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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF ACEBROPHYLLINE

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ABSTRACT

In the present study development of a polymer-based matrix tablet was undertaken to produce a sustained-release dosage form of Acebrophylline, since this dosage forms is relatively simple and cheap to produce when compared to other. Different batches of drug Acebrophylline tablets were manufactured by wet granulation technique, and evaluated for Pharmacopoeial and non-Pharmacopoeial specifications. Dissolution testing was undertaken using USP Apparatus 2 (Paddle Type), which allowed for a more realistic assessment and prediction of *in vitro* drug release rates. Samples were analysed using a high performance liquid chromatographic method (HPLC). Formulation F5 shows optimum drug release. Drug and rate retarding polymers ratio used in this formulation were Methocel K100 LV (14.86% w/w) and Methocel K4M (10.14%w/w), in ratio (5.4:1.34:1). The results of *in vitro* drug release studies were treated with zero order, first order kinetics, Higuchi, Hixon-Crowell and Korsemeyer-Peppas model. In our experiments, the *in-vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (r^2= 0.972 to 0.999) to confirm the diffusion mechanism. The data were fitted into Korsemeyer-Peppas model. All formulations F1 to F6 showed high linearity (r^2= 0.969 to 0.998), with slope (n) values ranging from 0.383 to 0.683. This indicates that F1,F2 and F3 shows purely diffusion and F4, F5 and F6 shows coupling of diffusion and erosion mechanism so called anomalous diffusion. Stability testing was carried out at 40^0C ± 2^0C/75% ± 5% and 25^0C ± 2^0C/ 60% ± 5% and indicated that the product was stable.

Keywords: Acebrophylline, Methocel K100 LV, Methocel K4M, Higuchi's equation, First order kinetics.

INTRODUCTION

In the recent years considerable attentions has been focused in the development of extended release drug delivery system (ERDDS). The basic rationale of ERDDS optimizes biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug in such a way that its utility is maximized, side effects were reduced and control of condition as well as cure, in the shortest possible time by using minimum quantity of drug administered by the most suitable route becomes possible. Sustained drug release system includes any drug delivery system which achieves slow release of drug over an extended period of time, and includes both prolonged and controlled drug release system. If such a release system is effective in maintaining substantially constant drug level in the blood or target tissues, it is considered as controlled release drug delivery system. If, however, a drug delivery system is unsuccessful at achieving substantially constant blood or tissue drug levels, but nevertheless extend the duration of action of drug over that achieved by conventional delivery, it is considered a prolonged release system (fig. 1).([1])

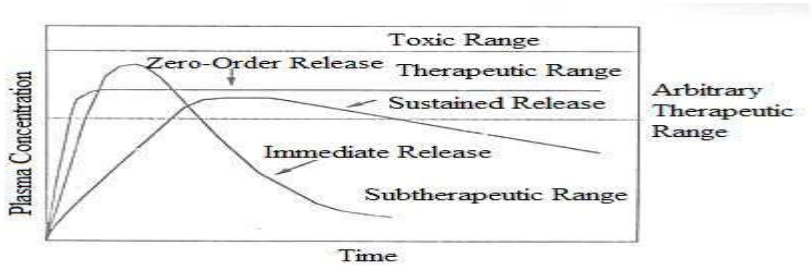

Fig. 1: Plasma drug concentration profiles for conventional tablets formulation, a sustained release formulation and a zero order controlled release formulation.

Acebrophylline is obtained by reaction of the Ambroxol base and Theophylline-7-acetic acid. The carboxyl group of Theophylline-7-acetic acid was solified 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 level of xanthine derivative which are nevertheless high enough to ensure a carrier effect for Ambroxol.([2])Acebrophylline is a bronchodilator with mucosecrytolytic and anti-inflammatory activity (fig. 2).([3, 4])

