



DEVELOPMENT AND *IN VITRO* EVALUATION OF ACEBROPHYLLINE SUSTAINED RELEASE MATRIX TABLETS EMPLOYING DIFFERENT GRADE OF HPMC AND ETHYL CELLULOSE

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ABSTRACT

Acebrophylline is a bronchodilator with mucosecretolytic and anti-inflammatory activity that is used for the treatment of asthma and chronic obstructive pulmonary diseases (COPD). The objective of the present studies is to optimize and characterize once-daily sustained release formulation of Acebrophylline to reduce the frequency of administration and improve patient compliance. The sustained released Acebrophylline matrix tablet were prepared by wet granulation technique using hydrophilic synthetic polymer like hydroxyl propyl methyl cellulose (HPMC K4M & HPMC K15M) and hydrophobic polymer like ethyl cellulose (EC). To check the flow properties of granules for all the formulations, different pre compression parameters like angle of repose, Carr's index and Hausner's ration were determined and results satisfied according to the specifications. The sustained release tablets of all formulations were characterised by FTIR and DSC analysis to know the compatibility between drug and polymers which confirmed the compatibility of drug and polymers. Different post compression parameters like weight variation, friability, hardness, content uniformity and swelling studies were performed and the results were satisfactory according to pharmacopeia specification. *In vitro* release study was performed by using USP type-II paddle type eight station dissolution apparatus. The formulation ASRF₁₀ that contained 20% of HPMC K15M and 5% of ethyl cellulose called as optimised formulation as the initial release was 16% with sustained release effect upto 12 h. Further more *In vitro* release data of optimized formulation (ASRF₁₀) were evaluated for mechanism of drug release by using different kinetic model like zero order, first order, Higuchi, Korse-Meyer Peppas and Hixon Crowell kinetic model. Accelerated stability studies were carried out for optimised formulation to confirm the stability of dosage forms.

Key Words: Sustained release tablet, Acebrophylline, Matrix tablets, HPMC, Ethyl cellulose.

INTRODUCTION

Oral drug delivery is the most preferred and convenient choice among all drug delivery system as the oral route provides maximum active surface area and hence increase residence time of the drug for absorption.

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency.¹ These factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.² Such dosage forms exhibit better pharmacological effect and prolonged therapeutic activity. Matrix tablets are one of the most

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commonly used controlled release dosage forms as they release the drug in a controlled manner.^{3,4} Such type of dosage form will be beneficial for the chronic disease like asthma, diabetes, hypertension and inflammation that require constant plasma level for maintenance therapy.⁵ Acebrophylline is a bronchodilator with mucosecretolytic and anti-inflammatory activity. It is used to treat the bronchial asthma and chronic obstructive pulmonary diseases. Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life threatening pulmonary disease that requires constant monitoring. Acebrophylline is obtained by targeted salification of the Ambroxol base [trans-4(2-amino-3, 5-dibromobenzylamino) cyclohexanol] and theophylline-7 acetic acid.

The carboxyl group of theophylline-7 acetic acid was salified with Ambroxol's amine group in a stoichiometric ratio (38.7% acid and 61.3% base) that ensures, after absorption, high plasma levels of Ambroxol with low levels of the xanthine derivative which are nevertheless high enough to ensure a carrier effect for Ambroxol. This means that one hour after administration lung levels of Ambroxol are 45% higher than in subjects treated with Ambroxol alone. It is a white crystalline powder with sparingly soluble in water and methanol, slightly soluble in ethanol. Ambroxol reaches its peak in serum (mean C_{max} 0.369 $\mu\text{g/ml}$) at 2 h and theophylline-7 acetic acid after 1 h (mean C_{max} 0.008 $\mu\text{g/ml}$).

Thus it appears that the latter is either poorly absorbed or metabolised very fast and is eliminated in a fairly short time. Its low blood levels mean it is not likely to cause the untoward effects seen in man after theophylline, whose therapeutic window corresponds to much higher plasma concentrations (10-20 $\mu\text{g/ml}$). Acebrophylline having plasma half-life 4-6 h administered with 100 mg as oral dose twice daily.^{5,6}

The objective of the present study was to develop sustained release tablets of Acebrophylline using hydroxyl propyl methylcellulose (HPMC K4M & K15M) and ethyl cellulose as polymeric retardant materials to reduce the frequency of dosing and to improve the therapeutic efficacy. Different proportions of HPMC K4M and HPMC K15M along with ethyl cellulose were selected to form different sustained release tablets formulation for optimization of drug release profile. The present formulation may improve patient compliance as it

reduce the frequency of dosing and useful for better control of disease condition.^{7,8}

MATERIALS AND METHODS

Materials

Acebrophylline was procured as a gift sample from Dr. Reddy's Laboratories Hyderabad, India. HPMC K4M, HPMC K15M polymers were received as gift sample from Glenmark Pharma, Nasik, India. The ethyl cellulose and lactose were purchased from Otto Manufacturers. PVP K30, talc and magnesium stearate were purchased from S.D. fine chemicals Pvt. Ltd' Mumbai, India. All the ingredients were of laboratory grade. The distilled water used in the process of research work was prepared by double distillation process in the laboratory.

