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Der Pharmacia Lettre, 2012, 4 (2):530-535
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Design and evaluation of acebrophylline sustained release matrix tablets

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ABSTRACT

In the present study sustained release matrix tablets of Acebrophylline (200mg) were prepared by wet granulation technique using hydrophilic polymers such as HPMC K 100Mwith Sodium CMC of various concentrations to examine their influence on tablet properties on drug release profile. The drug's approach involves several points of attack in obstructive airway disease. The tablets were evaluated for preformulation studies like angle of repose, bulk density, compressibility index and physical characteristics like hardness, weight variation, friability and drug content. In-vitro release of drug was performed in 0.1 N HCl for 2 hours and remaining hours with PBS pH6.8. All the physical characters of the fabricated tablet were within acceptable limits. The stability studies showed that it followed zero order kinetics when fitted to kinetic models (Higuchi, Hixson and Peppas).It was clear from the dissolution profile of acebrophylline from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent. As a concluding remark, F7 acebrophylline were found to be the best selected formulation based on the in vitro release studies.

Keywords: Acebrophylline, HPMC K100, HPMC K15, SCMC, First order release.

INTRODUCTION

Introduction of matrix tablet as sustained release (SD) have given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. Hydrophilic polymer matrix is widely used for formulating an SR dosage form [1-4]. Acebrophylline is therapeutically effective in patients with acute or chronic bronchitis, chronic obstructive or asthma-like 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. Basak SC et al., (2006) [5] has prepared matrix tablet by using employing hydroxypropyl methylcellulose polymer, and the sustained release behavior of the fabricated tablets was investigated. The tablets were prepared by wet granulation method.

Acebrophylline is a bronchodilator with mucosecrytolytic and anti-inflammatory activity. It is used to treat the bronchial asthma, and chronic obstructive pulmonary diseases A successful hydrophilic matrix system should possess a polymer that will wet, hydrate and swell to form a gelatinous layer and avoid disintegration of the tablet. To achieve this, different cellulose derivatives or their combinations have been extensively used in the preparation of matrix tablets. Hydroxy propyl methyl cellulose (HPMC) and sodium CMC is the most widely studied hydrophilic swell able matrix forming material for the preparation of modified drug release products. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading [6-7]. Standard immediate release

marketed tablet of Acebrophylline when taken 2 tablets 4 times daily are chemically equivalent to 300mgdaily dose. The main aim is to formulate cost effective therapeutic equivalent to sustained release matrix tablet of Acebrophylline. The objective of the present study is to design and evaluation of Acebrophylline oral sustained release tablets using polymers such as hydroxy propyl methyl cellulose were formulated in different concentration. Based on the Pre and post formulation characteristic ideal batch will be choose for further studies on release kinetics and stability studies as per ICH guidelines.

MATERIALS AND METHODS

Acebrophylline was received as a gift sample from Surien Pharma Pvt Ltd, Chennai. Hydroxypropylmethylcellulose K100 from Maral Labs, Chennai and Sodium carboxymethyl cellulose were obtained as gifts from Fischer Ltd, Chennai. Hydroxypropylmethylcellulose K 15was purchased from Maizelabs, Mumbai. Magnesium stearates, hydrochloric acid, Acetone, PVP, IPA k-30, Talc, Lactose were purchased from S.D. Fine-Chem Ltd, Ahmadabad, India. Other materials used were of analytical grade, and procured from commercial sources.

Preformulation studies:

Compatibility Studies

A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm-1 using AB.Bomemmodel no. MB 104, Canada. DSC thermograph analysis was also performed to test the interaction.

Evaluation of Acebrophylline Granules

The flow properties of granules (before compression) were characterized in terms of angle of repose [8], tapped density, bulk density [9], and Carr's index[10]and Hausner ratio.

Preparation of Acebrophylline matrix tablets

The required quantity of Acebrophylline was passed through 20#, ingredients such as MCCP, DCP, CMC and HPMC K 100M was weighed and passed through 40# sieve separately. The above ingredients were mixed thoroughly for 15min in a poly bag. The binder PVP K 30 was passed separately through 40#. The resultant mixture was wet massed using IPA and water as solvent (q.s) for granulation. The clear solution was mixed thoroughly to the above mixture to form a coherent mass and kept for drying at 40-60^0 C until LOD NMT 1%.The dried granule was passed through 20# sieve in order to form granules. This dried granule was mixed with Talc and HPMC K 15 for 10 minutes, which was previous, passed through 60# Sieve. The granules were punched to tablets using 10mm (D-tooling 27 station) multi-punching machine. The compositions of the tablet formulation is in (Table 1)

Table: 1 Composition of different batches of Acebrophylline matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
Acebrophylline	200	200	200	200	200	200	200
MCC	10	10	15	15	15	15	20
DCP	5	10	10	15	17	24	25
CMC Na	8	8	7	6	6	5	5
HPMC K 100	48	43	40	36	35	30	25
HPMC K 15	9	9	8	8	7	6	5
PVP K30	15	15	15	15	15	15	15
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	2	2	2	2	2	2	2
Magnesium Sterate	3	3	3	3	3	3	3
Avg Wt	300	300	300	300	300	300	300

Physical evaluation of tablet

Weight variation

20 tablets from each formulation were weighed using an electronic balance and mean and relative study deviations of weight were determined based on an official method [11].

