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FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE TABLET

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Abstract: The objective of the study was to develop matrix tablets of Ambroxol Hydrochloride for Sustained Release. Hydroxy Propyl Methyl Cellulose (HPMC) K4M and Guar Gum as the retardant polymers and study the effect of various formulation factors such as polymer proportion, polymer type and effect of filler type on the in vitro release of the drug. Matrix tablets were prepared by wet granulation method and prepared tablets were evaluated for weight variation, friability, hardness, thickness and in vitro dissolution studies. All the granules of formulations showed compliance with pharmacopieal standards. In vitro release studies revealed that the release rate decreased with increase polymer proportion and hydrophobic polymers retard the drug release more than hydrophilic polymers. The formulations F7 sustained release of drug for 12 hrs with 91.56%. Because of swelling property increased the drug release profile to a small extent due to change in swelling at the tablet surface. The kinetic treatment showed that the mechanism of drug release. The developed sustained release matrix tablets of Ambroxol Hydrochloride up to 12 hrs can overcome the disadvantages of conventional tablets.

Keywords: Ambroxol hydrochloride, Xanthan Gum, Guar gum, HPMC K4M, sustained release, matrix tablets

INTRODUCTION

There are many definitions of sustained release but the simplest definition is "Any drug or dosage form or medication that prolongs the therapeutic activity of drug". Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy to formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs. Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations [1]. Ambroxol HCl is sparingly water solubility. Hence it presents significant formulation challenges. Ambroxol HCl has a half-life of 4 hours and the usual oral dosage regimen is 75 mg[2, 3, 4]. HPMC, a semi synthetic derivative of cellulose, a swellable and hydrophilic polymer. It is very suitable to use a retardant material in sustained release matrix tablets, as it is nontoxic and easy to handle [5]. Guar gum is used as sustained release carrier and regarded as a nontoxic and non-irritant material[6]. The present study was designed to formulate matrix tablets using Guar gum and HPMC K4M polymers.

MATERIALS AND METHODS

MATERIAL

Ambroxol hydrochloride was a generous gift from Vintech Pharmaceuticals, Nasik. Guar gum was procured from Pure Chem. Lab, Mumbai. HPMC K4M was procured from Zim Laboratories, Nagpur.

METHOD

Preparation of Ambroxol Hydrochloride Sustained release Tablet[5, 6]

The wet granulation method involves sifting of drug along with the polymers and diluent through sieve # 40 and uniform mixing was carried out for 5 minutes. Granulation was performed by using starch as a binder and distilled water as a solvent to form dough mass. The mass was passed through sieve No.18 and the granules so prepared were dried at 25- 27 ^{0}C for 2 hrs. Afterwards granules were sized through sieve # 22. Finally magnesium stearate and aerosol were added separately and mixed

for further 2-3 minutes. The weights of the tablets were kept constant for all formulation. The detail of composition of each formulation is given in Table 1.

EVALUATION AMBROXOL HYDROCHLORIDE OF SUSTAINED RELEASE TABLET

Evaluation of Ambroxol Hydrochloride Granules[7,8,9]

All prepared granules were evaluated for angle of repose, Tapped density, Bulk density and Carr's index.

Determination of Swelling Index[12, 13]

The tablets kept for 12 hrs in petridish of 6.8 pH solution. The swelling behaviour of all the tablets after 1hr the tablet was withdrawn, soaked with tissue paper and weight were noted

Physiochemical evaluation of Ambroxol Hydrochloride tablets[10, 11]

All prepared matrix tablets were evaluated for uniformity of weight and drug content, as per I.P. method. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester. Thickness was measured by Micrometer screw gauge.

$$WU\% = \frac{\text{Wt. of swollen tablet} - \text{Initial Wt. of tablet}}{\text{Initial wt. of tablet}} \times 100$$

