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FORMULATION AND EVALUATION OF ACEBROPHYLLINE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

In the present work, an attempt has been made to prepare controlled release matrix tablets of Acebrophylline, an airway mucus regulator with anti-inflammatory action by wet granulation method using HPMC K 100, HPMC K 15 and CMC as polymer in different ratios. The prepared tablets were tested for physical parameters like weight variation, hardness, friability, content of active ingredient and *In-vitro* drug release studies. The results obtained were within the prescribed limits. The IR spectrum shows that both drug and polymer were not interacted each other and appear as separate entities which is clearly shown in the spectra. The release of Acebrophylline from the matrix tablets was sustained up to 24hrs. 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. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. 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 dissolution data was fitted to Korsmeyer equation which is used to describe the drug release behaviour from polymeric systems. Plots of Log cumulative percent drug release versus log time gives r^2 values. The values of slope n, is less than 0.66 (table 5) indicates the drug release is by diffusion and erosion mechanism. The stability studies were carried out for F-7 formulation at 45°C with 75% RH for 90 days revealed that no considerable differences in drug content and *in-vitro* drug release were observed.

KEY WORDS: Acebrophylline, Matrix Tablet, *In-vitro*, Diffusion.

1. INTRODUCTION

The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ of tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery system can be a major advance towards solving these two problems. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery.In the case of new drug delivery systems, which are based on controlled of programmed drug delivery methods in the vicinity of target tissue, this undeniable fluctuation of drug levels (concentration) between toxic level and sub-therapeutic level can be greatly reduced. This controlled drug-therapy offers a method for which therapeutic action is enhanced and the dangerous toxic level eliminated. The sustained-release products are often designed with an initial dose intended to establish rapidly therapeutic drug blood levels and additional drug intended to maintain those levels for prolonged periods. Those products providing only the slow-release Component and lacking the immediate-release component have sometimes been termed prolonged release. The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. Initial progress in product development rests heavily on a thorough understanding of the absorption, distribution and elimination characteristics of a drug. Absorption, distribution and elimination processes begin when a dose is administered, and may govern the appearance of any therapeutic effect. Pharmacokinetics is used to quantitate these processes. Several categories of drug have potential for their therapeutics improvement of efficacy via sustained-release oral routes e.g.Antianginal, Anti-inflammatory, Antihistaminic, Antigastric resistant agents, Antipsychotic agents and Antidiabetic drugs of agents. The common goal for increased duration is twice a day, or when feasible, once a day. Several properties of the drug itself can lead to the achievement of a 12 to 24 hours oral prolonged release dosage form. The selection of both the drug and

retardant polymers along with the filler excipients will impact on the mechanism and rates of drug release from monolithic systems. Cellulose derivatives and acrylic resin polymers comprise the group of polymers that are presently available as aqueous coatings for pharmaceutical dosage forms. These polymers in the dry state have been utilized in matrix type tablet formulations by directly compressing.

A polymer and active agent have been mixed to form a homogeneous system referred to as a matrix system: To control the release of the drug, which are having different solubility properties hydrophobic, and hydrophilic matrices have been used. For water-soluble drugs, the hydrophobic and hydrophilic polymeric matrices are mixed. The physicochemical properties of the drug are influence the design of oral controlled drug matrix system are Solubility, Partition coefficient and molecules weight, Drug stability, Protein binding. Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. These systems are described in terms of fronts. The following fronts have been defined, with regard to anomalous release systems. Acebrophylline is an airway mucus regulator with anti-inflammatory action. The drug's approach involves several points of attack in obstructive airway disease. The molecule contains Ambroxol, which facilitates various steps in the biosynthesis of pulmonary surfactant, Theophylline-7acetic acid whose carrier function raises blood levels of Ambroxol, thus rapidly and intensely stimulating surfactant production. The resulting reduction in the viscosity and adhesively of the mucus greatly improves ciliary clearance. By deviating phosphatidylcholine towards surfactant synthesis, making it no longer available for the synthesis of inflammatory mediators such as the leukotrienes, Acebrophylline also exerts an inflammatory effect. This is confirmed *in vivo* by the reduction in aspecific bronchial hyper responsiveness in patients with stable bronchial asthma. On a clinical level, 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 and reduces the need for β2-agonists, and improves indexes of ventilator. Standard immediate release marketed tablet of Acebrophylline when taken 2 tablets 4 times daily are chemically equivalent to 4 grams daily 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 choosed for further studies on release kinetics and stability studies as per ICH guidelines.

2. MATERIALS AND METHODS

2.1 Material: Acebrophylline obtained as a gift sample from Surien pharmaceutics, Chennai. Microcrystalline cellulose powder(MCCP) and Dicalcium phosphate (DCP) was obtained as a gift sample from Fischer Ltd, Chennai, Carboxy methyl cellulose sodium (CMC), Hydroxy methyl cellulose K100 (HPMC K100), Hydroxy methyl cellulose K15 (HPMCK 15), poly vinyl pyrrolidone K 30 (PVPK30), Talc and Magnesium stearate was obtained as gift sample from Nice Chemical Ltd, Chemical. All other excipients and solvents used are of analytical grade.