Hardness and friability: [11]
The diametrical crushing strength test was performed on 10 tablets from each formulations using Monsanto hardness tester. For each formulation, the friability of 20 tablets was determined using a Roche friabilator. 20 tablets from each formulation were weighed and tested at speed of 24 rpm for 4 min. After removing of dusts, tablets were reweighed and friability % was evaluated using the following equation,

$$\% F = W1 - W2/W1 X 100$$

W1 = Initial weight of tablet W2 = Final weight of tablet

Drug content: [12]
From each batch, 20 tablets were taken and finely powdered. A portion equal to100 mg of Acebrophylline was accurately weighed, suitably dissolved and diluted using pH 6.8. The absorbance was measured spectrophotometrically using UV spectrophotometer (Schimadzu UV1700 Pharmaspec) at 272nm.

Dissolution studies:[12]
The release rate of Acebrophylline from matrix tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus I1 (Paddle Type). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 100 rpm for 2 hours and pH 6.8 Phosphate buffer for 22 hours. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 272 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

***In vitro* drug release kinetic studies**
Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order [13], first order[14], Higuchi square root [15], Korsmeyer- Peppasmodel [16]. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

Stability studies
Selected formulation was subjected to stability studies as per ICH guidelines sample was taken and analyzed at a time interval of 30 days for 3 months.

RESULTS AND DISCUSSION

Compatibility studies
The compatibility between the drug and the selected polymers was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the polymer-drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymers. DSC analysis was also performed with polymers in combination with drug 1:1 it seems to be no interaction in the melting point of Acebrophylline.

Granular characteristics
The angle of repose of prepared Acebrophylline matrix tablet was in the range 20°-30°. Normally if the value falls between 20°-30°, it shows good flow property. The bulk density and tapped density were found to be in the range of 0.64 to 0.78 g/cm^3 and 0.82 to 0.89 g/cm^3 respectively. A Hausner ratio was within the range of 1.13 to 1.32, lesser than 1.25 is considered to be an indication of good flow property. The compressibility index was within the range of 10-25 hence falls within the good range .(Table 2)

Table: 2Precompression parameters of Acebrophylline granules

Formulation	Angleof Repose(θ)	Bulk density g/cc	Tapped density g/cc	Compressibility index (%)	Hausner,s ratio (%)
F1	25˚71’	0.74	0.86	13.95	1.16
F2	26˚42’	0.72	0.82	12.19	1.13
F3	28˚93’	0.69	0.87	20.68	1.26
F4	24˚32’	0.64	0.85	24.70	1.32
F5	25˚43’	0.75	0.89	15.73	1.18
F6	29˚47’	0.78	0.89	12.35	1.14
F7	28˚45’	0.74	0.86	13.95	1.16

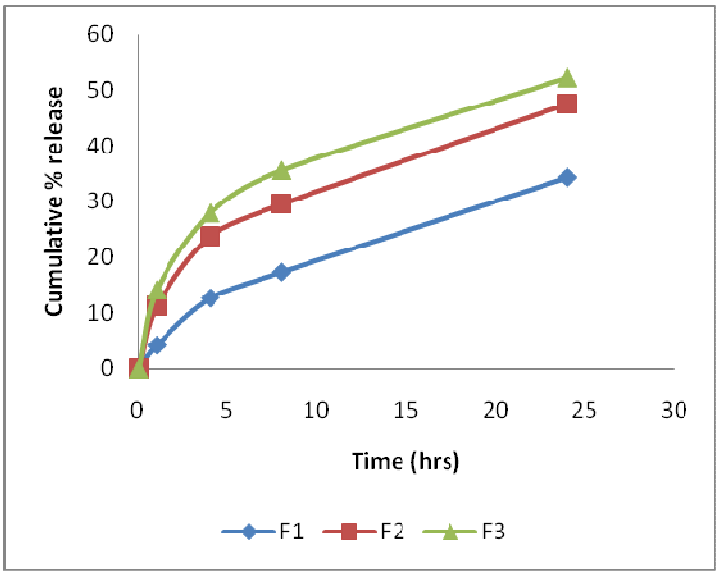
Post compression parameters

The post compression characteristic for all the formulated batches was found to be within the limits as per Indian pharmacopeia 2007. The hardness was found to be within 6-7 Kg/cm^2 in all the formulations. In all the formulations, the friability value is less than 1% giving an indication that tablets formulated are mechanically stable. All the tablet formulations compile the weight variation test. The weight of all the formulations was found to be within the limits. The assay of all the formulations was found to be within the 97% to 103% acceptable limit. The thickness and diameter of tablets was measured by vernier calipers (Table 3)