Methods

Formulation of sustained release matrix tablets of Acebrophylline

For preparation of Acebrophylline sustained release matrix tablets wet granulation methods were adopted. Accurate quantities of all ingredients were weighed and passed through sieve no #80 before their use in formulations. For each formulation specific and accurate quantities of powder like Acebrophylline, HPMC, ethyl cellulose, PVPK30, and lactose were blended uniformly and passed through #20. PVPK30 was used as binder and lactose was used as diluent. A wet lump mass was produced by adding required quantity of distilled water as granulating agent. The aggregates formed were initially dried for 10 min to reduce moisture level and to prevent sticking with sieve. The aggregates were passed through sieve # 20 to get granules. The granules are dried at 40 °C for 20 min to reduce moisture content upto 2-5 %. After lubrication with magnesium stearate and talc the formulations were evaluated for angle of repose, bulk density, compressibility; prior to compression.

The evaluated granules were compressed into sustained release matrix tablets on a 10 station rotary tablet punching machine using 10 mm concave punches. Each tablet contains 200 mg of Acebrophylline as sustained release matrix formulation. The compositions for different formulations are given in **table 1** and same method was followed for all the formulations. Then the prepared tablet formulations were evaluated for various post compression parameters like average thickness, weight variation, hardness, friability, swelling studies, drug content and *in vitro* dissolution studies.⁹

Table 1: Composition of different excipients used for sustained release matrix tablets of Doxofylline

F. No.	Acebromphylline (mg)	HPMC K4M-mg	HPMC K15M-mg	Ethyl cellulose -mg	Lactos-mg	PVPK30	Mg. stearate - mg	Talc - mg	Total wt.-mg
ASRF ₁	200	70	-	-	42	28	3	7	350
ASRF ₂	200	-	70	-	42	28	3	7	350
ASRF ₃	200	87.5	-	-	24.5	28	3	7	350
ASRF ₄	200	-	87.5	-	24.5	28	3	7	350
ASRF ₅	200	105	-	-	7	28	3	7	350
ASRF ₆	200	-	105	-	7	28	3	7	350
ASRF ₇	200	70	-	35	7	28	3	7	350
ASRF ₈	200	-	70	35	7	28	3	7	350
ASRF ₉	200	70	-	17.5	24.5	28	3	7	350
ASRF ₁₀	200	-	70	17.5	24.5	28	3	7	350
ASRF ₁₁	200	87.5	-	17.5	7	28	3	7	350
ASRF ₁₂	200	-	87.5	17.5	7	28	3	7	350

EVALUATION

Drug excipients compatibility studies

Drug excipients compatibility studies were done by FTIR and DSC analysis.

Fourier Transform Infrared (FTIR) spectroscopy:

Fourier transform infrared (FTIR) study was carried out to verify any physical or chemical interaction between the drug and the excipients used in the formulation. The FTIR studies of pure drug Acebromphylline, HPMC, ethyl cellulose and optimised formulation (ASRF₁₀) were carried out by comparing the obtained spectra for the presence of functional groups. It was performed by potassium bromide (KBr) pellet method. The samples were triturated with KBr and pellet was prepared by setting the pressure to 100 kg/cm² for 2 min. The obtained pellet was analyzed in FTIR 8400S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. The same procedures were repeated for the analysis of drug and for physical mixture of drug and excipients.¹⁰

Differential Scanning Calorimetric (DSC) analysis:

The DSC analysis of Acebromphylline, HPMC, ethyl cellulose and physical mixture of drug with excipients used for formulations were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and

heated at constant rate of 10 °C/min over a temperature range of 40 to 300 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.¹¹

Evaluation of precompression parameters Angle of Repose (θ)

The angle of repose was then calculated by measuring the height and radius of the heap of granules formed that were allowed to flow through the funnel fixed to a stand at definite height (h).

$$\theta = \tan^{-1} \frac{h}{r}$$

Where θ was called as angle of repose that indicates flow properties of granules, h and r were height and radius of the granule heap respectively. According to the specifications the angle of repose value less than 25° indicates excellent flow whereas angle greater than 40° indicates poor flow.¹²

Bulk density and tapped density

For the determination of both the bulk density (BD) and tapped density (TD) of prepared Acebromphylline sustained release granules of all the formulations, following formula were adopted.¹³

$$BD = \frac{\text{weight of the granule taken}}{\text{volume of the packing}}$$

$$TD = \frac{\text{weight of the granule taken}}{\text{tapped volume of the packing}}$$

Compressibility index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of powder and the rate at which it packed down. Compressibility index (Carr's

index) of prepared Acebrophylline sustained release granules were calculated by following formula

$$\text{Carr's index (\%)} = \frac{TD-BD}{TD} \times 100$$

According to the specification the Carr's index values ranging between 5-15 indicates excellent flow and between 12-16 indicates good flow whereas Values between 33-38 indicates very poor and greater than 40 indicates extremely poor flow.¹⁴

Hausner's ratio

Another method used for the determination of flow properties of granules is by calculating the Hausner's ratio and for all the formulations of prepared Acebrophylline sustained release granules; it was determined by using following formula.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), where as greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, glidant need to be added to improves flow.¹⁵

Evaluation of postcompression parameters of Acebrophylline sustained release matrix tablets formulations

Average thickness

From each formulation of Acebrophylline sustained release tablets; ten tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial thickness Gauge, Japan) and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a $\pm 5\%$ variation of standard value.¹⁶

Tablet hardness

The hardness of all the formulations of prepared Acebrophylline sustained release tablets were measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten sustained release matrix tablets with known weights were recorded in kg/cm^2 and average were calculated with standard deviation. According to specifications of USP; hardness values of 4 to 5 kg/cm^2 is considered as acceptable limit for sustained release tablets.¹⁷