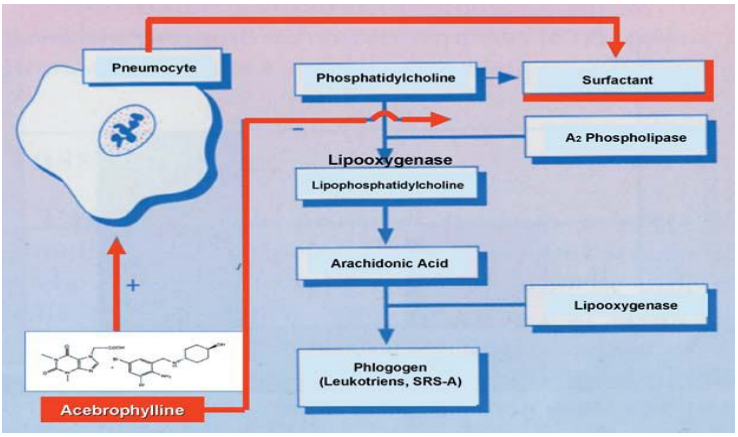

Fig. 2: Effects on mucus and antiinflammatory action of acebrophylline. (Modified from G Cocco, GIMT (Suppl 1); 1992: 103-107)

Acebrophylline is therapeutically effective in patients with chronic obstructive or asthma-like bronchitis, acute or chronic bronchitis, and recurrence of chronic bronchitis; it reduces the frequency of episodes of bronchial obstruction. The success of therapy depends on selection of appropriate delivery systems as much as it depends on drug itself. Sustained release formulation of Acebrophylline can reduce the fluctuation in plasma drug concentration, thus minimizing or preventing plasma peak related adverse event, and allow prolongation of dosing interval, thus allowing once daily administration with inherent benefits in term of patient compliance.

The objective of the present study is to design a sustained release tablets containing Acebrophylline using different grades of HPMC as matrix former by aqueous wet granulation technique for drug delivery through GIT.

MATERIALS AND METHODS

Acebrophylline, Methocel K100 LV & Methocel K4M were received as a gift sample from Akums Drugs & Pharmaceuticals Ltd. Haridwar, Uttarakhand. Other materials used were of analytical grade, and procured from commercial sources.

PREFORMULATION STUDIES

DRUG- EXCIPIENTS COMPATIBILITY STUDY

Excipients are generally a pharmacologically inactive substance used as a carrier for the active ingredients of a medication. Drug and excipients were mixed separately in 1:1 proportion used for tablet formulation. The glass vials were sealed and placed in the stability chamber at 25°C/60% RH, 40°C /75 % RH and 60°C for 21 days. The sample was analyzed

for colour change, and odours after 7, 15, and 21 days. The IR spectra was taken after 10 days and 15 days and analyzed for any shift in major peaks. The primary objective of this investigation was to identify any incompatibility existing between ingredients.

FORMULATION DEVELOPMENT

Preparation of acebrophylline tablet was carried out by wet granulation method. A batch size of one thousand tablets was planned for each formulation based on trial-error method and the quantity for each tablet was expressed in milligram (Table 1).

Table 1: Formulation development of different trial batches.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Premix materials						
Acebrophylline	202.5	202.5	202.5	202.5	202.5	202.5
Methocel K-100 LV	60.00	56.00	52.00	48.00	50.00	50.00
MCC PH 01	18.25	18.25	18.25	18.25	18.25	16.25
Binder						
PVP K30 IP (2.5%)	8.75	8.75	8.75	8.75	8.75	8.75
IPA (ml)	0.15	0.15	0.15	0.15	0.15	0.15
Lubrication						
MCC PH 102	27.50	27.50	27.50	27.50	27.50	27.50
Methocel K4M	27.50	31.50	35.50	39.50	37.50	39.50
Magnesium Stearate IP	3.75	3.75	3.75	3.75	3.75	3.75
Colloidal SiO_2 IP (0.5%w/w)	1.75	1.75	1.75	1.75	1.75	1.75
Total Wt. (mg)	350.00	350.00	350.00	350.00	350.00	350.00

PREPRATION OF GRANULES

All ingredients were accurately weighed according to the formula. Acebrophylline and Methocel K-100LV passed through sieve number 40, MCC through sieve number 100. All the sifted materials were mixed and transferred to a polyethylene bag and dry mixed for 30 min. PVP K-30 was taken in a stainless steel container and dissolved in hydrated isopropyl alcohol with continuous stirring to get clear binder solution. This solution was filtered through #100 filter cloth. The parameters for granulation were set in Fluidized Bed Processor and binder solution was added at controlled rate for about 20 minutes. After complete addition of binder solution the mixture was continuously mixed to get the desired mass. Necessary additional quantity of IPA was added to get the desired consistency. The wet granules were passed through the multimill using with 8.0 mm screen with knives in forward orientation at slow speed. The wet granules were loaded in the fluidized bed processor and dried till percentage loss on drying (LOD) of 0.5 to 1.0 % w/w was obtained. Percentage loss

