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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Matrix Tablets of Ambroxol Hydrochloride

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ABSTRACT

Oral sustained release matrix tablets of Ambroxol HCl were formulated in order to improve efficacy, reduce the frequency of administration, and better patient compliance. The overall objective of the present work was to develop an oral sustained release Ambroxol HCl tablets prepared by direct compression method, using hydrophilic hydroxyl propyl methylcellulose and hydrophobic ethyl cellulose polymer as a rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Mean dissolution time is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer.

Keywords: Ambroxol Hydrochloride, Sustained Release, Matrix Tablets, Granules.

INTRODUCTION

Ambroxol hydrochloride has been used to increase surfactant secretion in the lungs. It is an expectoration improver and a mucolytic agent used in the treatment of bronchial asthma and chronic bronchitis. Ambroxol hydrochloride has also been reported to have a cough-suppressing effect and anti-inflammatory action.[1] Ambroxol hydrochloride is a metabolite of bromhexine and is official in the Martindale Extra Pharmacopoeia.[2] It is chemically described as trans-4-[(2-Amino-3,5-dibromobenzyl) amino] -cyclohexanol. It is widely used as a mucolytic agent prescribed in respiratory infections like bronchitis and bronchial asthma.[3] It has a short biological half life of 3 – 4 hours and is

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administered in a dose of 30mg 3-4 times a day.[4] Therefore it is an ideal candidate for design as a Sustained release (SR) dosage form, which would result in prolonged clinical efficacy, reduced frequency of administration and lesser side effects. Oral sustained release systems continue to dominate the market despite the advancements made in other drug delivery systems in order to increase the clinical efficacy and patient compliance. From a practical pharmaceutical view point, numerous types of polymers are employed to control the drug release from the pharmaceutical dosage form. Oral sustained release systems are mainly grouped into three types, e.g. reservoir, monolithic and matrix types.[5, 6] Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs. In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose.[7, 8] Numerous methods and techniques have been used in the manufacturing of oral extended release dosage forms. Amongst them the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix.[9] In polymeric system, the active agent is physically blended with the polymer powder and then fused together by compression molding, which is a common process in pharmaceutical industry.[10-12] These dosage forms are designed to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time and therefore reducing the frequency of dosing and improving patient compliance.[13, 14] With the aim of maximizing the bioavailability of conventional drugs with minimum side effects, new drug delivery systems continue to attract much attention.[15] In recent years, considerable attention has been focused on biocompatible polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Among these polymers, cellulose derivatives such as hydroxyl propyl methyl cellulose, and ethyl cellulose, are generally considered to be stable and safe as release retardant excipients in the development of oral controlled release dosage forms. These semi synthetic polymers are commercially available and are widely used in the sustained release tablet

formulations.[16-26] The purpose of this study was to develop controlled release matrix tablets of Ambroxol hydrochloride using varying concentrations of hydroxyl propyl methyl cellulose and ethyl cellulose as polymers and to evaluate various pre and pro evaluation parameters, to obtain the required release rate of Ambroxol hydrochloride matrix tablets and to determine the mechanism and kinetics of drug release from Ambroxol hydrochloride matrix tablets.

MATERIALS AND METHODS

Materials

Ambroxol hydrochloride was a gift sample from South Shorn Formulations (P) Ltd., Vadodara. Hydroxy Propyl Methyl Cellulose (HPMC) (E 5 LV), Ethyl Cellulose (EC) (7-10 cups) Micro crystalline cellulose (MCC) Polyvinyl Pyrolidone (PVP K-30) Magnesium stearate and Talc used to be of USP/NF quality and were procured from Loba Chemie Pvt. Ltd. Mumbai. All other ingredients used throughout the study were of analytical grade and were used as received,

Preparation of Ambroxol hydrochloride matrix tablets:

Matrix tablets, each containing 75mg ambroxol hydrochloride were prepared by a direct compression method. The composition of various formulations of the tablets with their codes is listed in Table 1. All the powders were passed through sieve no 80#. Required quantities of the drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent isopropyl alcohol: water (1:1) was added slowly. After enough cohesiveness was obtained, the mass was passed through sieve no 12#. The obtained wet granules were dried at 50°C in hot air oven till constant weight was obtained (until dry). The dried granules were then passed through sieve no 16#. Talc and magnesium stearate were finally added as glidant and lubricant.