Friability

Previously weighed ten tablets (W_i) from each batch of Acebrophylline sustained release tablets were taken in Roche friabilator (Roche friabilator, Secor India). After hundred revolutions of friabilator; tablets were recovered with cleaning

to make free from dust and the total remaining weight (W_f) was recorded. Friability was calculated by using following formula.

$$\%F = \frac{(W_i - W_f)}{W_i} \times 100$$

For any compressed uncoated tablet; friability lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.¹⁸

Weight variation test

All the formulations of Acebrophylline sustained release tablets were evaluated for weight variation as per USP monograph. Twenty tablets from each batch were weighed collectively and individually using an electronic balance. The average weight was calculated with percent variation of each tablet and the process is repeated thrice to calculate standard deviation. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130 mg or less is 10% whereas for average weight between 130-324 mg is 7.5% and for average weight more than 324 mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.^{17,18}

Content uniformity studies

For determination of content uniformity of the all formulations of Acebrophylline sustained release tablets; twenty tablets from each batch were triturated to form powder. Powder equivalent to one tablet was taken and dissolved in 100 ml of phosphate buffer P^H 6.8 and heated at 37 °C for 60 min with constant stirring. The solution was cooled, filtered and after suitable dilution the Acebrophylline content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 273 nm. Each measurement was carried out in triplicate and the average drug content in each formulation was calculated.¹⁹

Swelling Index (SI)

The swelling behaviour of all formulations of Acebrophylline sustained release tablets were measured by studying its weight gain in the dissolution medium under study. The swelling index were determined by placing the tablets in the basket of dissolution apparatus containing 100 ml of phosphate buffer P^H 6.8 as dissolution medium maintaining at 37 \pm 0.5 °C. After every one hour interval and upto 12 h, each dissolution basket

containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.^{18,19}

$$\text{Swelling Index (SI)} = \frac{W_f - W_i}{W_i} \times 100$$

Where W_f and W_i is called as wet and dry weight of the tablet respectively.

In vitro drug release study

The *in vitro* release studies were conducted for all Acebrophylline sustained release matrix tablet formulations using eight stations USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.) maintaining at 37 ± 0.5 °C. To simulate the physiological conditions of GIT, first 2 h of dissolution was carried out in 900 ml of simulated gastric fluid (SGF, 3.2 mg/ml pepsin in 0.05M HCl, P^H 1.2) and the rest of the time in 900 ml of simulated intestinal fluid (SIF, 10 mg/ml pancreatic fluid in phosphate buffer, P^H 6.8). At regular intervals of time (every 1 h interval), the aliquots were withdrawn and analyzed for drug using the UV-Visible spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at λ_{max} 273 nm both for HCl buffer P^H 1.2 and phosphate buffer P^H 6.8. After each sampling an equal volume of fresh dissolution media was added to the dissolution medium. All the dissolution studies were repeated thrice and mean and standard deviation was calculated. The obtained mean percentage cumulative drug release was plotted with respect to time.²⁰

In vitro drug release kinetic studies

The rate and mechanism of release of Acebrophylline from prepared sustained release tablets were analyzed by fitting the dissolution data of optimised formulation (ASRF₁₀) into following exponential equations. Zero order release equation is calculated by following equation.

$$Q = K_0 t$$

Where Q is the amount of drug released at time t and K_0 is the zero order release rate constant. The first order equation is calculated by following equation.

$$\log(100 - Q) = \log 100 - \frac{K_1 t}{2.303}$$

Where, K_1 is the first order release rate constant. When the data are plotted as logarithm of cumulative percent drug remaining versus time, it yields a straight line, indicating that the release follows first order kinetics. The constant K_1 can be obtained by multiplying 2.303 with slope.

The dissolution data was fitted to the following Higuchi's equation.

$$Q = K_2 t^{1/2}$$

Where, K_2 is the diffusion rate constant. When the data are plotted as accumulative drug released versus square root of time, it yields a straight line, indicating that the drug released by diffusion mechanism. The slope is equal to K_2 .

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems.

$$\log \left(\frac{M_t}{M_\infty} \right) = \log K + n \log t$$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug release after infinite time, K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation. Hixson-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where W_0 is the initial amount of drug, W_t is the remaining amount of drug in dosage form at time t, and K_s is a constant incorporating the surface volume relation. The graphs are plotted as cube root of percent drug remaining versus time.^{19,20}

Stability studies of optimised formulation

The tablets of optimized batch (ASRF₁₀) were packed in air tight bottles and subjected to accelerated stability studies according to ICH guidelines. The accelerated condition that chosen for stability study was 40 ± 2 °C/ $75\% \pm 5\%$ RH (Climatic zone III condition for accelerated testing) using humidity control oven NEC 210R10 (Newtronic Instruments, India) for 90 day. The sample were withdrawn from the humidity control oven on 30th day, 60th day and 90th day for evaluation of physicochemical parameters *i.e.* physical appearance, weight variation, hardness, friability, swelling index, drug content and *in vitro* drug release characteristics.^{21,22}

Results and Discussion

By comparing the spectra of Acebrophylline drug, HPMC, EC and optimised formulation (ASRF₁₀), the sharp peaks that appear in spectra of Acebrophylline at $\sim 3500 \text{ cm}^{-1}$ also appears in optimised formulation (ASRF₁₀) at $\sim 3568 \text{ cm}^{-1}$ due

to presence of -OH functional group. Sharp peak that appears in spectra of HPMC at ~3443 cm⁻¹ also appear in spectra of optimised formulation (ASRF₁₀) at ~3432 cm⁻¹. The broad peak between ~3500 cm⁻¹ to ~3000 cm⁻¹ appears both in HPMC, EC and optimised formulation (ASRF₁₀). The characteristic IR absorption peaks of Acebrophylline at ~1709 cm⁻¹ (C=O stretch), at ~1667 cm⁻¹ (C=C stretch), at ~1475 cm⁻¹ (C-H bend), and at ~1317 cm⁻¹ (C-O bend) were also present in the optimised

formulation (ASRF₁₀) with no shifting in the major peaks and there was no additional peaks formed in the optimised formulation, that indicated no interaction occurred between the Acebrophylline and excipients used in the preparation of different sustained released matrix formulations. The FTIR spectra of Acebrophylline drug, HPMC, EC and optimised formulation (ASRF₁₀) were shown in figure 1.

