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Research Article

FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE MATRIX TABLETS

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ABSTRACT

The main objective is to formulate and evaluate the ambroxol Hcl sustained release matrix tablets for treating bronchial asthma and chronic bronchitis. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in and cost-effective manufacturing process. Ambroxol hydrochloride tablets were prepared by direct compression method by using hydrophilic polymer like HPMC K4M, HPMC K15M and HPMC K100M. The prepared matrix tablets were tested for evaluation parameters such as drug content, hardness, friability, weight variation, in-virto drug release and release kinetics. The formulation FS12 showed better sustained release of about 99.81% and follows Higuchi order with high regression value of 0.993 with complete drug release in 12 hrs made it to select as an optimized formulation compared with other formulations. Thus it was selected for *in vivo* investigation.

Keywords: Ambroxol hydrochloride, HPMC K4M, HPMC K15M, HPMC K100M.

INTRODUCTION

Ambroxol hydrochloride 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. Ambroxol hydrochloride has been used to increase surfactant secretion in the lungs.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. The overall process of oral delivery is frequently impaired by several physiological and pharmaceutical challenges that are associated with the inherent physicochemical nature of the drugs and/or the variability in GI conditions such as pH, presence of food transit times as well as enzymatic activity in the alimentary canal. Manipulation of these problems and challenges is considered an important strategy for improving oral drug delivery.

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. The onset of its pharmacologic action is often delayed and the duration of its therapeutic effect is sustained. Hydrophilic matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications because of their good compatibility among the hydrophilic polymers.

MATERIALS AND METHODS

Materials

Ambroxol Hydrochloride drug as gift sample from Dr. Reddy's Laboratories, Hyderabad, India. And all other excipients were procured from SD Fine Chem, Mumbai, India.

Preparation of Ambroxol Hydrochloride matrix tablets

Ambroxol hydrochloride tablets were prepared by direct compression method. Accurately weighed quantities of polymer of HPMC K4M, HPMC K15M and HPMC K100M and MCC were taken in a mortar and mixed geometrically, to this required quantity of Ambroxol was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no. 40 and mixed with the drug blend which is also passed through sieve no 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 400mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm^2.

SOLUBILITY STUDY OF AMBROXOL

Excess amount of Ambroxol was placed in 0.1 N HCl, Acetate buffer pH 4.5, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 respectively in order to determine its solubility. The samples were shaken for 24 h at 37 °C in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). The supernatant was filtered and the filtrate was diluted with the respective medium and assayed by UV/ Visible Spectrophotometer at 248 nm.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1}.

Table 1: Composition of matrix tablets of Ambroxol

Ingredients (wt. in mg)	Formulations											
	FS1	FS2	FS3	FS4	FS5	FS6	FS7	FS8	FS9	FS10	FS11	FS12
AMBROXOL*	75	75	75	75	75	75	75	75	75	75	75	75
HPMC K4M	87	232	174	131	-	-	-	-	-	-	-	-
HPMCK15M	-	-	-	-	58	174	116	87	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	29	116	87	70
Avicel pH 102	211	66	124	167	240	124	182	211	269	182	211	228
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Mg Stearate	4	4	4	4	4	4	4	4	4	4	4	4

*equivalent to 75mg of Ambroxol
Total tablet weight: 381mg

Evaluation of matrix tablets of Ambroxol

Weight Variation test

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight.

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliperse. The average thickness and standard deviation were reported.

Hardness test

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness, and the standard deviation was reported.

Friability test

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was

rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets

***In vitro* Drug Release Studies**

The *in vitro* drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus under the following conditions:

Dissolution test parameters

Medium : 900ml of 01.N HCl
Rotation speed : 50 rpm
Temperature : 37±0.5ºC
Sampling Volume : 5ml
Sampling Time : 0.5, 1, 2, 4, 6, 8, 10, 12 hours

At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 220 nm.

RESULTS AND DISCUSSION

Ambroxol hydrochloride matrix tablets were prepared with HPMC with different formulations by direct compression method.

Table 2: Physical parameters of single unit Sustained release matrix tablet of Ambroxol HCl

Formulation code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
FS1	381.12±3.84	6.5±0.3	6.84±0.05	0.32	98.23
FS2	379.45±2.87	6.6±0.5	6.76±0.06	0.19	99.65
FS3	380.00±2.73	6.8±0.4	6.86±0.03	0.26	99.12
FS4	381.11±2.13	6±0.5	6.76±0.04	0.33	98.44
FS5	380.00±3.48	7±0.2	6.63±0.06	0.29	99.23
FS6	381.11±2.3	6.8±0.4	6.65 ±0.06	0.22	98.63
FS7	381.12±1.19	6.8±0.5	6.68±0.05	0.37	99.65
FS8	381.12±2.27	5.9±0.2	6.55±0.25	0.23	98.65
FS9	381.23±3.84	6.8±0.5	6.506±0.04	0.29	98.45
FS10	380.00±3.84	6.5±0.3	6.62±0.07	0.37	99.64
FS11	381.12±2.87	6.8±0.5	6.78±0.02	0.41	98.12
FS12	381.12±2.73	6.7±0.2	6.60±0.04	0.24	99.72