on drying was recorded by use of IR moisture balance at 65 ^{0}C for 10 minutes. The dried granules were first passed through sieve of 18 mesh size using a vibro sifter. The granules retained on sieve no.18 were then passed through Cad mill using screen of 1.5 mm with knives in forward orientation at slow speed. Methocel K4M, MCC and Colloidal silicon dioxide were passed through sieve of mesh size 100. Magnesium stearate was passed through sieve of mesh size 40. The granules were added into mixer along with Methocel K4M, colloidal silicon dioxide and blended for 15 min. MCC was then added and mixing was carried out for another 20 minutes. Finally the powder blend was transferred to a polyethylene bag and magnesium stearate, was added and mixed for 15 min. to obtain a uniform blend.

EVALUATION OF ACEBROPHYLLINE GRANULES

The flow properties of granules were characterized in terms of bulk density, tapped density, angle of repose, Carr's index and Hausner ratio.

COMPRESSION

The lubricated granules were compressed in 12 station rotatory punching machine by applying 6-8 Kg/ cm^2 pressure at 12-15 rpm speed with the following specifications. Punch type- D- tooling. Upper punch- 10.7 mm × 4.6 mm (concave and scored). Lower punch- 10.7 mm × 4.6 mm (concave and plain). Die- 10.7 mm × 4.6 mm, round.

EVALUATION OF TABLETS

Tablets of all batches were evaluated for different parameters like physical description, hardness, thickness, friability, drug content, disintegration time and in-vitro drug release.

HARDNESS

The tablets from various trials were evaluated for hardness using the Monsanto hardness tester (Cadmach). Six tablets were used for hardness testing from each batch.

FRIABILITY

Friability was determined by taking 19 tablets (as weight of individual tablet was less than 0.65 gm). Tablets were dedusted and weighed accurately and placed in Roche Friabilator (Electrolab, Mumbai). The apparatus was rotated at 25 rpm for 4 min. After completion of revolution the tablets were again dedusted and weighed. Friability was calculated by the

formula:

$$F = [1- W / W_0] \times 100$$

Where: W_0 = weight of the tablets before the test & W = weight of the tablets after the test.

THICKNESS

The thickness of the tablet was measured by Vernier calipers.

DISINTEGRATION TIME

Six tablets was taken and introduced individually in each tube at same time and disc was added to each tube. Assembly was suspended in beaker containing 900 ml purified water and apparatus was operated for specified time. Assembly was removed from the liquid and observation taken.

WEIGHT VARIATION

Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

IN VITRO DISSOLUTION

In-vitro dissolution of tablet was studied in USP Type-2 dissolution apparatus (Electrolab) employing a paddle stirrer. The dissolution medium used was 900 ml of phosphate buffer pH 6.8. The stirrer was adjusted at a speed of 50 rpm. The temperature of dissolution media was previously warmed to 37 ± 0.5 °C and was maintained throughout the experiment. Five millilitre sample of standard and test solution were withdrawn from dissolution medium by means of syringe at known time intervals and filtered through 0.45 micron nylon membrane filter and analyzed for drug release by measuring the absorbance at 274 nm after suitable dilution in HPLC for chromatogram recording. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium to maintain sink condition. Cumulative percentage amount of Acebrophylline released was calculated.

Percentage drug release =

$$\frac{\text{Sample reading}}{\text{Standard reading}} \times \frac{\text{Wt. of Std.}}{\text{Dilution}} \times \frac{\text{Dilution}}{\text{Wt. of sample}} \times \frac{\text{Potency}}{100} \times 100$$

DRUG RELEASE KINETICS

To analysis the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into Zero order, First

order, Higuchi matrix, Korsemeyer-Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

STABILITY STUDIES

The optimized sustained release tablet of Acebrophylline (F5) was placed in containers covered and stored at ambient humidity conditions at 40^0C and at room temperature i.e. 25^0C for a period of 90 days. The samples were assayed for drug content at regular intervals of 15 days.

RESULTS AND DISCUSSION

DRUG- EXCIPIENTS COMPATIBILITY STUDY

Drug-excipients compatibility study revealed that physical mixture of drug and excipients were compatible upon exposure to room temperature (25°C±2°C/60%±5%), accelerated condition (40°C±2°C/75%±5% RH) and at extreme condition (60°C) at intervals of 1, 2 and 3 weeks. By using these excipients prototype formulation was developed.

