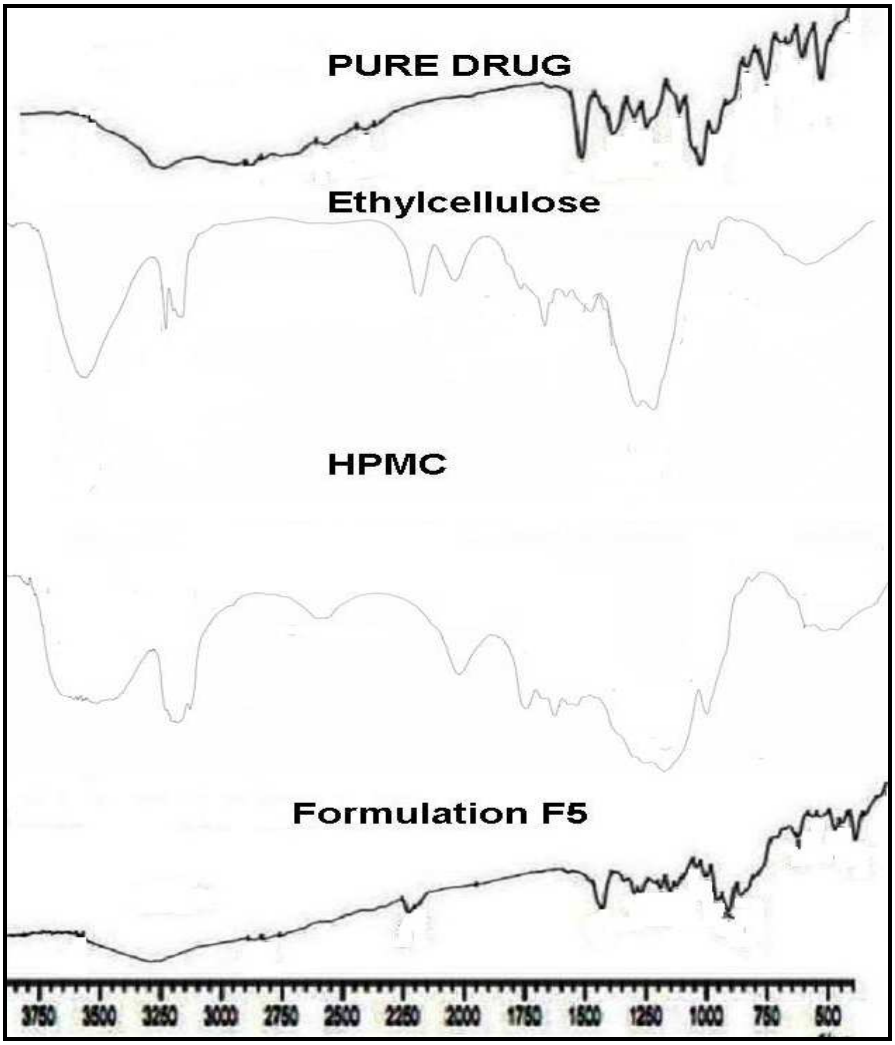

Figure 3: IR spectra of a) Pure drug Terbutaline sulphate b) Ethyl cellulose c) HPMC e) Formulation (F5).

DSC studies: To study the thermal stability of the drug it is subjected for DSC **(Figure 4)** studies in the range of 30^0C to 250^0C. During the process of study it is observed that the thermo gram of the pure drug shows an endothermic peak in the range of 244-248^{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. The optimized formulation F5 when it is subjected for DSC studies, it give rise to wider degree of onset of melting process and finished at 262°C suggesting that the formulated batch is a mixture of drug and polymers (Ethylcellulose and Hydroxypropylmethylcellulose) but not pure reaction product. DSC studies of the above mentioned formulations realized that, during the process of formulation chemical reaction has not taken place and the drug has remained in the free state to show its desired effects. DSC studies revealed that, there was no incompatibility with the excipients used.

Pellet characterization: It was observed that the pellets were of uniform in size and shape. The uniform size of pellets indicates good content uniformity, good flow and ease of capsule filling.

Friability: Friability of pellets is an important parameter to withstand handling, shipping, storage and other processing parameters such as coating. The weight loss (%F) after friability testing was calculated as 0.47±0.24 showing good friability.

