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Research Article

Formulation and Evaluation of Sustained Release Tablets of Ambroxol Hydrochloride

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ABSTRACT

In the present study, an attempt was made to formulate the oral sustained release matrix tablets of AmbroxolHCl in order to improve the efficacy, reduce the frequency of administration, and better patient compliance. Ambroxol Hydrochloride is a potent mucolytic agent which induces bronchial secretions used in the treatment of respiratory disorders. FTIR analysis confirmed the absence of any drug polymer interaction. Sustained release tablets of Ambroxol Hydrochloride were formulated employing hydrophilic polymers HPMC K4M and HPMC K100M. The powder blend was evaluated for micromeritic properties. The sustained release tablets were prepared by wet granulation method. The tablets were evaluated for thickness, weight variation test, hardness, friability, and drug content. The in vitro drug release characteristics were studied in simulated gastric fluid (2 hours) and intestinal fluid for a period of 10 hours using USP type II dissolution apparatus (total 12hours). The results of dissolution studies indicated that formulation F11 is the most successful of the study with satisfactory drug release. At the end of 12 hrs, the drug release was found to be 96.1%.

Keywords: Ambroxol HCl, Hydroxy propyl methylcellulose, sustained release

INTRODUCTION

Oral route is one of the most popular routes of drug delivery due to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods, as well as traditional belief that by oral administration the drug is as well absorbed and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other tablets [1, 2].

Sustained release drug delivery aimed at controlling the rate of release as well as maintains desire drug level in the blood that is therapeutically effective and non toxic for extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. It provides prolonged but not necessarily uniform release of the drug. The rationale for development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition [3, 4].

Ambroxol is a metabolite of bromhexine with similar actions and uses. It is chemically described as Trans-4-[(2-amino-3, 5-dibromobenzyl) amino]-cyclohexanol. Ambroxol hydrochloride is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as, bronchial asthma, chronic bronchitis characterized by the production of excess or thick mucus.

Ambroxol hydrochloride has also been reported to have a cough suppressing effect and anti inflammatory action. It has been successfully

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used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders. Its short biological half life (4 hrs) that calls for frequent daily dosing (3 to 4 times) and therapeutic use in chronic respiratory diseases necessitates its formulation in to sustained release dosage forms [5, 6].

MATERIALS AND METHODS

Ambroxol Hydrochloride was received as a gift sample from Richer Pharmaceuticals Ltd, Hyderabad, HPMC K4M & HPMC K100M, MCC, Starch, Talc and Mg stearate were obtained from Drugs India Ltd, Hyderabad.

Equipment

Double rotary tablet compression machine (karnavati, Rajasthan), Electronic balance (Shimadzu), Vernier caliper (Mitutoyo south Asia pvt ltd.), Hardness tester (Pfizer), Friabilator (Roche), PH meter (EI), Hot air oven (Minicon Equipments Pvt Ltd.), Dissolution Apparatus (LAB INDIA), UV spectrophotometer (Shimadzu 1800), FT-IR spectrophotometer (Shimadzu).

Methodology

Tablets were prepared by wet granulation method. Various steps (Sieving, Dry mixing, Preparation of binder solution, Granulation, wet mass sieving, Drying, sieving of dried granules and finally compression after addition of lubricants) involved in wet granulation method.

Micromeritic properties

The physical mixture of the drug with different excipients was prepared by triturating drug and additives in a dried mortar for 5 min.

Angle of repose

The angle of repose was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The powders were allowed to flow through the funnel freely onto a clean surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [9].

$\tan \theta = h/r$

where h is the height of powder cone and r is the radius of the powder cone.

Bulk density and tapped density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. Both bulk density (BD) and tapped bulk density (TBD) of powder blends were determined using the following formula [10].

BD = Weight of the powder/Volume of the powder

TBD = Weight of the powder/Tapped volume of the powder

Carr's compressibility index

The compressibility indices of the formulation blends were determined using following Carr's compressibility index formula [11].

Carr's Compressibility Index (%) = [(TBDBD)/ TBD] x100

Hausner ratio

Hausner ratio is the ratio between tapped density and bulk density.

Hauser's ratio = Tapped density/poured density.

Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.5 shows poor flow of powder. Hausners ratio between 1.25 to 1.5 can be improved by addition of glidants [12].

Granulation of Ambroxol:

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Sieving: The active ingredient Ambroxol was passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Dry mixing: Ambroxol, HPMC K100M, HPMC K4M, MCC were taken and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Preparation of binder solution: Weigh 9 mg of Starch accurately and it is mixed with warm water to form a paste. It is used as binder solution.

Granulation: The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules.

Drying: Then the wet granules were dried in trays and pass the air for drying since the IPA is corrosive and also get evaporated quickly. So air drying is only suitable for drying, samples were removed randomly at different time intervals from the total bulk of the granules.

Sieving: The dried materials were passed through the sieve#20.Then desired amount of blend was compressed using 8mm punch in Double rotary tablet compression machine (karnavati, Rajasthan).