Table 1: Composition of Various Formulations for the Ambroxol HCl

Formulation Code	Ingredients (mg)							
	Ambroxol HCL	HPMC	Ethyl Cellulose	MCC	PVP-K30	Magnesium stearate	Talc	Total
F1	75	172	189	36	10	10	8	500
F2	75	183	172	42	10	10	8	500
F3	75	194	155	48	10	10	8	500
F4	75	205	138	54	10	10	8	500

Evaluation of Granules

The angle of repose was measured by using the funnel method[27], which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formulae: LBD= weight of the powder / volume of the packing. The TBD = weight of the powder / tapped volume of the packing.[28] Compressibility index of the granules was determined by using the formula CI (%) = [(TBD - LBD) / TBD] × 100.[29] Drug content was determined as follows: An accurately weighed amount of powdered Ambroxol granules (100mg) was extracted with 0.1N HCl (pH 1.2) and the solution was filtered through filter paper. The absorbance was measured at 248 nm after suitable dilution.

Evaluation of Compressed Tablets

Evaluations of prepared tablets such as hardness, friability, weight variation have been done according to IP specifications.[30]

Drug content uniformity

For determining the drug content, three tablets were crushed and powder containing 75 mg of Ambroxol hydrochloride was dissolved in 75 ml of methanol.

Drug content of Ambroxol hydrochloride was carried out by measuring the absorbance of samples at 248 nm using UV/Visible spectrophotometer (Shimazdu-1700, Japan). The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 0-10 µg/ml.

In vitro drug release studies: The in vitro dissolution studies were carried out using USP apparatus type II (paddle) at 100 rpm. The dissolution medium ((900 ml) consisted of 0.1N

hydrochloric acid for the first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37 ±0. 5°C. Five ml of samples was withdrawn and analyzed spectrophotometrically at 248 nm using a UV-visible spectrophotometer after suitable dilution of the samples. Fresh dissolution medium was replaced after each withdrawal.[31]

RESULT AND DISCUSSION

Evaluation of Granules

The granules of different formulations were evaluated for angle of repose, LBD (Loose bulk density), TBD (Tapped bulk density), compressibility index, Hausner's ratio. The results of angle of repose ranged from 23.20 ±0. 02 to 23.41 ±0. 07 respectively. The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower compressibility index values. The results of Hausner's ratio range from 1.10 ±0. 08 to 1.13 ±0. 08. The results of LBD and TBD ranged from 0.306 ±0. 03 to 0.307 ±0. 03 and 1.713 ±0. 03 to 1.842 ±0. 07. The tablet hardness, thickness, weight variations, and friability for each formulation are presented in Table 2.

Table 2: Physico chemical properties of Ambroxol granules

Formulation Code	Angle of Repose (θ)	Tapped bulk density (g/ml)	Carr's index (%)	Hausners	Loose bulk density (g/ml)
F1	23.12 ± 0.06	1.713 ±0.03	0.354	1.19±0.08	0.307±0.03
F2	23.41 ±0.07	1.842 ±0.07	0.362	1.04±0.06	0.314±0.02
F3	23.32 ± 0.03	1.778±0.04	0.347	1.65±0.05	0.321±0.02
F4	23.20 ± 0.02	1.783±0.02	0.334	1.22±0.07	0.306±0.03

The weight variation test revealed that, all formulations weights were found to be within pharmacopoeia limits. A plain punch with the same radius each time was used for all formulations in tablet pressing, and the differences in tablet radius was not significant (P<0.05). The friability value of all formulations and commercial tablets were less than 1%. Which indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed. The average percentage deviation of all tablet formulations was found to be

within the above limit, as per official pharmacopeia requirements. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 97%. in all formulations. The results of physical properties are shown in table-3.