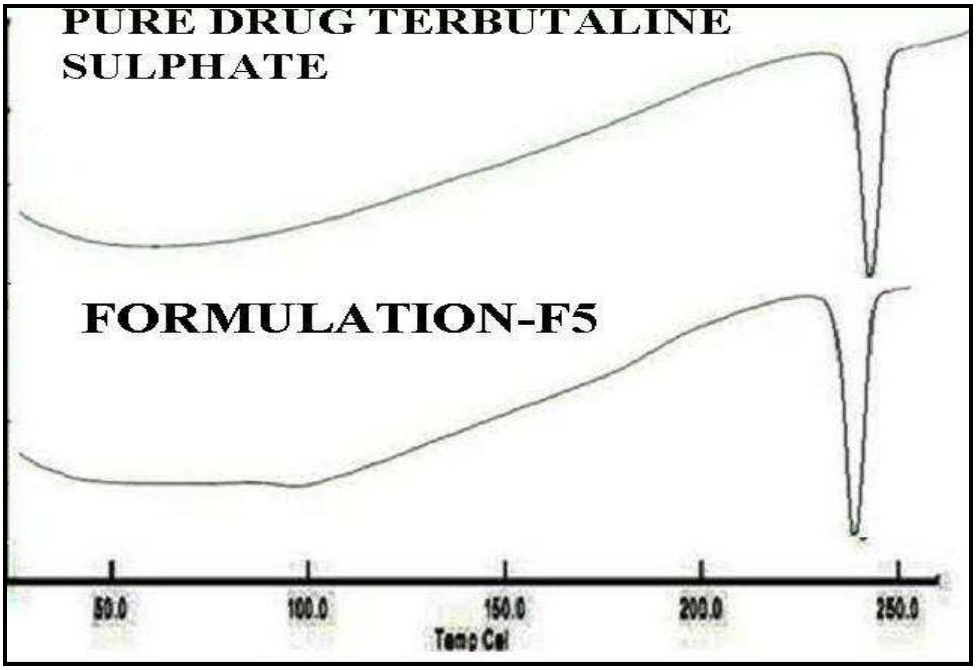

Figure 4: DSC spectra of a) Pure drug Terbutaline sulphate b) Formulation (F5).

Micromeritic Properties: The micromeritic properties of pure drug, film coated pellets were depicted in **Table 6**. The Carr's compressibility index of film coated pellets was significantly improved with plain drug.

Table 6: Pre-compression evaluation of the prepared blend

Parameters	Terbutaline sulphate	Film coated pellets
Angle of repose (degree) ± SD, n=3	33°.18"±0.62	13.98±0.20
Bulk density (gm/cc) ± SD, n=3	0.252±0.045	0.726±0.022
Tapped density (gm/cc) ± SD, n=3	0.378±0.085	0.790±0.016
Carr's index (%) ± SD, n=3	33.33±0.50	8.101±0.030
Hausner's ratio ± SD, n=3	1.50±0.012	1.088±0.017

Drug content: The drug content uniformity was performed for the Terbutaline sulphate core pellets. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations were also calculated. The percentage drug content was found to be 98.86 ± 0.32 % for the core pellets indicating good content uniformity. This indicates that drug was uniformly distributed through out the core pellets.

In-vitro drug release study:

In order to assess the effect of combination of hydrophilic and hydrophobic polymers, separate *in-vitro* dissolution testing was performed for pellets-filled-capsule system. Before starting to study the effect of combination of hydrophilic and hydrophobic polymers, individual polymer study was done by coating on pellets. When, HPMC (5cps) was alone coated it was found that 95.88±1.30 % of the drug was released within 1 hour. It is due to the reason that HPMC is a hydrophilic polymer and its coating has dissolved within a short period of time due to its hydrophilic tendency. But when, ethylcellulose (18-22cps) was alone coated, it was found that only 43.17±1.70 % of the drug was released for a period of 24 hours. This polymer coat remain as an intact film on the surface of the pellets which resulted in very slow release of the drug. This is due to the reason that ethylcellulose is an hydrophobic polymer and it is insoluble in the dissolution medium. Again further, the combination of both polymers were coated for formulations F3, F4 and F5 and dissolution study was carried out. The results were 76.32±1.52, 94.69±1.42,

96.83±1.64 % of drug was released for F3, F4, F5 formulations respectively. It was found that the release rate of terbutaline sulphate increased with increasing HPMC concentration in the film which was shown in **Table 7** and graphical representation shown in **Figure 3**. It is due to the reason that HPMC is water soluble and it created pores in the ethylcellulose film. Its increased concentration leads to increased pore size which inturn leads to increased release of drug. Hence, formulation F5 was considered as the best formulation.

