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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF AMBROXOL HYDROCHLORIDE SUSTAINED-RELEASE MATRIX TABLETS

S. Jaya * and G. Srilaxmi

Department of Pharmaceutics, Anurag Pharmacy College, Ananthagiri, Kodad, Suryapet - 508206, Telangana, India.

Keywords:

Ambroxol hydrochloride, Matrix tablets, HPMCK15, Xanthan gum

Correspondence to Author:
Dr. S. Jaya

Associate Professor,
Department of Pharmaceutics,
Anurag Pharmacy College,
Ananthagiri, Kodad, Suryapet-508206, Telangana, India.

E-mail: jayamay24@gmail.com

ABSTRACT: The present study involves the formulation and *in-vitro* characterization of sustained release matrix tablets of Ambroxol hydrochloride, a potent mucolytic agent used in the treatment of respiratory disorders. FTIR analysis confirmed the absence of drug-polymer interactions. Sustained release matrix tablets containing 75 mg were formulated employing HPMCK15 and xanthan gum as release retarding polymer and dicalcium phosphate and microcrystalline cellulose as diluents. The powder blend was evaluated for micromeritic properties. The matrix tablets were prepared by direct compression technique. The prepared tablets were evaluated for uniformity of weight, hardness, friability, and uniformity of content. All the formulations showed compliance with pharmacopoeial standards. The *in-vitro* drug release studies were carried out for a period of 12 h using USP type II dissolution apparatus at 50 rpm by taking 900 ml of 0.1 N HCl (pH 1.2) as dissolution medium for first 2 h and later replacing it with 900 ml pH 6.8 phosphate buffer solution for a period of 10 h at 37 ± 0.5 °C. Among the different combinations of polymers in different ratios studied, the desired *in-vitro* drug release (97.65% for 12 h) was found with the combination of HPMC K15M and xanthan gum with the drug in the ratio of 1: 0.75 (F7). The drug release from the F7 formulation followed zero order kinetics and mechanism was found to be erosion.

INTRODUCTION: Oral drug delivery has been the most popular and widely utilized route of administration among all the routes for the systemic delivery of drugs *via* various pharmaceutical products of different dosage forms because of ease of administration, greater flexibility of dosage form design, ease of production and low cost of a system.

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The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and nontoxic for an extended period [1]. Among various dosage forms, matrix systems are widely accepted for sustained oral release (SR) as they are simple and easy to formulate.

Hydrophilic matrix system is the release system, where the drug is mixed with a water-swellable, hydrophilic polymer, excipients and compressed into a tablet. Sustained release formulations are preferred because they maintain uniform drug levels, reduce dose and side effects, better patient compliance and increase safety margin for high potency drugs [2]. Hydroxypropyl methylcellulose (HPMC) is a semi-synthetic derivative of cellulose,

a swellable and hydrophilic polymer [3]. It is very suitable to use a retardant material in sustained release matrix tablets, as it is nontoxic and easy to handle. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media. xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture aerobic fermentation of a carbohydrate with *Xanthomonas campestris* [4].

Ambroxol hydrochloride is a metabolite of bromhexine and is official in the Martindale Extrapharmacopoeia [5]. It is chemically described as Trans-4-[(2-Amino-3, 5-dibromo benzyl) amino] - cyclohexanol. It is widely used as an expectorant and a mucolytic agent used in the treatment of respiratory disorders such as chronic bronchitis and bronchial asthma. Ambroxol hydrochloride is capable of inducing thin copious bronchial secretion [6]. It depolymerizes mucopolysaccharides directly as well as by liberating lysosomal enzymes network of fibers in tenacious sputum is broken [7]. Ambroxol hydrochloride is sparingly water solubility. Hence, it presents significant formulation challenges. Ambroxol hydrochloride has a half-life of 4 h, and the usual oral dosage regimen is 75 mg. Therefore it is an ideal candidate for design as a sustained release dosage form, which would result in prolonged clinical efficacy, reduced frequency of administration and lesser side effects [8]. The main objective of the present work is to develop Ambroxol hydrochloride sustained release matrix tablets using HPMCK15 and Xanthan gum as release retardants.