Where,

WU % = Water uptake

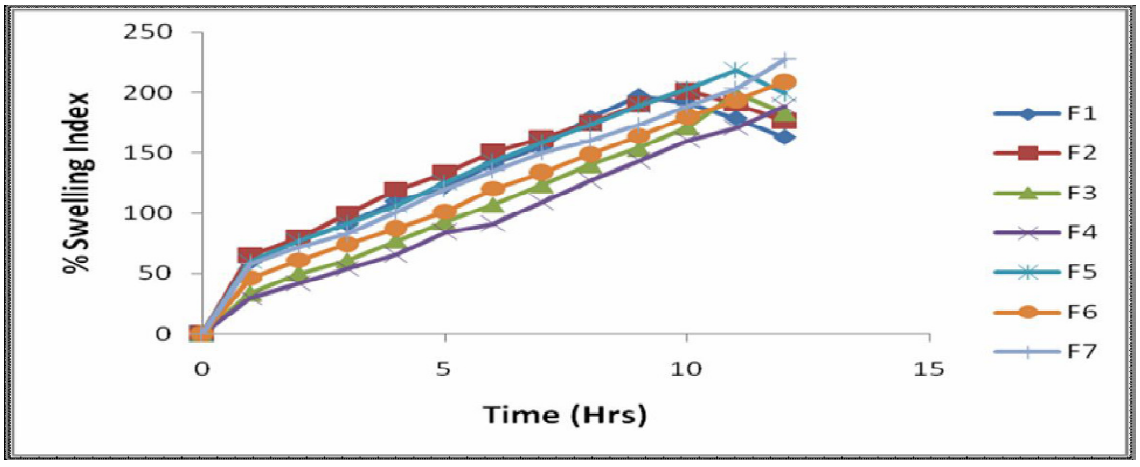

Figure 1. Plot for % Swelling Index of F1 to F7

***In vitro* dissolution studies[16, 17]**

In vitro release study was carried out (USP dissolution test apparatus Type-II Paddle type) using 900 mL of sodium chloride and hydrochloride acid buffer pH 1.2 solution, for two hours and later on phosphate buffer pH 6.8 for further ten hours as a dissolution medium. The paddles are rotated at 75 rpm. The medium was set at 37 ± 0.50C. Aliquot (10 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 spectrophotometer (Lab India) at 244 nm using sodium chloride and hydrochloride acid buffer pH 1.2 or phosphate buffer pH 6.8 as a blank. Aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Drug content in dissolution sample was determined by software (PCP disso v2.08) version. Accelerated stability studies18-21 Stability testing of formulations was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at various temperatures. The samples were kept at condition of 45°C/70% RH and were analyzed at 15th, 30th and 45th days for their physical changes and in drug content.

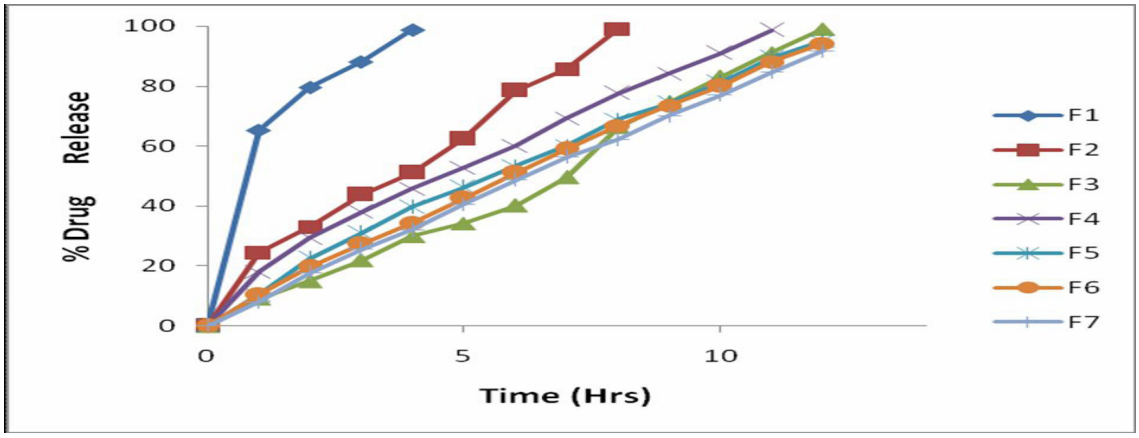

Figure 2. % Drug Release of Formulation F1 toF7

Accelerated stability studies[18-21]

Stability testing of formulations was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at various

temperatures. The samples were kept at condition of 45°C/70% RH and were analyzed at 15th, 30th and 45th days for their physical changes and in drug content