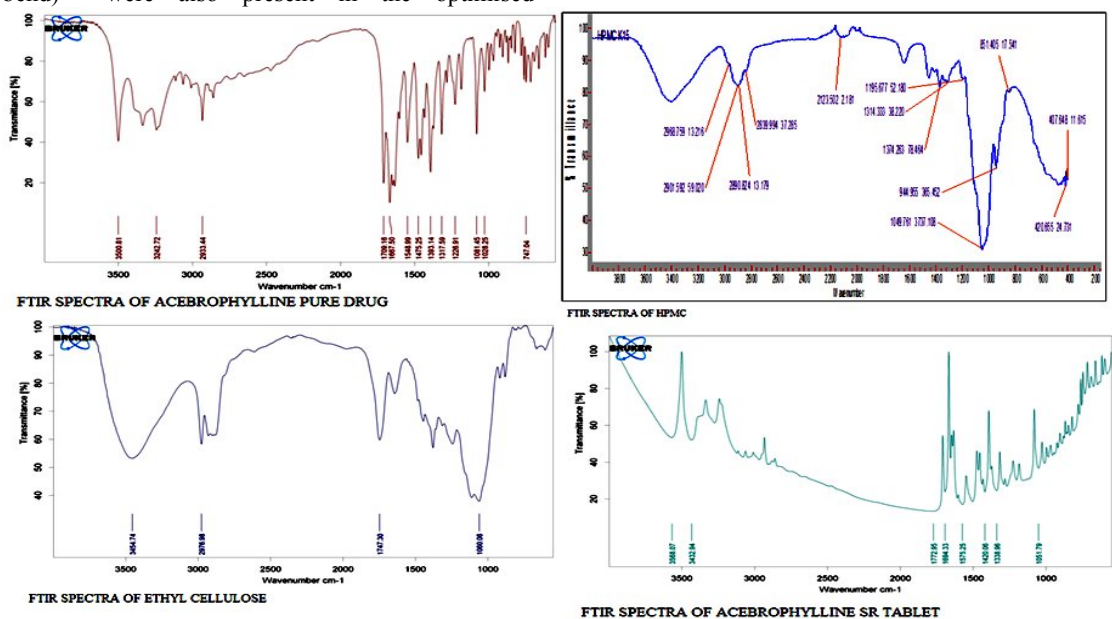


Fig. 1: Compatibility studies through FTIR analysis

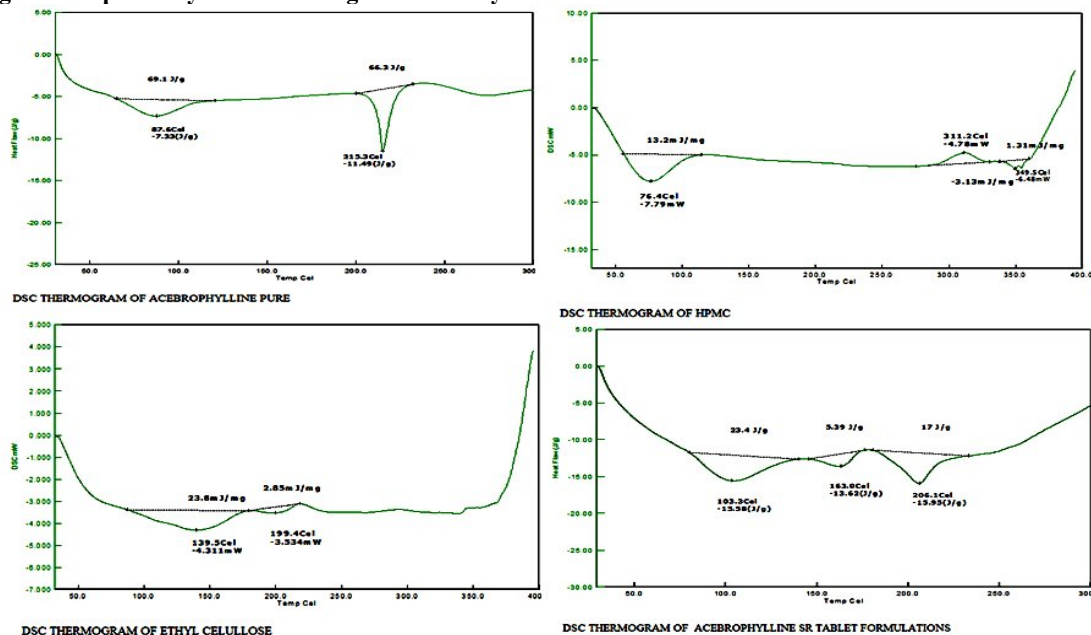


Fig. 2: Compatibility studies through DSC analysis

By comparing the DSC thermogram between pure drug Acebrophylline and optimised formulation (ASRF₁₀), the endothermic peak that appeared between 200-220 °C for Acebrophylline also appeared between 185-220 °C for optimised formulation (ASRF₁₀) that indicated thermodynamically stability of the formulation in addition of Acebrophylline. By comparing the DSC thermogram of EC and optimised formulation (ASRF₁₀) it were observed that the endothermic peak that was found between 100-160 °C in EC also observed with optimized formulation between 90-140 °C. Similarly by comparing the DSC thermogram of HPMC and optimised formulation (ASRF₁₀) it were observed that the endothermic peak that was found between 60-110 °C with HPMC was also observed with optimized formulation between 90-140 °C. The DSC thermogram of pure drug, HPMC, EC and the formulations showed no major shifting *i.e* from endothermic to exothermic with appearance of major thermal peaks in the optimised formulation. The DSC thermogram of Acebrophylline, HPMC, EC and optimised formulation is shown in **figure 2**.

Angle of repose is suited for particle > 150µm. Values of angle of repose ≤ 25° generally indicates the free flowing material and angle of repose ≥ 40° suggest a poor flowing material. The

angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 18.62°±0.25 to 24.56°±0.31 *i.e.* granules of Acebrophylline sustained release tablets showed good flow properties. The bulk densities of Acebrophylline sustained release granules of all formulations were found to be in the range of 0.254±0.06 to 0.294±0.08 g/cm³ and the tapped densities were found to be in between 0.303±0.07 to 0.340±0.06 g/cm³. This indicates good packing capacity of granules. Measurements of bulk density and tapped density found that density of granules depends on particle packing and density changes as the granules consolidates.

All the formulations except ASRF₂ showed Carr's index value less than 16% that indicated good flow properties and values more than 16% indicates presences of more fines with lack of uniformity in particles.

Hausner's ratio is simple method to evaluate stability of power and granule column and to estimate flow properties. In all formulations the Hausner's ratios values were found 'between' 1.10 to 1.19 that indicates good flow characteristics. The precompression characterizations of different batches of sustained released granules are given in **table 2**.