MATERIALS AND METHODS:

Materials: Ambroxol hydrochloride was obtained from Yarrow chemicals, Mumbai. HPMCK 15 and Xanthan Gum was obtained from Aman scientific products, Vijayawada, Microcrystalline cellulose, Dicalcium phosphate, and Talc were purchased from SD Fine Chem. Limited, Mumbai. Magnesium stearate was purchased from Loba Chemie Pvt. Ltd, Mumbai. All other ingredients used were of analytical grade.

Estimation of Ambroxol Hydrochloride: Lab India double beam UV- Visible spectrophotometer was used to estimate Ambroxol hydrochloride in pure form and formulations developed using various concentrations of polymers at 244 nm in a pH 1.2 buffer and pH 6.8 phosphate buffers in the present study.

Drug - Excipient Compatibility Study: FTIR studies were conducted to know the compatibility between drug and excipients. In these studies pure Ambroxol hydrochloride and its mixture with HPMC K15M and xanthan gum were grounded thoroughly with IR grade KBr and then compressed in a hydraulic press at a pressure of 10,000 psig, to get a disc. Each disc was scanned over a range of 400-4000 cm^{-1} using FTIR instrument (FTIR-1600, Shimadzu, Japan). The characteristic peaks were observed and recorded.

Preparation of Matrix Tablets: Tablets were prepared by direct compression method. All the ingredients listed in **Table 1** were accurately weighed and passed through a # 40 sieve. Ambroxol HCl (75 mg) was mixed with various concentrations of polymer and a microcrystalline cellulose or dicalcium phosphate until a homogeneous blend was achieved. Then magnesium stearate and talc were added to the above blend. The flow property of the final blend was found to be satisfactory to allow the mixture to be directly compressed into tablets on a 12- station rotary tablet punching machine (CEMACH Machineries Ltd., India) using 8 mm dome-shaped punches.

TABLE 1: COMPOSITION OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS

Formulation code	Ambroxol HCl (mg)	HPMCK15 (mg)	Xanthan Gum (mg)	DCP (mg)	MCC (mg)	Magnesium stearate (mg)	Talc (mg)	Total weight of the tablet
F1	75	56.25	-	113.75	-	2.5	2.5	250
F2	75	75	-	95	-	2.5	2.5	250
F3	75	93.75	-	76.5	-	2.5	2.5	250
F4	75	42.19	14.06	113.75	-	2.5	2.5	250
F5	75	56.25	18.75	95	-	2.5	2.5	250
F6	75	70.32	23.43	76.5	-	2.5	2.5	250
F7	75	42.19	14.06	-	113.75	2.5	2.5	250
F8	75	56.25	18.75	-	95	2.5	2.5	250
F9	75	70.32	23.43	-	76.5	2.5	2.5	250

Evaluation of Ambroxol Hydrochloride Tablets: All prepared matrix tablets were evaluated for uniformity of weight. Friability was determined using Roche friabilator. Hardness was measured by using Monsanto hardness tester.

Uniformity of Drug Content: Tablets of each type of formulation were weighed and triturated in a mortar. Powder equivalent to 75 mg of ambroxol was weighed and transferred into 100 ml volumetric flask. 50 ml of pH-6.8 phosphate buffer solution was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with pH-6.8 phosphate buffer solution, the solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45 µm. 1 ml of the filtrate was diluted to 10 ml with pH-6.8 phosphate buffer solution. The absorbance was measured at 244 nm using double beam UV-Visible spectrophotometer [9].

***In-vitro* Drug Release Studies:** *In-vitro* drug release studies were carried out using USP dissolution test apparatus type II Paddle (DBK dissolution testing apparatus, Mumbai, India) at 50 rpm. The dissolution medium consists of 900 ml of pH 1.2 buffer for first two hours and later on pH 6.8 phosphate buffer for a further ten hours. The medium was maintained at 37 ± 0.5 ºC. An aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly and was replaced with fresh dissolution medium. The withdrawn samples were analyzed by an UV-Visible spectrophotometer (Lab India) at 244 nm using (0.1N hydrochloride acid) pH 1.2 buffer or pH 6.8 phosphate buffer as a blank. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating paddle [10].

