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Formulation and Evaluation of Sustained Release Bilayer Tablets of Ambroxol Hydrochloride

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ABSTRACT

The aim of the present investigation was to develop bilayer matrix tablets of Ambroxol hydrochloride. Ambroxol hydrochloride bi-layer matrix tablets were formulated consisting of two layers such as fast releasing layer and sustaining layer. Fast releasing layer was prepared by using super disintegrant such as sodium starch glycolate and sustaining layer was prepared by using C.R grade polymers such as Hydroxy propyl methylcellulose(Methocel K_4M), Ethyl cellulose independently and also in combinations. Bilayered tablets were prepared by direct compression process, this method was ideal for making the bilayered tablets. The *in-vitro* dissolution studies of various bilayered matrix tablets showed an initial burst effect followed by sustained release over a period of 12hrs. Formulation F_9 consists of Drug:HPMC:EC at ratio of (1:0.5:30%) as sustained release layer exhibited drug release patterns ideal with the theoretical release profiles of Ambroxol hydrochloride. The dissolution data obtained for various formulations were fitted into Higuchi's and Peppas models, which are linear with Higuchi's plot and "n" value obtained from peppas were within 0.45 to 0.89 indicate (anomalous diffusion) the mechanism of drug release diffusion coupled with erosion. FT-IR studies clearly indicated that there is no drug-polymer interaction.

Keywords: Ambroxol hydrochloride, bilayer tablets, sodium starch glycolate, direct compression method, methocel K_4M, Ethyl cellulose.

INTRODUCTION

Multi layered tablet concept has long been utilized to develop sustained release formulations. Such a tablet has a fast releasing layer and may contain bi (or) triple layers, to sustain the drug release (Abraham MA *et al*., 1997). The pharmacokinetic advantage relies on the fact that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from sustaining layer.

Ambroxol is an active-N-desmethyl metabolite of the bromohexine with similar actions and uses (Martindale Extrapharmacopoeia., 2002). It is chemically described as Trans-4-((2)-Amino-3, 5-dibromo benzyl amino)-cyclohexanol. It is an expectoration improver and a mucolytic agent used in the treatment of acute and chronic disorders characterized by the production of excess or thick mucous. Its mucolytic activity by which it facilitates breakdown of acid mucopolysaccharide fibres in the mucous making it thinner and less viscous and therefore, easy for expectoration. It has been successfully used for decades in the form of its hydrochloride as a secretion-releasing expectorant in a variety of respiratory disorders. Conventional forms are also available, but due to raising problems with the conventional tablet resulting in fluctuations of drug plasma levels and also the drug has short biological half life(3-4 hrs) (Respiration.,1987) favors for sustained release dosage form.

In the present study, Ambroxol hydrochloride bilayered matrix tablets were formulated consisting of two layers such as fast releasing layer and sustaining layer. Fast releasing layer was prepared by using super-disintegrant such as sodium starch glycolate and sustaining layer was prepared by using C.R grade polymers such as Hydroxy propyl methyl cellulose (Methocel K_4M), Ethyl cellulose (EC) independently and also in combinations.

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Materials and Methods

Materials

Ambroxol hydrochloride was a gift sample from Darwin Pharmaceuticals, Vijayawada. Hydroxy propyl methylcellulose (Methocel K_4M) was a gift sample from Colorcon Asia pvt-ltd, Mumbai. Ethyl cellulose with an ethoxyl content of 47.5%by weight and viscosity of 22cps was purchased from Loba chemie Pvt.Ltd. Magnesium stearate and talc were purchased from S.D Fine chemicals Ltd, Mumbai, India. Sodium starch glycolate, microcrystalline cellulose was purchased from Kemphasol, Mumbai, India.

METHOD

Preparation of bilayer tablet

The bilayer tablets of Ambroxol hydrochloride were prepared by the direct compression method. The drug and polymers for both fast release and sustaining layer were passed through an 180µm sieve before their use in the formulation.

Formulation of the fast release layer

The dose in the formulation for the fast release was 20 mg, the maintenance dose (55 mg) of Ambroxol hydrochloride was calculated as per the reported method (Rawlins, 1996., Wagner JG, 1976). Composition of the immediate release (IR) layer is given in table 1. The final weight of the IR layer was fixed to 50mg. Drug, sodium starch glycolate and microcrystalline cellulose were passed through a mesh (1150µm) and blended in a planetary mixer for 5 minutes. The blend was mixed with talc and magnesium stearate for 2 minutes.

Formulation of the sustaining layer

Compositions of different formulations for the SR layer are given in table 2. All the ingredients were passed through a mesh (1150µm) and blended in a planetary mixer for 5 minutes. The blend was lubricated and subjected to compression with suitable tablet tooling with fill weight of 250 mg.

Characterization of Powder blends

Prior to compression powder blends were evaluated for their characteristic parameters such as tapped density, Carr's index and angle of repose (Martin A *et al.*, 2002).