Table 3: Physical Properties of the Matrix tablets of Ambroxol HCl

Formulation Code	Hardness† (Kg/cm^2)	Friability* (%)	Weight Variation (%)	Drug Content** (%)	Thickness** (mm)
F1	5.5 ± 0.63	0.19 ± 0.03	500 ± 1.24	98.62 ± 0.02	3.54 ± 0.04
F2	5.8 ± 0.54	0.24 ± 0.04	500 ± 1.24	98.34 ±0.03	3.58 ± 0.02
F3	5.7 ± 0.45	0.28 ± 0.09	500 ± 1.23	97.98 ±0.02	3.56 ± 0.05
F4	5.7 ± 0.54	0.23 ± 0.01	500 ± 1.24	98.73 ±0.04	3.54 ± 0.03

†All values are expressed as mean ± SE, n=20; *All values are expressed as mean ± SE, n=6; **All values are expressed as mean ± SE, n=5;

Drug release studies

The results of in-vitro release studies as shown in fig 1 and 2 indicate that formulations F1, released 46.32 % drug while formulations F2, F3 and F4 released 22.45, 23.09 and % of drug, respectively, after 2hrs and Formulations F1, and F4 released 98.6 % drug after 5h and 6h respectively whereas formulation F2 and F3 released 98.32 and 96.84 % of drug, respectively at the end of 7.5h and 8 h. The results show that the release rate decreased as the concentration of HPMC increased. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug. This indicates that the drug / polymer ratio is important factors affecting the rate of release drugs from HPMC matrices Factors that may contribute to differences in drug dissolution profile as a function of changes in the total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling. The dissolution profile of Ambroxol hydrochloride tablets containing combinations of a hydrophilic polymer HPMC with a hydrophobic polymer EC in the different polymer/polymer ratio shows that the appropriate combination of both the polymers taken in this study shows the sustained release of the drug up to 8 hours.