Kinetics of Drug Release: The kinetics of drug release from the matrix tablets was determined by fitting the appropriate drug release data to zero order, first order, Higuchi equation, Hixson-Crowell equation and the Korsmeyer-Peppas model.

$$\text{Zero-order equation: } Q = Q_0 + K_0 t,$$

$$\text{First order equation: } \ln Q = \ln Q_0 K_1 t$$

$$\text{Higuchi Model: } Q = K_H t^{1/2}$$

$$\text{Hixon -Crowell Model: } Q_0^{1/3} - Q_R^{1/3} = K_S t$$

$$\text{Korsmeyer- Peppas model: } Q/Q_T = K_{KP} t^n$$

Where Q is the amount of drug release at time t, Q_0 is the initial amount of drug, Q_R is the amount of drug remaining at time t, and Q_T is the total amount of drug release. k_0, k_1, k_H, k_s, and k_{kp} are the kinetic constants for zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models, respectively, and n is the release exponent [11].

RESULTS AND DISCUSSION:

FTIR Studies: The results of the FTIR spectrum of pure Ambroxol hydrochloride and optimized formulation F7 was shown in **Fig. 1** and **2** respectively. The characteristic peaks of the drug were observed in the spectra of drug, and optimized formulation F7 indicates that there is no interaction between the drug, polymer and other excipients.

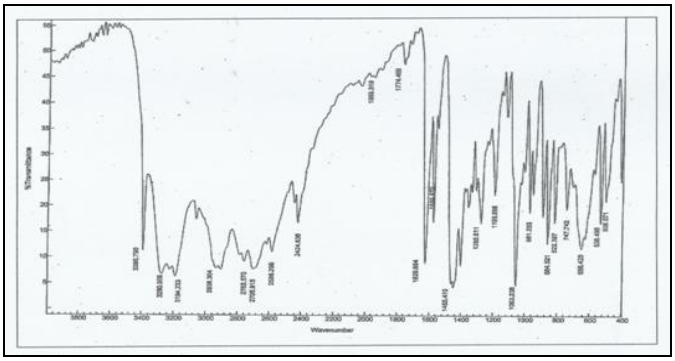

FIG. 1: FTIR SPECTRA OF PURE AMBROXOL HYDROCHLORIDE

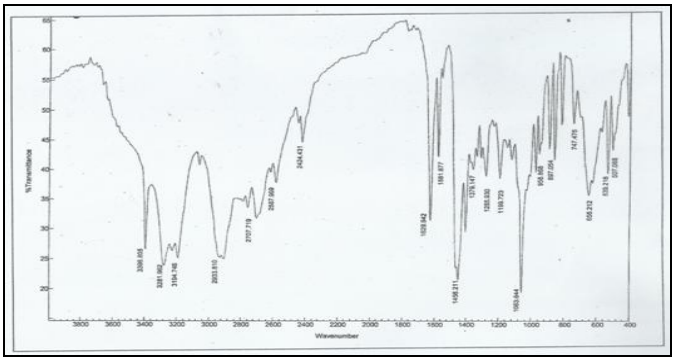

FIG. 2: FTIR SPECTRA OF OPTIMIZED FORMULATION (F-7) OF AMBROXOL HYDROCHLORIDE

Physicochemical Evaluation of Matrix Tablets: Tablets with a weight of 250 mg were obtained and subjected to quality control tests such as hardness, friability and drug content **Table 3**. The hardness of the tablets was found to be in the range of 4.82 ± 0.22 to 5.18 ± 0.16 kg/cm^2. It was within the range of monograph specification.

The friability of the tablets was found to be less than 1%, and it was within the range of standard specification. The drug content for all the batches was found to be in the range of 98.23 ± 0.35 to 99.37 ± 0.75. The results are given in **Table 2**.