Table: 3 Post compression parameters of Acebrophylline matrix tablets

Formulation	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Friability(%)	Drug content (%)
F1	Compiles	3.31	9.87	6	0.05	99.56
F2	Compiles	3.46	9.78	7	0.06	98.45
F3	Compiles	3.27	9.76	6	0.03	99.12
F4	Compiles	3.34	9.87	7	0.005	98.22
F5	Compiles	3.66	9.91	6	0.06	97.44
F6	Compiles	3.23	9.92	6	0.001	99.61
F7	Compiles	3.56	9.89	6	0.05	99.82

Figure: 1 Comparison of in vitro dissolution of F1- F3



***In vitro* dissolution studies**

The Invitro release studies are given in table 4. All the formulation was subjected to dissolution studies and it was absorbed that the batch F7 showed about 91.11% of release and was found to be maximum when compared to other batches. Formulated batch F1 and F2 showed a slow release pattern with about only 47.66% and 59.11% of drug release at the end of 24 hours, and the batches F3, F4, F5, F6 showed a release of about 64.55 to 87.32% of drug

release (Table 4). Release profile was given in (Figure 1 and 2).*Invitro* studies were carried out only for that formulation which passed in their physical parameters. The % drug release of final formulation F_7 was found to be 91.11% and came within the limits.

Figure: 2 Comparison of in vitro dissolution of F5- F7

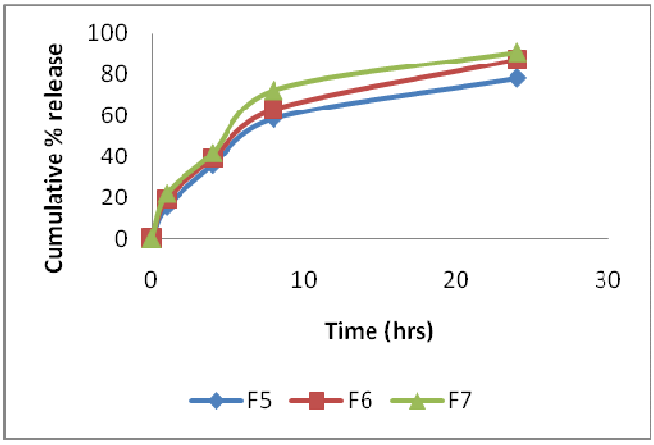


Table: 4 Percentage cumulative drug release of Acebrophylline

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
1	4.2	11.2	14.11	14.75	15.39	18.97	21.76
4	12.68	23.78	27.89	33.91	35.9	39.22	41.61
8	17.32	29.56	35.57	51.57	58.46	62.86	72.31
24	34.36	47.56	52.17	69.67	78.23	87.32	91.11

***In vitro* release mechanism**

The model that gives high "$r^2 > 0.98$" value is considered to be the best fit for the release data. The "r^2" values for zero order, first order, and Higuchi model and korsmeyers plot are given in table-5. The results given in table 5 indicate that the drug release from the matrix tablets follows first order kinetics.

Table: 5 Kinetics data for optimized formulation F7

Kinetics model	R^2
Zero order	0.7752
First order	0.9803
Higuchi	0.9755
Koresmeyer Peppas	0.9788

Stability study for the optimized formulation F7

The formulations were tested for accelerated stability studies, to access the long term stability for 6 months. When estimated for the evaluation studies for the period of 3 months, the formulation F7 doesn't show much change in their characteristics. Thus the formulation is stable.

Table: 6 Stability study (40 °C/75%RH) of Optimized Formulation (F7)

Time in days	Physical changes	Drug content (%)	*In vitro* drug release (%)
0	----	99.40 ± 0.92	90.15
30	No change	99.30 ± 0.97	90.18
60	No change	99.10 ± 0.98	90.06
90	No change	99.06 ± 0.90	89.87

The sustained release formulations of Acebrophylline were studied in this work. From the study it was concluded that high viscosity grade HPMCK100 with K 5M showed a good retardation effect over drug release. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. Increase in the concentration of the polymer results in a decrease in cumulative percentage drug release. To evaluate drug release mechanism from

the tablets, plots of percent released versus square root of time as per Higuchi's equation were constructed. The formulations F7 show better linearity for Higuchi release kinetics with (r>0.9755). It indicates that the drug release is by diffusion mechanism. The values of n<0.66 indicates Therefore the drug release is by diffusion and erosion mechanism throughout the period.

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