FORMULATION OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE TABLETS

Table 1: Trial with HPMCK4M

Ingredients	F1	F2	F3	F4
Ambroxol Hcl	75	75	75	75
HPMC K4M	45	60	75	90
MCC	162	147	132	117
Starch	9	9	9	9
Water	q.s	q.s	q.s	q.s
Talc	6	6	6	6
Mg.stearate	3	3	3	3

Table 2: Trial with HPMCK100M

Ingredients	F5	F6	F7	F8
Ambroxol Hcl	75	75	75	75
HPMC K100M	45	60	75	90
MCC	162	147	132	117
Starch	9	9	9	9
Water	q.s	q.s	q.s	q.s
Talc	6	6	6	6
Mg.stearate	3	3	3	3

Table 3: Trial with HPMC K4M &HPMCK100M

Ingredients	F9	F10	F11	F12
Ambroxol Hcl	75	75	75	75
HPMC K4M	45	45	21	42
HPMC K100M	45	45	84	63
MCC	117	115	102	107
Starch	9	9	9	9
Water	q.s	q.s	q.s	q.s
Talc	6	6	6	6
Mg stearate	3	3	3	3

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Table 4: Results of study of Physical Parameters of powders

Formulation	Angle of Repose (^{0})	Bulk Density (LBD)(g/ml)	Tapped Density (TBD)(g/ml)	Carr's index%	Hausner ratio
F1	$21^0$04	0.304	0.351	13.41	1.15
F2	$21^0$09	0.317	0.367	13.63	1.16
F3	$21^0$46	0.310	0.360	13.89	1.16
F4	$24^0$88	0.318	0.378	15.87	1.19
F5	$24^0$23	0.294	0.346	15.02	1.18
F6	$24^0$09	0.307	0.360	14.72	1.17
F7	$24^0$78	0.311	0.368	15.21	1.18
F8	$25^0$56	0.265	0.312	15.06	1.18
F9	$23^0$98	0.332	0.391	14.91	1.18
F10	$21^0$14	0.299	0.346	13.54	1.16
F11	$22^0$53	0.270	0.317	14.63	1.17
F12	$24^0$96	0.282	0.336	15.82	1.19

Table 5: Results of study of physical parameters of tablets

Formulation	Uniformity of Weight mg ± SD (n=20)	Hardness Kg/cm^2 ± SD (n=10)	Thickness mm ± SD (n=5)	Friability (%)	Drug content (%)
F1	301±1.25	7.4±0.32	1.5±0.055	0.435	98.70
F2	301±1.21	8.4±0.29	1.7±0.010	0.492	99.25
F3	301±0.15	8.9±0.24	1.4±0.017	0.501	99.42
F4	300±3.28	8.3±0.41	1.3±0.012	0.963	97.52
F5	301±0.98	8.1±0.32	1.5±0.072	0.478	98.24
F6	299±2.32	7.8±0.32	1.9±0.021	0.242	98.63
F7	300±2.67	7.8±0.39	1.7±0.054	0.414	98.15
F8	302±0.96	6.9±0.42	1.6±0.034	0.417	99.42
F9	301±1.56	7.5±0.29	1.4±0.022	0.318	99.14
F10	300±2.23	7.5±0.12	1.3±0.071	0.021	99.25
F11	300±0.56	8.4±0.14	1.4±0.042	0.113	99.30
F12	300±1.12	7.9±0.51	1.7±0.088	0.124	99.17

In vitro drug release studies

The release rate of Ambroxol Hcl from tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method). The dissolution test was performed using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 6.8 from 2- 12 hrs at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably. Absorbance of these solutions was measured at 244 nm using UV-VISIBLE spectrophotometer [15], [16].

Drug release kinetics [17, 18]

For finding out the mechanism of drug release from tablets, the dissolution data obtained from

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the above experiments were treated with the different release kinetic equations.

Zero order release equation: Q = K0 t,

First order equation: Q = Kf t

Higuchi's square root of time equation:

$$Q = KH\ t^{1/2}$$

Korsmeyer and Peppas equation:

$$F = (Mt / M) = Km\ tn$$

Dissolution kinetics of Ambroxol hydrochloride SR tablets

Formulation	%CDR	Zero order r^2	First order r^2	Korsmeyer-peppas model		Higuchi model r^2	Best fit model
				r^2	N		
F1	95.2	0.966	0.877	0.929	0.526	0.931	Zero order
F2	93.4	0.969	0.870	0.930	0.543	0.926	Zero order
F3	94.7	0.988	0.888	0.954	0.555	0.953	Zero order
F4	84.5	0.997	0.952	0.976	0.544	0.971	Zero order
F5	98.1	0.989	0.847	0.978	0.505	0.974	Zero order
F6	92.5	0.976	0.919	0.953	0.532	0.949	Zero order
F7	97.8	0.990	0.843	0.962	0.559	0.958	Zero order
F8	91.3	0.991	0.888	0.963	0.535	0.951	Zero order
F9	89.2	0.956	0.852	0.895	0.463	0.892	Zero order
F10	86.4	0.960	0.861	0.902	0.468	0.897	Zero order
F11	96.1	0.977	0.803	0.919	0.512	0.920	Zero order
F12	75.3	0.994	0.948	0.992	0.644	0.972	Zero order

CONCLUSION

From the obtained results, it can be concluded that:

IR spectra of pure drug and with the excipients are identical and do not show any incompatibility, thus the excipients are compatible with the drugs.

Lower values of angle of repose below 30 indicate good flow properties of powder blends. Friability and hardness were within the pharmacopoeial limits thus showing good mechanical strength of tablets.

Optimized bilayer formulation showed drug release for salbutamol sulphate layer faster release and for Ambroxol hydrochloride layer showed maximum delayed release.

Curve fitting analysis showed the drug release data of extended release layer fitted well into zero order kinetics and drug release data of immediate release fitted well into first order kinetics.

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