Table 2: Evaluation of precompression parameters of Acebrophylline sustained release granules (ASRF₁ – ASRF₁₂)

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
ASRF ₁	0.266±0.05	0.315±0.05	21.45±0.26	15.56	1.18
ASRF ₂	0.254±0.06	0.303±0.07	24.56±0.31	16.17	1.19
ASRF ₃	0.282±0.07	0.331±0.05	22.38±0.21	14.80	1.17
ASRF ₄	0.278±0.05	0.323±0.06	21.27±0.28	13.93	1.16
ASRF ₅	0.265±0.08	0.302±0.04	22.64±0.19	12.25	1.14
ASRF ₆	0.292±0.07	0.340±0.06	23.72±0.27	14.12	1.16
ASRF ₇	0.284±0.07	0.327±0.07	20.48±0.32	15.14	1.15
ASRF ₈	0.273±0.05	0.321±0.08	21.55±0.35	14.95	1.18
ASRF ₉	0.282±0.08	0.310±0.06	19.38±0.23	09.03	1.10
ASRF ₁₀	0.271±0.05	0.309±0.05	20.52±0.16	12.30	1.14
ASRF ₁₁	0.285±0.07	0.312±0.08	18.62±0.25	08.65	1.10
ASRF ₁₂	0.294±0.08	0.326±0.05	19.74±0.18	09.82	1.11

All values are expressed as mean± SD; (n=3)

The tablets from all formulations were found as white, circular. The surface texture was smooth. Typical tablet defects, such as capping, chipping and picking, were not observed. The average thicknesses of the tablets were ranged from 3.22±0.35 to 3.29±0.34 mm and the variation observed were within prescribed limits. Weight

variations for different formulations were ranged between 352.51±2.54 to 348.64±2.48 mg. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement.

The hardness of all the Acebrophylline sustained released matrix tablets formulations were ranged from 4.65 ± 0.76 to 5.16 ± 0.61 kg/cm² which indicated good handling and transportation characteristics of tablets under study. The percentage friability of all the formulations was ranged from 0.42 ± 0.07 % to 0.62 ± 0.09 %. In the present study, the percentage friability for all for formulations was within the prescribed limits that indicated the product is resistant to wear and tear

during handling and transportation. The percentages of drug content for Acebrophylline sustained released matrix tablet formulations (ASRF₁ to ASRF₁₂) were found to be in between 97.85 ± 1.62 % to 102.82 ± 1.57 % which were within the acceptable limits. The value ensures good uniformity of the drug content in the tablet. The physicochemical characterizations of different formulation of sustained released tablets are given in **table 3**.

Table 3: Evaluation of post compression parameters of Acebrophylline sustained release matrix tablets (ASRF₁-ASRF₁₂)