CONCLUSION

The granules was evaluated by angle of repose, bulk density, tapped density and compressibility index. The granules show good result (Table 2). The formulated matrix tablets met the pharmacopoeial requirement of uniformity of weight. All tablets confirmed to the requirement of drug content. Hardness, % friability was well within acceptable limits (Table 3). All formulations showed very low drug release in pH 1.2. Sustained but complete drug release was displayed by all formulations in phosphate buffer pH 6.8. The swelling index was calculated with respect time (Fig. 1). As time increases the swelling index was increased because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of guar gum. The inverse relation was noted between amount of guar gum and release rate of Ambroxol Hydrochloride. Increasing amount of gum, decreasing amount of HPMC K4M in the formulation, resulted in slower release rate, and decrease amount of drug release from the tablet (Fig. 2). This slow release is because of the formation of a thick gel structure that delays drug release from the matrix. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet and retarding further penetration of the dissolution medium. Dissolution was carried out by paddle method, keeping rotation speed at 75 rpm. Physically it was observed that tablets in buffer solution settle down at bottom of flask. It swelled considerably to release drug from matrix. Stability studies revealed that there was no significant change in colour, hardness, Drug content and dissolution profile of F7. Thus formulation was stable at different condition of temperature. It was concluded that combination of guar gum and HPMC K4M can be used as an effective matrix former, to retard the release of Ambroxol Hydrochloride for long period of time.

Table 1.

Formulation of Ambroxol hydrochloride sustained release tablet

Formulation Code	Drug (mg)	Xanthan Gum (mg)	HPMC K4M (mg)	Guar gum (mg)
F1	75	-	6.25	18.75
F2	75	-	12.5	12.5
F3	75	-	18.75	6.25
F4	75	12.5	37.5	-
F5	75	25	25	-
F6	75	37.5	12.5	-
F7	75	9.375	-	28.125
F8	75	18.75	-	18.75
F9	75	28.125	-	9.375

Table 2.

Blend properties of formulation of Ambroxol hydrochloride matrix tablets prepared by wet granulation method.

Formulations	Bulk Density (g/ml)* (± SD)	Tapped Density (g/ml)* (± SD)	Compressibility Index (%)* (± SD)	Angle of Repose* (± SD)
F1	0.39±0.52	0.46±0.62	15.22±0.78	24.14±0.67
F2	0.39±0.43	0.47±0.78	17.88±0.33	27.25±0.48
F3	0.37±0.91	0.46±0.24	18.45±0.64	24.41±0.50
F4	0.36±0.35	0.42±0.62	14.29±0.80	25.73±0.45
F5	0.38±0.71	0.48±0.34	20.63±0.77	27.68±0.57
F6	0.39±0.12	0.45±0.93	15.22±0.42	28.21±0.90
F7	0.37±0.20	0.41±0.32	12.06±0.71	27.41±0.66
F8	0.37±0.43	0.46±0.74	19.3±0.49	28.41±0.32
F9	0.38±0.02	0.45±0.02	14.42±0.5	27.00±0.5

* (n=3)

Table 3.

Physical evaluation of Ambroxol hydrochloride sustained release matrix tablet

Formulation	Thickness ± SD*	Hardness (kg/cm^2) ± SD*	Friability (%) ± SD*	Weight Uniformity (mg) ± SD*	Uniformity of content ± SD*
F1	3.48±0.14	6.0±0.28	0.85±0.29	Complies	98.56±0.25
F2	3.49±0.83	6.2±0.62	0.63±0.12	Complies	97.35±0.92
F3	3.49±0.67	5.8±0.40	0.53±0.10	Complies	98.73±0.37
F4	3.53±0.32	6.1±0.97	0.69±0.87	Complies	99.46±0.59
F5	3.49±0.14	5.7±0.64	0.67±0.19	Complies	98.57±0.41
F6	3.54±0.38	6.1±0.14	0.54±0.26	Complies	100.74±0.94
F7	3.54±0.21	6.3±0.36	0.51±0.66	Complies	100.25±0.23
F8	3.52±0.73	5.7±0.32	0.53±0.43	Complies	98.22±0.40
F9	3.46±0.20	6.1±0.48	0.72±0.19	Complies	99.38±0.37

* (n=3)

Table 4.

Accelerated stability studies Optimized of F7

Parameters	Days			
	Initial	**15**	**30**	**45**
Colour	No change	No change	No change	No change
Hardness ± SD	5.7±0.95	5.5±0.47	5.5±0.29	5.3±0.70
Drug Content (%) ± SD	98.23±0.54	97.52±0.31	97.07±0.43	96.12±0.95
% Release (in 12 Hrs) ± SD	89.16±0.18	88.56±0.46	88.32±0.67	87.64±0.83

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