EVALUATION OF GRANULES

Wet granulation method was used to prepare formulations by utilizing the compatible ingredients. A total of six trial batches were prepared. Prepared granules were evaluated for bulk density, tapped density, compressibility index, angle of repose and Hausner's ratio and results are presented in table 2. Batch F1 had higher Hausner's ratio and percentage compressibility index than other batches because of lower concentration of lubricant than others hence having comparatively poor flow properties. From table 2 it is clear that batch F5 exhibited lowest Hausner's ratio and percentage compressibility index compared to other batches. Angle of repose of batch F5 was < 25 which shows excellent flow properties in comparison to other batches (Table 2).

Table 2: Precompression results for trial batches.

Batches	Precompression Parameters				
	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (degrees)	Percentage compressibility	Hausner's ratio
F1	0.529	0.612	23.48±0.01	13.56	1.16
F2	0.528	0.588	28.61±0.03	10.20	1.11
F3	0.555	0.625	35.69±0.01	11.20	1.13
F4	0.607	0.683	25.18±0.04	11.13	1.13
F5	0.510	0.562	24.18±0.01	9.25	1.10
F6	0.544	0.610	24.73±0.02	10.82	1.12

EVALUATION OF UNCOATED TABLETS

The in-process quality control parameters like average diameter, thickness, weight variation, hardness, friability and disintegration were evaluated and result are shown in table 3. The average length, width, and thickness were found to be within limit (10.70 mm± 0.2 mm, and 4.4 mm ± 0.4 mm respectively) (Table 3).

Table 3: In-process quality control parameters of the trial batches

Tests	Batch						
	F1	F2	F3	F4	F5	F6	Innovator
Average Diameter (10.7 ±0.2mm)	10.74	10.74	10.80	10.77	10.79	10.75	10.79
Average Thickness (4.4 ± 0.4mm)	4.13	4.14	4.20	4.22	4.11	4.40	4.09
Average Weight (mg)	345.26	351.63	348.63	354.73	352.16	349.16	351.41
% Wt. variation (± 5% of avg.Wt)	± 3.7	± 3.6	± 2.8	± 3.3	± 3.7	± 2.7	± 3.6
Hardness (Kg/cm^2)	6.9	7.1	7.42	7.5	6.5	7.2	6.6
Friability (NMT 1 % w/w)	0.30	0.20	0.21	0.10	0.30	0.15	0.30
Disintegration time(NMT 15min)	13min	14min	14min	16min	12min	13min	12min

IN VITRO DISSOLUTION

Cumulative percentage drug release of uncoated sustained release tablets was estimated for the all six batches at different time intervals and it was showed in (Table 4).

Table 4: In-vitro dissolution of tablets of various trial batches

Test	Time (In House Specification)	Batches					
		F1	F2	F3	F4	F5	F6
Dissolution * (6.8 Buffer) Medium Apparatus- IP Type 1	1^{st}hr (NMT 30 %)	38	35	31	20	26	17
	4^{th}hr (30-65 %)	73	67	66	51	55	49
	8^{th}hr (50-80 %)	88	84	83	70	78	66
	12^{th} hr (NLT- 80 %)	95	96	97	94	98	89

*Dissolution of each batch was taken by means of average value (cumulative release)

In batch F5 drug release was much more controlled & found to be maximum when compared to other batches. Thus in comparison to other batches, batch F5 showed excellent release profile (fig. 3).

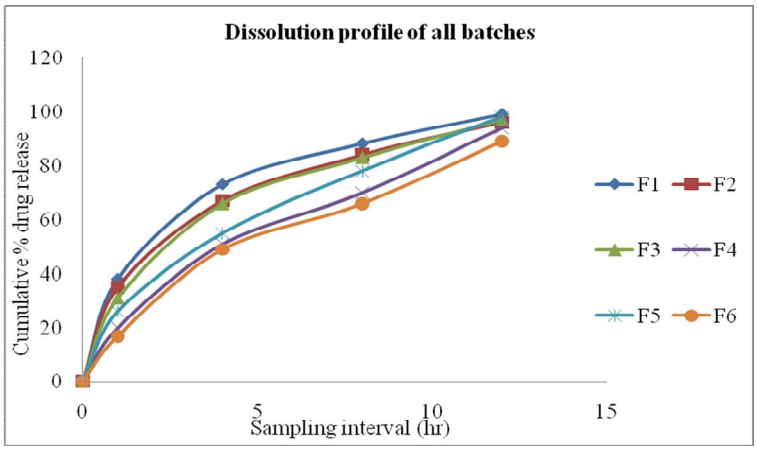

Fig. 3: Comparative cumulative drug releases of trial batches

DRUG RELEASE KINETICS

The correlation coefficients for the different drug release kinetic models are shown in (Tables 5). Models with the highest correlation coefficient were judged to be the most appropriate model for the dissolution data.