F. No.	Average hardness (kg/cm ²)	Average weight Variation (%)	Average friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)
ASRF ₁	5.15±0.72	351.42±2.34	0.58±0.06	3.23±0.23	98.45 ±1.55
ASRF ₂	4.82±0.86	349.52±2.45	0.52±0.08	3.25±0.25	99.24±1.62
ASRF ₃	5.16±0.61	350.36±3.43	0.48±0.07	3.26±0.21	101.35±1.70
ASRF ₄	4.92±0.85	352.51±2.54	0.54±0.06	3.24±0.32	101.54±1.36
ASRF ₅	4.86±0.74	351.48±2.72	0.59±0.08	3.23±0.28	100.67±1.64
ASRF ₆	4.90±0.69	348.82±2.56	0.52±0.07	3.29±0.34	99.46±1.53
ASRF ₇	4.65±0.76	349.32±3.68	0.57±0.08	3.22±0.35	97.85±1.62
ASRF ₈	5.08±0.82	350.68±2.12	0.62±0.09	3.26±0.24	98.45±1.45
ASRF ₉	4.75±0.76	351.57±2.28	0.61±0.06	3.22±0.38	101.62±1.52
ASRF ₁₀	5.12±0.82	352.26±2.65	0.48±0.05	3.25±0.25	99.53±1.54
ASRF ₁₁	5.18±0.92	351.51±2.56	0.42±0.07	3.24±0.31	101.67±1.48
ASRF ₁₂	4.92±0.75	348.64±2.48	0.46±0.05	3.25±0.27	102.82±1.57

All values are expressed as mean± SD; (n=3)

Swelling study was performed on all the formulations (ASRF₁ to ASRF₁₂) upto 12 hours. The formulation containing more concentration of HPMC K4M, HPMC K15M showed higher swelling indices due to higher hydrophilicity and more water uptake of the polymers. But reverse is observed with the formulations containing higher percentage of ethyl cellulose, as it is a hydrophobic polymer. The formulations ASRF₁ to ASRF₆ those were containing HPMC in different proportion, showed higher swelling index. The formulation ASRF₆ that containing 30% of HPMCK15M showed highest swelling indices whereas the formulation ASRF₇ containing 20% of HPMC K4M and 10% of ethyl cellulose showed lowest swelling indices. Formulations ASRF₇ to ASRF₁₂ that contained ethyl cellulose along with HPMC had lower swelling indices compared to other formulations as ethyl cellulose is a hydrophobic polymer. The comparative swelling index for all the formulations were shown as histogram in **figure 3**.

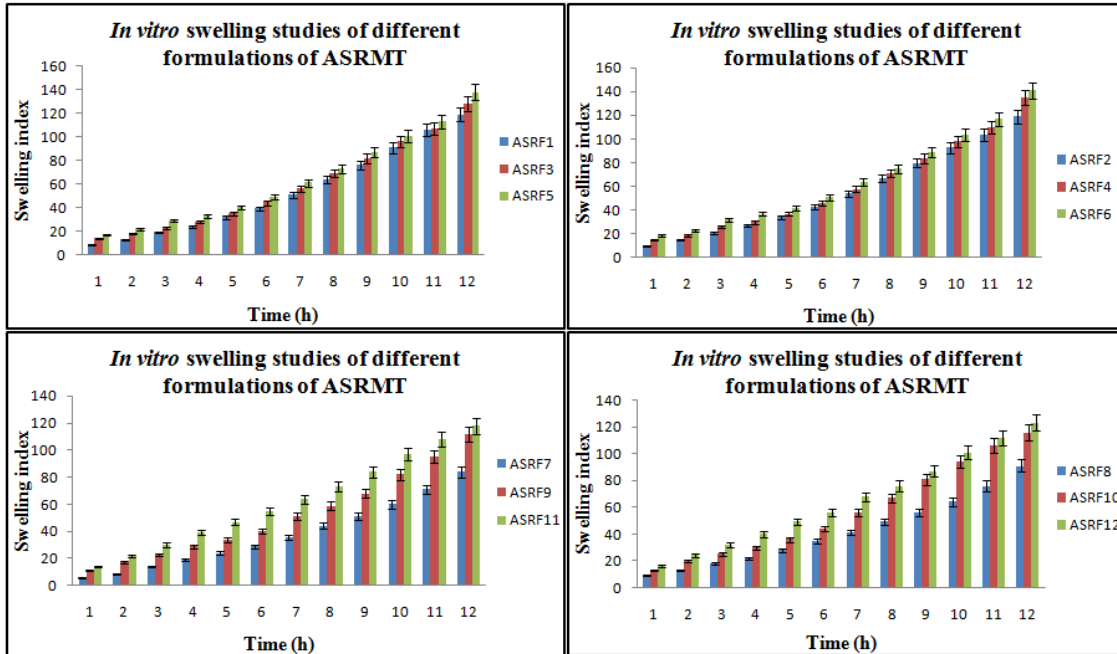
In order to optimise the *in vitro* drug release profile of Acebrophylline sustained released matrix tablets; different hydrophilic matrix polymers *viz.*, HPMC K4M, HPMC K15M and hydrophobic matrix polymer *viz.*, ethyl cellulose were used and twelve different formulations were prepared.

Between the two grades of HPMC used, HPMC K15M having better controlled release profile than HPMC K4M as it is having higher viscosity. It was observed that using HPMC polymer alone causes initial burst release because drug is hydrophilic in nature and maximum of drug was released upto 8 to 10 h which is noticed in case of formulation ASRF₁ to ASRF₆. To reduce the initial burst release of drug and to maintain sustained release effect for required period of time, one more hydrophobic polymer *i.e.* ethyl cellulose was added.