Table 7: *In-vitro* release study of Pellets-filled-capsule systems

Percentage amount of drug released*					
Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	95.88±1.30	4.29±1.11	6.91±1.79	14.54±1.77	24.80±0.98
2		6.43±1.49	16.21±1.20	32.19±1.51	56.76±1.21
4		9.77±1.56	28.62±1.68	50.08±1.22	65.83±1.58
6		14.07±1.22	33.39±1.99	64.63±1.46	72.74±1.05
8		16.69±1.49	40.78±1.91	74.17±1.81	76.80±1.44
10		18.60±1.39	45.31±1.34	83.24±1.90	79.42±1.09
12		20.03±1.26	50.32±1.02	85.86±1.67	85.15±1.48
16		31.24±1.96	57.24±1.44	89.92±1.95	89.44±1.56
20		36.73±1.34	64.39±1.33	92.78±1.79	94.45±1.96
24		43.17±1.70	76.32±1.52	94.69±1.42	96.83±1.64

NOTE: **F1:** 0:100 (EC: HPMC), **F2:** 100: 0 (EC: HPMC), **F3:** 75:25 (EC: HPMC), **F4:** 70:30 (EC: HPMC), **F5:** 65:35 (EC: HPMC).

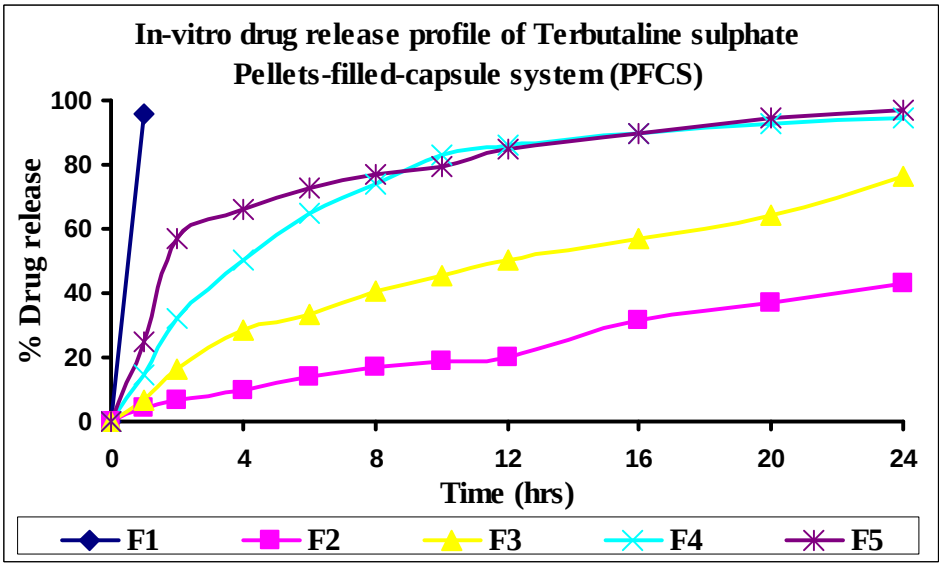

Figure 3: In-vitro drug release profile of Pellets-filled-capsule systems.

Stability studies: The optimized formulation F5 developed was subjected to stability testing by conducting accelerated stability testing at 40°C / 75 % RH for three months as per ICH guidelines. The results **(Table 8)** revealed that no considerable difference in dissolution rate was observed.

Table 8: *In-vitro* release data of stability formulation F5

Time (Hrs)	**Formulation F5**			
	1st day (%)	**30th day (%)**	**60th day (%)**	**90th day (%)**
6	72.74±1.05	72.56±1.64	72.03±1.92	71.34±1.10
12	85.15±1.48	84.78±1.66	84.75±40	84.18±1.06
18	91.94±1.40	91.16±1.42	90.39±1.77	90.15±1.04
24	96.83±1.64	96.16±1.24	95.27±1.55	95.02±1.96

**** Average of 3 determinations*

CONCLUSION

The addition of HPMC to ethylcellulose barrier membrane coatings resulted in increase in drug release over 24 hours. Dissolution rate and extent of drug release increased with increasing HPMC content. The HPMC content influenced film mechanical properties. The results demonstrate the utility of HPMC as a pore-former in modulating drug release from organically applied ethyl cellulose film coatings. A pellets-filled-capsule system sustained release dosage form was developed by filling film coated Terbutaline sulphate pellets into an empty HPMC capsule shell which releases 96.83±1.64 % of drug of the dose within for a period of 24 hrs. Thus, this system increases the half-life and bio-availability of the drug and can be useful for the treatment of Nocturnal asthma.

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