2.2 Drug-Excipient Compatibility Studies

2.2.1 Fourier Transform Infrared Spectroscopy: Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture (1:2) of drug and polymer was prepared and mixed with suitable quanta of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a Shimadzu FTIR 8400 Spectrophotometer. The IR spectrum of the physical mixture was done to detect any appearance or disappearance of peaks. The compatibility between the drug and the polymer were evaluated using FTIR matching method.

2.3 Formulation 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 entire above ingredient was 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 (qs) 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 granules 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. To the above mixture Magnesium stearate as lubricant was added which was previous, passed through 40# Sieve. The granules were punched to tablets using 10mm (D-tooling 27 station) multi-punching machine.

2.3.1 Evaluation of blend characteristics of Acebrophylline matrix tablets: The prepared granules has been studied for blend characteristic such as angle of repose, bulk density, tap density, compressibility index and hausner's ratio. The results were tabulated in table no. 2.

2.3.2Evaluations of post compression characteristics of Acebrophylline sustained release matrix tablets: The formulation of Acebrophylline matrix tablet has been carried out and post compressional evaluation characters such as diameter, thickness, hardness, friability were carried out and tabulated in table 3. Dissolution was also carried out and the results were tabulated in table 4.

2.3.3 In- vitro dissolution studies of Acebrophylline control released tablets: According to USP, dissolution test for Acebrophylline control release tablets was done by using 0.1N HCL for 2hrs and PH 6.8 Phosphate buffer for 22hrs used as a dissolution media. Determine the amount of Acebrophylline dissolved from UV absorbance at the wavelength of maximum absorbance of about 272 nm of filtered portion of the solution under test. The dissolution test was carried out using USP apparatus II with (900ml) dissolution medium Stirring speed was maintained at 37±0.5^{O}C. at 100 rpm, 0.1N HCL was used as dissolution medium for first 2hrs followed by pH 6.8 phosphate buffer for further 22hrs. 10ml of Samples were withdrawn at predetermined time intervals, filtered, dilute suitably and assayed spectrophotometrically. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume. The samples were analyzed spectrophotometrically at 272 nm. Using spectrophotometer to assay the amount of Acebrophylline released at each time interval. Dissolution studies were performed two times for 24 hours for each tablet formulation and the mean values were taken.

2.3.4 Stability Studies: Selected formulation was subjected to stability studies as per ICH guidelines; sample has been withdrawn and analyzed at a time interval 30 days for 3 months.

3. RESULTS AND DISCUSSIONS

3.1. Preparation of Acebrophylline Drug-Excipient Compatibility Studies

3.1.1. Fourier Transform Infrared Spectroscopy: Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture (1:2) of drug and polymer was prepared and mixed with suitable quanta of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a Shimadzu FTIR 8400 Spectrophotometer. The IR spectrum of the physical mixture was done to detect any appearance or disappearance of peaks. The compatibility between the drug and the polymer were evaluated using FTIR matching method. The IR spectra of pure drug and polymer are shown in (figure 1).

3.2. Pre-Formulation Studies: 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's 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.

3.3. Post-Compressional studies: The post compressional 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 pharmacopoeial limit of 95 to 105% (Table 3).

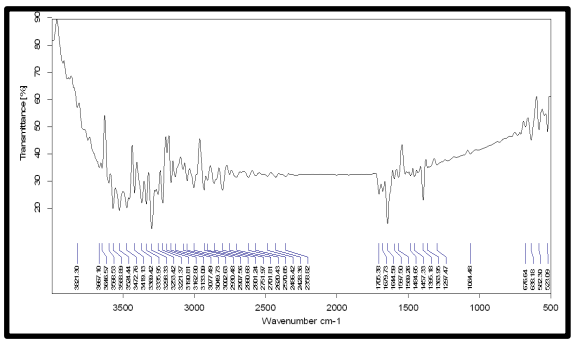
3.4. *In-vitro* dissolution study: All the formulation was subjected to dissolution studies and it was absorbed that the batch F7 showed about 91.11% of release and was found to be maximum when compared to other

batches. Formulated batch F1 and F2 showed a slow release pattern with about only 34.36% and 47.56% of drug release at the end of 24 hours (table 4), and the batches F3, F4, F5, F6 showed a release of about 52.17% to 87.32% of drug release. For the formulation f7 the percentage amount of drug release was found to be with the pharmacopeial limits (not less than 90% within 24 hours), so drug release kinetic studies were conducted to F7 (table 5).