The formulation (ASRF₇ and ASRF₈) that contained 20% of HPMC and 10% of ethyl cellulose had low initial release with less than 95% of release upto 12 h. By increasing the concentration of HPMC the prolong release effect increased and it was found optimum at HPMC polymer concentration of 30%. The formulation ASRF₁₀ that contained 20% of HPMC K15M and 5% of ethyl cellulose was considered as optimised formulation as the initial release was 15% and maximum release upto 12 hours. This release profile complies with the release profile of marketed formulation. Further increase in the concentration of ethyl cellulose; the initial release rate was much slower which was not desirable. So 5% of ethyl cellulose was considered as optimum. The optimised formulation is supposed

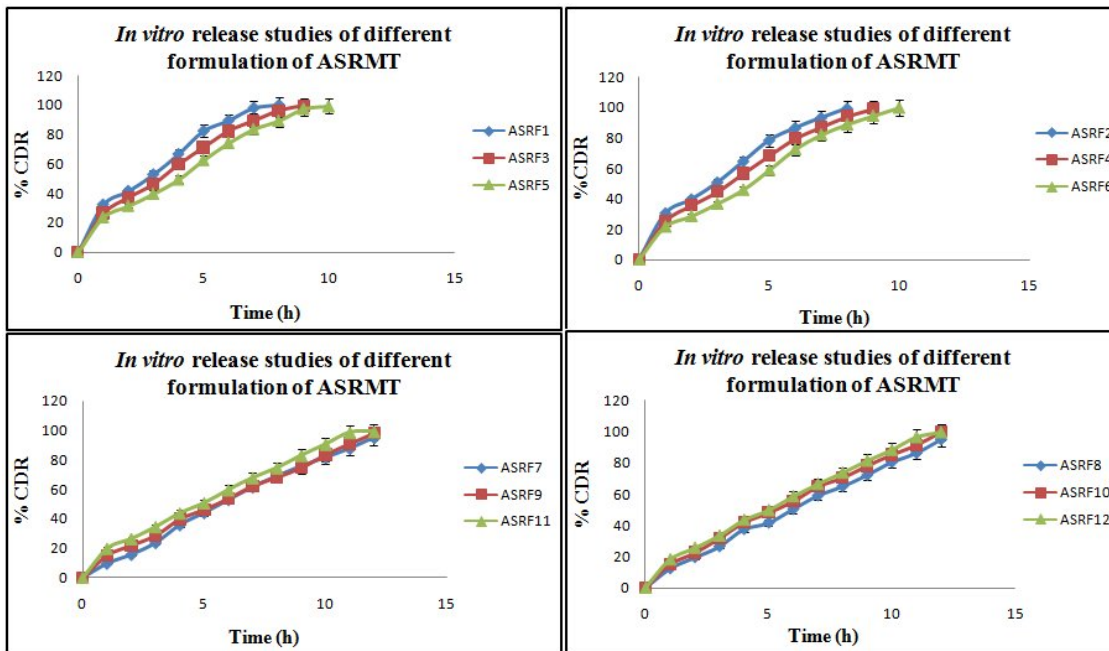
to be superior in comparison to available marketed conventional dosage form as once daily medication is possible that may improve patient compliance and may give therapeutic benefit to patient. The

comparative drug release profiles with respect to concentration of polymers for different formulations were shown in figure 4.



All values are expressed as mean± SD; (n=3)

Fig. 3: Comparative swelling studies of all the formulations with respect to concentration of polymers used



All values are expressed as mean± SD; (n=3)

Fig. 4: Comparative dissolution profile of different formulations of Acebrophylline sustained release tablet with respect to concentration of polymer used

The *in vitro* dissolution data of optimised formulation (ASRF₁₀) were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppas kinetic model equation and the graphs were plotted (Figure 5). The zero order release plot was found fairly linear as indicated by its highest regression (0.992) values. The release exponent 'n' for optimised formulation ASRF₁₀ was found to be 0.779 (0.5 < n < 1), which

appeared to indicate an anomalous diffusion coupled with erosion. So in present study *in vitro* drug release kinetic of optimised formulation of Acebrophylline sustained release matrix tablets (ASRF₁₀) followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. The comparative regression values of different kinetic models for the optimised formulation were given in table 4.

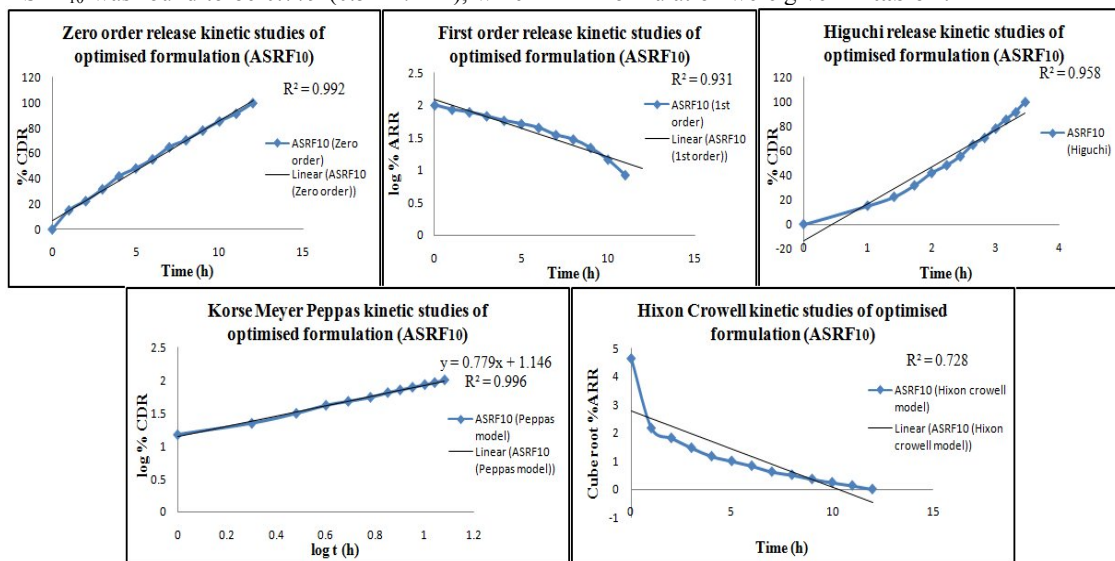


Fig. 5: *In vitro* release kinetic studies of optimized formulation (ASRF₁₀)