In-vitro drug release

i.) Release profiles of formulations containing HPMC K_4M

Table 3: Cumulative percentage drug release of formulations with HPMC K4M

Time (hrs)	Cumulative % drug released			
	FS1	FS2	FS3	FS4
0	0	0	0	0
0.5	23.27±1.77	17.04±2.94	22.69±2.73	18.73±3.23
1	29.47±4.57	22.22±1.6	28.71±5.47	23.96±1.83
2	42.33±3.59	31.08±2.57	33.95±3.14	26.47±2.01
3	53.25±2.65	39.44±1.49	42.96±2.26	33.83±1.86
4	67.81±5.46	45.3±3.35	45.55±3.7	47.67±3.09
6	84.16±2.97	49.67±2.57	62.39±4.82	58.28±2.74
8	97.12±1.77	60.77±1.71	67.26±1.42	70.5±4.61
10		72.5±2.09	79.36±2.72	84.35±4.38
12		78.86±3.57	85.1±2.68	97.57±2.4

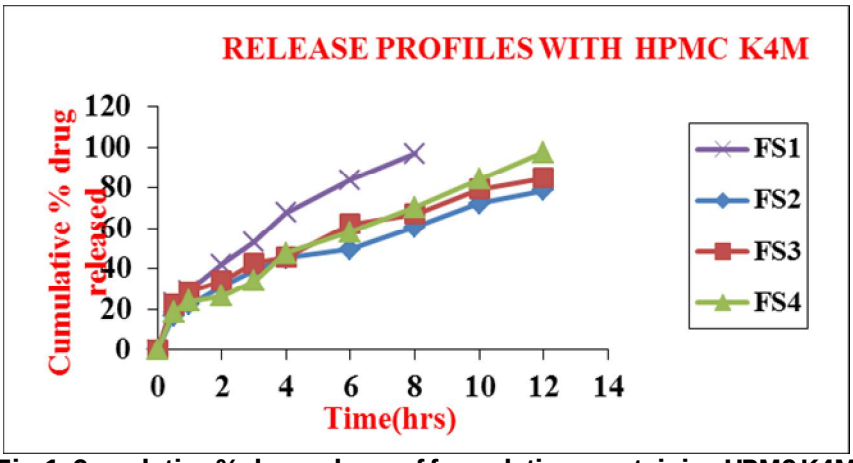

Fig. 1: Cumulative % drug release of formulations containing HPMC K4M

ii.) Release profiles of formulations containing HPMC K15M

Table 4: Cumulative percentage drug release of formulations with HPMC K15M

Time (hrs)	Cumulative % drug released			
	FS5	FS6	FS7	FS8
0	0	0	0	0
0.5	20.13±2.84	20.23±2.41	22.34±1.34	19.61±3.27
1	30.91±1.39	23.7±3.1	25.22±4.61	24.35±1.59
2	43.18±2.72	32.96±1.72	35.7±3.15	35.45±2.92
3	51.72±1.48	40.81±3.13	42.31±2.06	44.31±2.77
4	65.19±2.4	44.18±1.99	48.67±1.82	53.79±1.67
6	81.15±4.66	51.79±2.59	61.77±0.92	65.89±4.08
8	96.53±2.12	60.15±1.42	67.51±3.29	73.49±2.53
10		73±3.67	80.6±2.57	83.47±4.28
12		77.62±2.27	87.09±1.27	96.82±3.19