TABLE 2: PHYSICAL PROPERTIES OF TABLET FORMULATION (F-1 TO F-9)

Formulation code	Hardness (kg/cm^2) *	Friability (%)	Drug content (%) #	Weight variation
F1	4.82 ± 0.22	0.02	98.57 ± 0.55	Pass
F2	4.93 ± 0.27	0.03	99.17 ± 0.85	Pass
F3	5.07 ± 0.20	0.12	99.37 ± 0.75	Pass
F4	4.98 ± 0.26	0.28	98.73 ± 0.23	Pass
F5	5.13 ± 0.16	0.24	99.60 ± 0.20	Pass
F6	5.18 ± 0.16	0.22	98.23 ± 0.35	Pass
F7	4.70 ± 0.17	0.36	99.33 ± 0.35	Pass
F8	5.0 ± 0.22	0.32	99.03 ± 0.67	Pass
F9	5.03 ± 0.15	0.30	99.13 ± 0.50	Pass

*All the values are expressed as mean ± SE, n=6; # All the values are expressed as mean ± SE, n=3.

***In-vitro* Drug Release Study:** The *in-vitro* dissolution studies of all the formulations of sustained release matrix tablets of Ambroxol hydrochloride were carried out for 12 h. As per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8 and F-9 showed 93.32, 79.43, 70.34, 80.67, 77.87, 75.76, 97.65, 89.45 and 85.34% respectively at the end of 12 h. (2 h in pH 1.2 and 10 h in pH 6.8 buffer).

F-1, F-2, and F-3 formulations were prepared by using HPMCK15 alone in the ratios of drug: polymer 1:0.75, 1:1 and 1:1.25. Dicalcium phosphate was used as diluents. The Ambroxol hydrochloride release from the tablets was shown in **Fig. 3**.

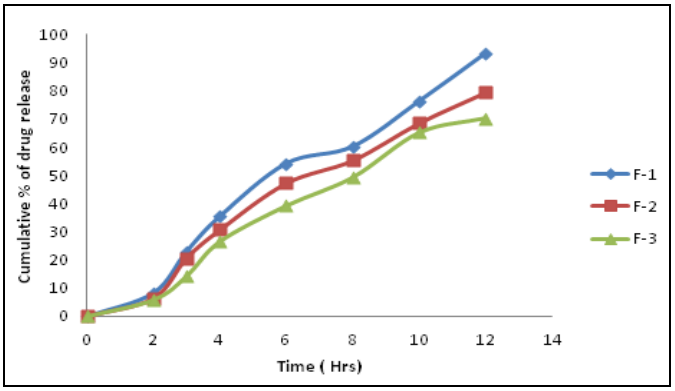

FIG. 3: DISSOLUTION PROFILE OF AMBROXOL HYDROCHLORIDE MATRIX TABLETS FORMULATED WITH HPMCK15 AND DICALCIUM PHOSPHATE AS DILUENT

F-4, F-5, and F-6 formulations were prepared by using HPMCK15 and xanthan gum in the ratios of drug: polymer 1:0.75, 1:1 and 1:1.25. dicalcium phosphate was used as diluents. The Ambroxol hydrochloride release from the tablets was shown in **Fig. 4**.

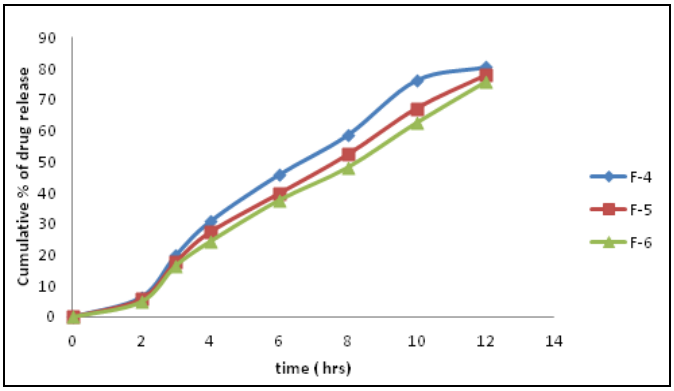

FIG. 4: DISSOLUTION PROFILE OF AMBROXOL HYDROCHLORIDE MATRIX TABLETS FORMULATED WITH HPMCK15 & XANTHAN GUM AND DICALCIUM PHOSPHATE AS DILUENTS

F- 7, F-8 and F-9 formulations were prepared by using HPMCK15 and xanthan gum in the ratios of drug: polymer 1:0.75, 1:1 and 1:1.25. Microcrystalline cellulose was used as diluents. The Ambroxol hydrochloride release from the tablets was shown in **Fig. 5**.