Table 4: Regression values of *in-vitro* release kinetic study of optimized Acebrophylline sustained release matrix tablet (ASRF₁₀)

Formulation	R ² value of Zero order	R ² value of 1 st order	R ² value of Higuchi model	R ² value of Hixon-Crowell model	R ² value of Peppas model	'n' value of Peppas model
ASRF ₁₀	0.992	0.931	0.958	0.728	0.996	0.779

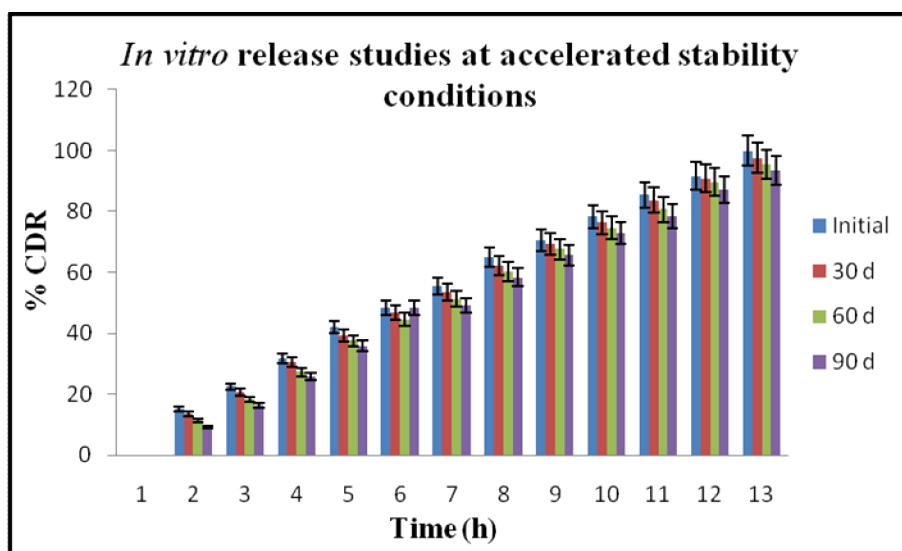
The optimised formulation ASRF₁₀ of Acebrophylline sustained release matrix tablets was selected for the accelerated stability studies. It did not show any significant change in physicochemical characteristics *i.e* physical appearance, weight variation, hardness, friability, swelling studies, drug content and *in vitro* drug release characteristics. More than 90% of the drug had been retained after *in vitro* dissolution studies stored under stressed

condition for 3 months. Thus, it was found that the sustained release matrix of Acebrophylline (ASRF₁₀) were stable under accelerated storage conditions for at least 3 month. The results of change in physicochemical characteristics and *in vitro* release profile of optimised formulation at different time interval in accelerated stability conditions were shown in table 5 and figure 6 respectively.

Table 5: Comparative physicochemical characterization of optimized batch (ASRF₁₀) at accelerated conditions (40 °C ± 2 °C/ 75% ± 5% RH)

Sl. No.	Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
1	Physical appearance	White, circular, concave smooth surface without any cracks	No change	No change	No change
2	Weight variation	352.26±2.65	352.08±2.48	351.86±2.32	351.65±2.51
3	Hardness	5.12±0.82	5.04±0.85	4.95±0.66	4.86±0.74
4	Friability	0.48±0.05	0.52±0.03	0.56±0.04	0.63±0.05
5	Swelling index	116 ±2.35	112 ±2.38	109 ±2.14	105 ±1.96
6	Drug content	99.53±1.54	98.65±1.36	95.56±1.62	92.72±1.40

All values are expressed as mean± SD; (n=3)



All values are expressed as mean \pm SD; (n=3)

Fig. 6: Histogram showing in vitro drug release profile of optimised formulation at stressed condition

CONCLUSION

In the present investigation Acebrophylline sustained release matrix tablet were successfully developed. The major challenge in these studies was to design a sustained release matrix tablet of Acebrophylline that can provide sustained release effect upto 12 h by using different grade of hydrophilic polymer HPMC and hydrophobic polymer ethyl cellulose and weight granulation techniques were adopted. The main objective of using hydrophobic polymer ethyl cellulose with HPMC was to prevent the burst release effect the hydrophilic drug under study which was successfully developed. Formulation ASRF₁₀ that contained 20% of HPMC K15M and 5% of ethyl cellulose showed 15% of drug release within first hour that may be essential to elicit pharmacological response and sustained release upto 12 h with almost complete release (99.89%) emerged as optimised formulation. The precompression and postcompression evaluation studies satisfied according to pharmacopoeia specification. Kinetic of *in vitro* drug release of ASRF₁₀ followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. FTIR and DSC studies revealed that there is no chemical and thermal interaction between drug and excipients used in the present studies. The accelerated stability studies for the optimised formulation were revealed that the formulation was stable without any remarkable physicochemical changes. Thus the results of the current study clearly indicate a promising potential of the Acebrophylline sustained release matrix tablets system as an alternative to the conventional dosage form as it enhance bioavailability of the Acebrophylline by producing a sustained release effect and can be therapeutically

beneficial for sustainable asthma. However, further clinical studies are needed to assess the utility of this system for patients suffering from asthma.

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