Table 5: In vitro drug release model of different trial batches

S. No	Formulation/model and parameter					
	Formulation	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Korsemeyer - Peppas (r^2)/n	Hixon - Crowell (r^2)
1	F1	0.637	0.951	0.972	0.969/0.383	0.978
2	F2	0.691	0.985	0.984	0.974/0.404	0.976
3	F3	0.747	0.970	0.989	0.982/0.464	0.983
4	F4	0.914	0.937	0.991	0.997/0.614	0.979
5	F5	0.873	0.914	0.999	0.992/0.523	0.978
6	F6	0.918	0.966	0.987	0.998/0.683	0.985

The results of *in vitro* drug release studies were treated with zero order, first order kinetics, Higuchi, Hixon-Crowell and Korsemeyer-Peppas model. As clearly indicated in (Table 5), the formulations F4 and F6 follow a zero-order release with higher r^2 value from 0.9142 to 0.918 respectively. All formulation shows high linearity (r^2=0.9000 to 0.985) in case of first order release profile this shows that all formulation follow first order release kinetic. In our experiments, the in-vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (r^2= 0.972 to 0.999). To confirm the diffusion mechanism, the data were fitted into Korsemeyer-Peppas model. All formulations F1 to F6 showed high linearity (r^2= 0.969 to 0.998), with slope (n) values ranging from 0.383 to 0.683. This indicates that F1,F2 and F3 shows purely diffusion and F4, F5 and F6 shows coupling of diffusion and erosion mechanism so called anomalous

diffusion. It might be concluded that the drug release is controlled by more than one mechanism i.e. diffusion coupled with erosion mechanism. As all formulation shows high linearity (r^2= 0.969 to 0.985) in case of Hixon-Crowell plot this shows that surface area continuously decreases with time (Table 6). In our study from all kinetic data we conclude that F5 containing methocel K-100 LV and methocel K4M in 14.28 and 10.71 percent respectively is our best formulation.

Table 6: Release mechanism with variation of n* values

'n'	Mechanism
<0.5	Fickian diffusion
0.5 < n < 1	Non Fickian diffusion or anomalous release
>1	Case II Transport

*The diffusional exponent is based on Korsemeyer-Peppas equation, $Mt/M\infty = Kt^n$

EVALUATION OF ACCELERATED STABILITY

Stability study was conducted on tablets of Batch F5 stored at 25°C ± 2°C/60% RH ± 5% RH (Room temperature) and 40°C ± 2°C/75% RH ± 5% RH (Accelerated condition) for 90 days. Tablets were evaluated for drug content and *in-vitro* release profile. No significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation of Batch F5 was stable (Table 7).

Table 7: Stability data of optimized batch (F5) of Acebrophylline sustained release tablet

S. No.	Sampling Interval (days)	% Residual Drug Contents*		Physical Appearance	
		40^0C / 75%RH	Room temperature	40^0C / 75%RH	Room temperature
1.	0^{th}	99.96 ± 0.010	99.96 ± 0.010	+	+
2	15^{th}	99.83±0.005	99.86±0.012	+	+
3.	30^{th}	99.69±0.015	99.73±0.010	+	+
4.	45^{th}	99.37±0.014	99.55±0.012	+	+
5.	60^{th}	99.03±0.020	99.38±0.016	+	+
6.	75^{th}	98.85±0.018	99.22±0.017	+	+
7.	90^{th}	98.67±0.021	99.07±0.018	+	+

Where (*)= Mean ± SD (n=3), (+) = No change

CONCLUSION

A stable and effective sustained release (SR) tablet containing Acebrophylline in combination with retarding agent Methocel K100 LV (14.86% w/w) and Methocel K4M (10.14%w/w) was successfully developed.

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