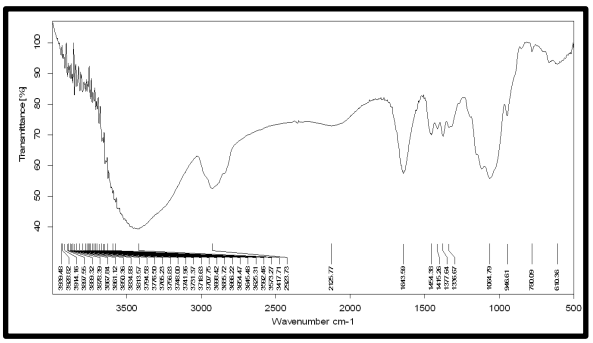
3.5. *In-vitro* release kinetics: The release data of matrix tablets were fitted into various mathematical models (Zero order, First order, Higuchi equation and korsmeyersequation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation co-efficient(r) value in various models. The model that gives high "r" value is considered as the best fit of the release data. The "r" values for zero order, first order, Higuchi model and Kosermeyers peppas are given in table 5. The results given in table 5 indicate that the drug release from the matrix tablets follows Kosermeyers Peppas model, hence the value of Slope (n) is greater than 0.5 and the regression is closer to 1(r=0.9803).

4. CONCLUSION

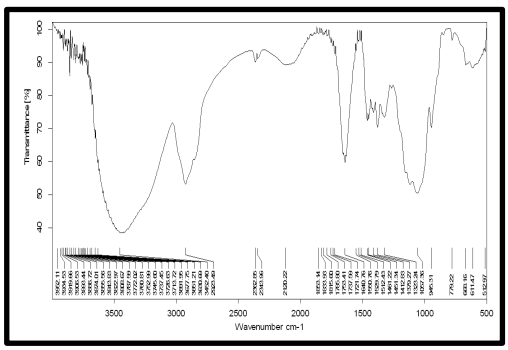
Matrix tablets of Acebrophylline granules showed satisfactory flow properties and compressibility index. Quality control tests were performed for prepared tablets and they are within the prescribed limits as per I.P specifications. The drug content was uniform in all the formulations of tablets prepared. The results indicate uniform distribution of drug within the matrices.IR spectroscopic studies indicated that the drug is compatible with the polymer. The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer level is increased, the drug release rates were found to be decreased. Drug release was found to follow First order kinetics and the mechanism of drug release was found to be diffusion and erosion. Accelerated term stability studies indicated that no appreciable changes in the drug content and In-vitro drug release rates of formulation.



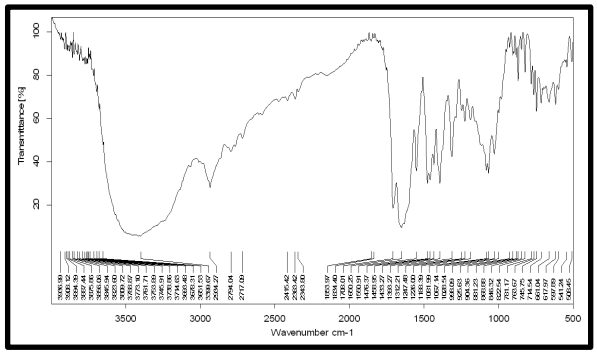
Infrared spectra of the pure drug



Infrared spectra of Acebrophylline and



Infrared spectra of Acebrophylline and HPMC K 100M



Infrared spectra of Acebrophylline tablet

Fig 1: Drug-Excipient Compatibility Studies

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Table.1.Formulation of Acebrophylline SR matrix tablet (quantities are in mgs)

Formulation code	F1	F2	F3	F4	F5	F6	F7
Acebrophylline	200	200	200	200	200	200	200
MCCP	10	10	15	15	15	15	20
DCP	5	10	10	15	17	24	25
CMC	8	8	7	6	6	5	5
HPMCK100	48	43	40	36	35	30	25
HPMCK15	9	9	8	8	7	6	5
PVPK30	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
MS	3	3	3	3	3	3	3

Table.2.Pre-Formulation Studies

Formulation code	F1	F2	F3	F4	F5	F6	F7
Angle of Repose	25˚71’	26˚42’	28˚93’	24˚32’	25˚43’	29˚47’	28˚45’
Bulk Density(gm/ml)	0.74	0.72	0.69	0.64	0.75	0.78	0.74
Tapped Density(gm/ml)	0.86	0.82	0.87	0.85	0.89	0.89	0.86
Compressibility Index(%)	13.95	12.19	20.68	24.70	15.73	12.35	13.95
Hausners ratio	1.16	1.13	1.26	1.32	1.18	1.14	1.16

Table.3.Post compression studies

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

Table.4. *In-vitro* dissolution study

Time(hrs)	Formulation (%Drug release)						
	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

Table.5. *In-vitro* release kinetics data for the batch F7

S.no.	Zero Order	First Order		Higuchi	Kosermeyer Peppas	
	R	k	r	r	n	r
1.	0.7752	0.4568	0.9788	0.9755	0.6684	0.9803

Tab: 6 Accelerated Stability studies data for optimized batch F7

Days	40°C 75%RH		
	Physical changes	Assay (mg)	Dissolution profile at the end of 24 hrs (%CDR)
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

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