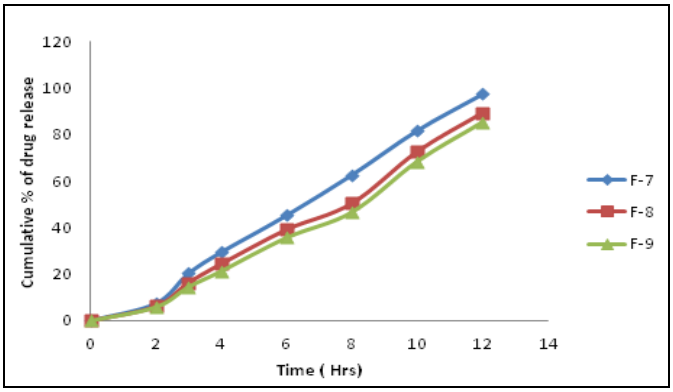

FIG. 5: DISSOLUTION PROFILE OF AMBROXOL HYDROCHLORIDE MATRIX TABLETS FORMULATED WITH HPMCK15 & XANTHAN GUM AND MICROCRYSTALLINE CELLULOSE AS DILUENT

When the cumulative percentage of drug release *vs*. time graphs were plotted for all the formulations, and it was observed that as the polymer concentration increases drug release from the tablets decreases. Diluent also plays a very important role in drug release retarding ability in matrix tablets. F-1 to F-6 formulations were prepared with dicalcium phosphate. F-7, F-8, and F-9 formulations were prepared with microcrystalline cellulose as diluents.

The percentage of drug release from the tablets was observed higher at the end of 12 h from formulations made with microcrystalline cellulose because of its hydrophilic nature.

Determination of the Release Kinetics: The release data were fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The data of drug release kinetics was shown in **Table 3**.

TABLE 3: RELEASE KINETICS OF AMBROXOL HYDROCHLORIDE SUSTAINED-RELEASE MATRIX TABLETS

Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model		Hixon - Crowel Model R^2
				R^2	n	
F1	0.986	0.865	0.981	0.977	0.98	0.985
F2	0.991	0.974	0.990	0.966	0.90	0.990
F3	0.991	0.983	0.986	0.992	0.79	0.999
F4	0.985	0.970	0.984	0.974	0.88	0.994
F5	0.994	0.963	0.979	0.973	0.80	0.993
F6	0.994	0.953	0.971	0.967	0.74	0.991
F7	0.993	0.785	0.953	0.988	0.99	0.981
F8	0.983	0.903	0.927	0.982	0.92	0.992
F9	0.977	0.865	0.916	0.976	0.86	0.988

The models giving a correlation coefficient close to unity were taken as the order of release. The regression coefficient obtained from zero order kinetics were found to be higher (R^2 0.977 to 0.994) when compared with those of first-order kinetics (R^2 0.785 to 0.983) indicating that the drug release follows zero order kinetics.

To evaluate drug release mechanism data was fitted to Higuchi, Korsmeyer-Peppas and Hixon-Crowell model to describe the drug release from matrix tablets. The regression coefficient values were found to be higher for Hixon-Crowell model indicating that drug release from tablets was by erosion mechanism.

CONCLUSION: Ambroxol hydrochloride matrix tablets were successfully prepared by using a direct compression method. From the present study, it was concluded that HPMC K15M, Xanthan gum were compatible with Ambroxol hydrochloride based on the results obtained from compatibility studies and hence are suitable for formulation of sustained release matrix tablet. The cumulative percentage of drug release was decreased with increasing concentration of polymer and hydrophilic diluent, microcrystalline cellulose increase the drug release from the tablets. The mechanism of drug release was erosion.

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CONFLICT OF INTEREST: The author declares no conflict of interest.

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