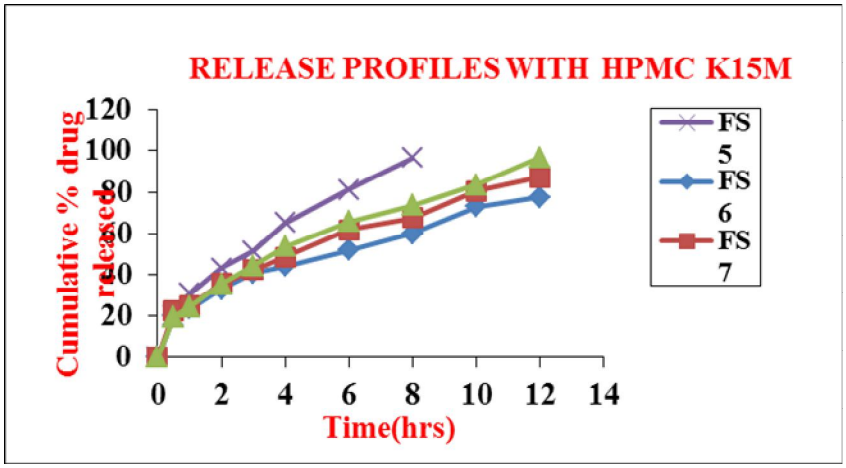

Fig. 2: Cumulative % drug release of formulations containing HPMC K15M

iii.) Release profiles of formulations containing HPMC K100M

Table 5: Cumulative percentage drug release of formulations with HPMC K100M

Time (hrs)	Cumulative % drug released			
	FS9	FS10	FS11	FS12
0	0	0	0	0
0.5	31.28±1.67	19.52±2.59	27.97±1.92	23.72±3.72
1	42.25±2.74	25.85±2.08	29.09±3.1	31.83±4.28
2	52.95±3.48	37.2±1.41	38.69±2.65	41.81±3.64
3	65.81±2.51	44.68±1.92	46.05±2.95	49.3±2.73
4	81.01±1.653	50.54±2.54	54.78±3.83	59.27±1.53
6	95.53±2.45	57.78±3.94	59.77±1.92	66.88±4.17
8		64.39±1.48	69.13±1.18	75.24±2.97
10		74.37±3.84	73.87±3.23	86.09±3.98
12		77.99±2.77	85.22±4.37	99.81±2.87

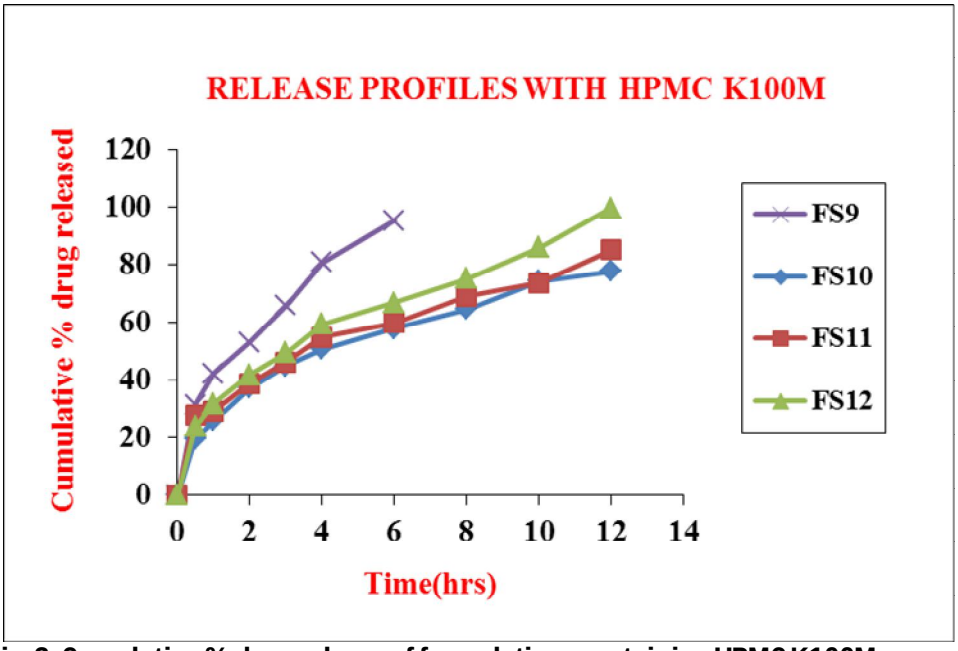

Fig. 3: Cumulative % drug release of formulations containing HPMC K100M

From the above figure it is evident that the polymer HPMC K100M has sustaining effect on the release of drug from the Sustained release matrix tablet. The percent of drug release from formulations FS1 to FS11 were failed to release the drug within the desired time (12 hrs). The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymers. Formulation **FS12** was considered as best formulation among all the formulations sustained the drug release was found to be 99.8% for desired period of time (12 hrs).

In-vitro release kinetics

Table 6: Regression coefficient (R2) values of Sustained release matrix tablets for different kinetic models

Formulation	zero-order	First-order	Higuchi	Korsmeyer Peppas	
				R^2	N
FS1	0.944	0.491	0.991	0.487	0.394
FS2	0.932	0.478	0.993	0.399	0.328
FS3	0.92	0.441	0.99	0.412	0.292
FS4	0.974	0.533	0.97	0.454	0.379
FS5	0.946	0.497	0.913	0.49	0.41
FS6	0.919	0.449	0.992	0.371	0.289
FS7	0.928	0.454	0.995	0.435	0.313
FS8	0.94	0.483	0.996	0.489	0.37
FS9	0.979	0.455	0.994	0.464	0.334
FS10	0.948	0.429	0.992	0.412	0.301
FS11	0.968	0.394	0.982	0.382	0.247
FS12	0.973	0.429	**0.993**	0.471	0.316

CONCLUSION

Systematic studies were conducted for the preparation of SR matrix formulations of Ambroxol HCL. Ambroxol hydrochloride matrix tablets were prepared by direct compression technique employing different concentrations of HPMCK100M to achieve sustained release of drug. The drug and polymer were found to be compatible as indicated by FT-IR studies. The granules possessed satisfactory flow properties, compressibility index and drug content. All tablet formulations showed acceptable properties and complied with the in-house specifications for weight variation, drug content uniformity, hardness, and friability. It may be concluded from the present study sustained and complete release of Ambroxol hydrochloride over a period of 12 hours was obtained from matrix tablets (Fs12) of about 99.8% and follows the Higuchi order of release. It was found that drug release from the matrix tablets was found to be decrease with increase in drug-polymer ratio.

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