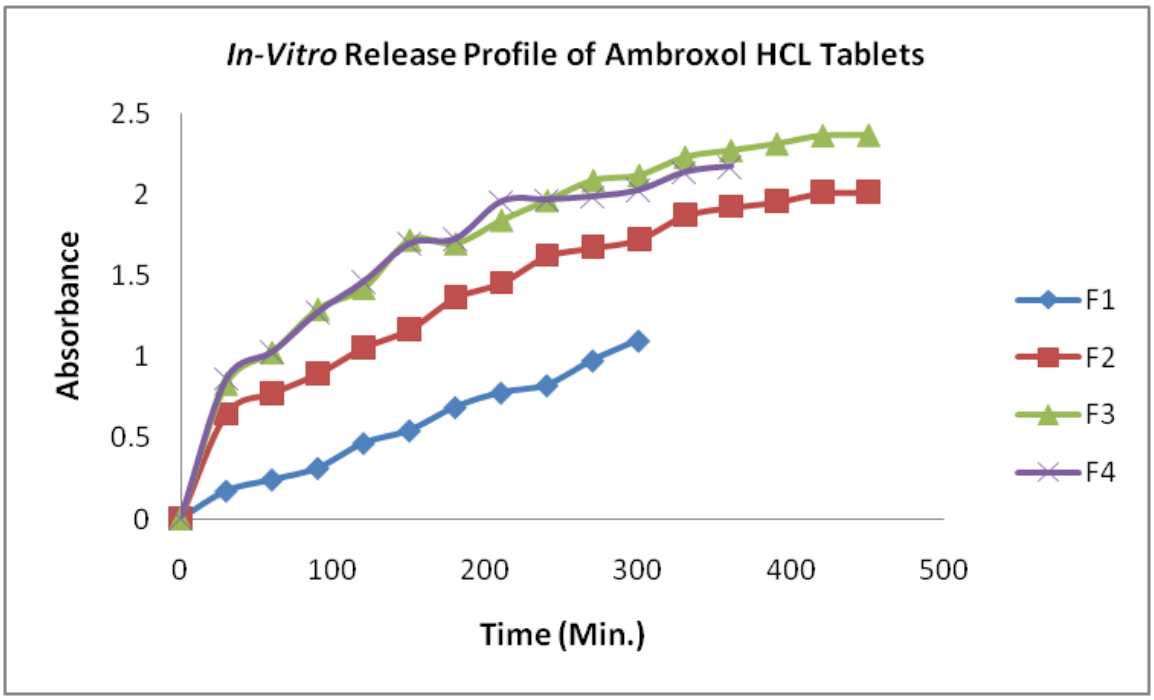

Figure 1: In-Vitro Release profile of Ambroxol hydrochloride formulations

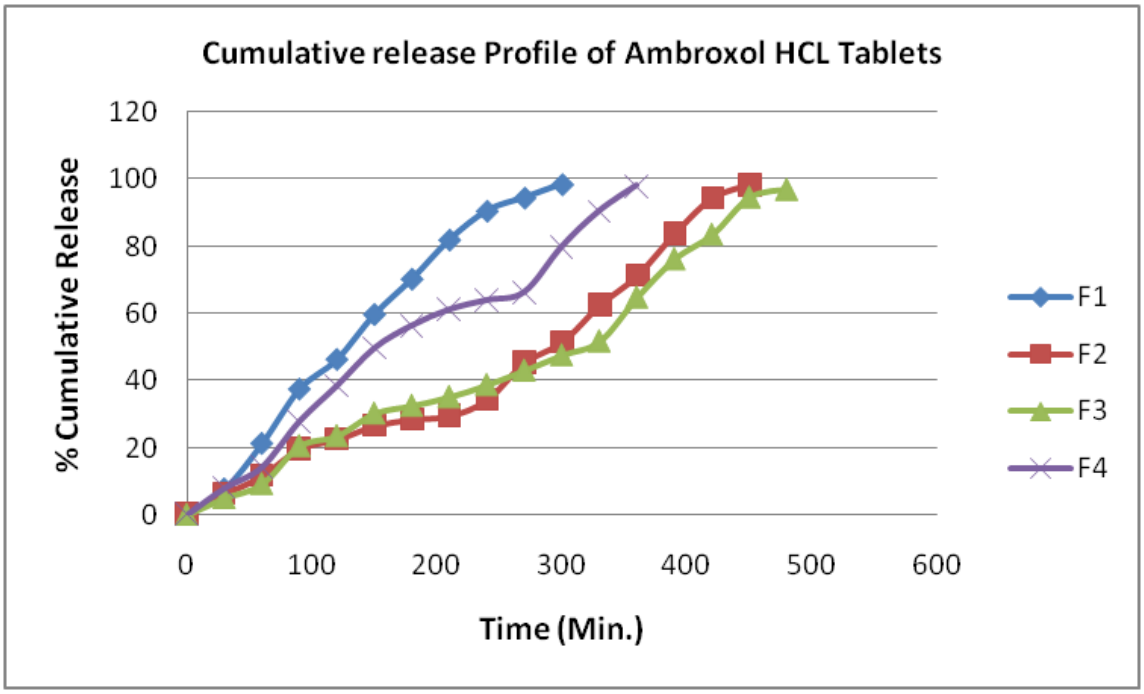

Figure 2: Cumulative Release of Ambroxol hydrochloride formulations

CONCLUSION

From the results of present investigation we conclude that hydrophilic matrix of HPMC alone could not control the Ambroxol HCL release effectively for 8 h where as when combined with EC could slow down the release of drug from their matrices and can be successfully employed for formulating sustained release matrix tablets. Combination of HPMC and EC retain drug more than that individual matrix polymer. In study concluded HPMC and EC is hydrophilic and hydrophobic matrix polymer which using matrix foaming agent by wet granular technique to sustain the release of Ambroxol hydrochloride. Diffusion coupled with erosion might be the mechanism for the drug release from hydrophilic and hydrophobic polymer based matrix tablets which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional Ambroxol HCL tablets.

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