Compression of bilayer tablets

The quantity of powder blend for the sustained release layer was compressed lightly using single punch tablet machine (Cadmach machinery co Pvt. Ltd, India) equipped with 8mm circular, flat and plain punches. Over this compressed layer, the required quantity of the fast release layer was placed and compressed to obtain hardness in the range of 6-7kg/cm^2 to form a bilayered matrix tablet.

Physical tests for bilayer tablets

The standard physical tests for the bilayer matrix tablets were performed and average values were calculated. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet was calculated. Hardness was determined by taking 6 tablets from each formulation using a Monsanto tester (Electrolab Pvt. Ltd, India) and the average of pressure (kg/cm^2) applied for crushing the tablet was determined. Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Electrolab Pvt. Ltd, India), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated.

Estimation of Ambroxol hydrochloride

An ultraviolet spectrophotometric method based on the measurement of absorbance at 240nm in phosphate buffer (pH 7.4) was used for the estimation of Ambroxol. The method obeyed Beer Lambert's law in the concentration range of 10-40 µg/ml. Ambroxol hydrochloride when assayed in distilled water, 0.1N Hcl and phosphate buffer (pH7.4) respectively (n=6), the relative error and standard deviation were found to be within limits. The excipients talc and magnesium stearate did not have any interference with the absorbance of Ambroxol hydrochloride (Ramana G *et al.*, 2005).

In-vitro drug release study

Release of Ambroxol hydrochloride was determined using a USP XXI eight stage Dissolution rate test apparatus (Type 1) (Labindia Pvt. Ltd. India) at 50 rpm. The dissolution was studied using 900 ml of simulated gastric fluid (pH 1.2) for first 2 hrs and followed by simulated intestinal fluid (pH 7.4) for the remaining hours. The temperature was maintained at $37^0 \pm 0.2^0$C. The sample (5 ml) was withdrawn at different time intervals and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Ambroxol hydrochloride content at 240nm.

Drug release kinetics

The rate and mechanism of release of propranolol hydrochloride from the prepared bilayer tablets were analyzed by fitting the dissolution data into the zero-order equation (Merchant HA *et al*., 2006).

$$Q=k_0t$$

where 'Q' is the amount of drug released at time 't', and k_0 is the release rate constant, fitted to the first order equation(Bourne Dw, 2002).

$$\ln (100-Q) = \ln 100 - k_1t$$

Where k_1 is the release rate constant. The dissolution data was fitted to the Higuchi's equation (Higuchi T, 1963).

$$Q = k_2 t^{1/2}$$

where k_2 is the diffusion rate constant.

The dissolution data was also fitted to the well known equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems (Korsmeyer RW *et al.*, 1983).

$$\log (M_t/M_\infty) = \log k + n \log t$$

Where 'M_t' is the amount of drug released at time 't', 'M_∞' is the amount of drug release after infinite time, 'k' is a release rate constant incorporating structural and geometric characteristics of the tablet and 'n' is the diffusional exponent indicative of the mechanism of drug release.

FT-IR study

Infrared spectrum was taken (FT-IR spectrum RX1, Perkin Elmer ltd, Switzerland) by scanning the sample in potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually.

Results and Discussion

The prepared bilayer tablets were evaluated for various physical properties. The bulk densities for the powder blend of various formulations were ranged between 0.91±0.12 and 2.11±0.38 g/cc, as determined by the tap method. This value of bulk density indicates good packing character. The compressibility index (CI) for all the formulations was found to be below 15%, indicating desirable flow properties. The flow properties of powder blend were further analyzed by determining the angle of repose, it ranged between 21.32±0.41 to 26.20±0.21^0. The value indicates good flow properties of all the prepared formulations.

All the batches of tablets were produced under similar conditions to avoid processing variables. Mass of the bilayer tablets was 300±4 mg, hardness was 5.4±1.2 kg/cm^2. The percentage friability for all the formulations was 0.6±0.1%. The values of the hardness test and percent friability indicate good handling properties of the prepared bilayer tablets. The drug content uniformity in the bilayer matrix tablets was 99±1.8%.

Table.1 COMPOSITION OF FAST RELEASE LAYER OF AMBROXOL HCL PREPARED BY DIRECT COMPRESSION

Ingredients	Quantity (mg/tab)
Ambroxol hydrochloride	20
Sodium starch glycolate	15
Microcrystalline cellulose	13
Talc	1
Magnesium stearate	1

Table.2 COMPOSITION OF VARIOUS SUSTAINED RELEASE LAYERS OF AMBROXOL HCL PREPARED BY DIRECTCOMPRESSION

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ambroxol Hcl	55	55	55	55	55	55	55	55	55
Methocel K4M	27.5	55	82.5	110	137.5	165	27.5	27.5	27.5
Ethyl cellulose	-	-	-	-	-	-	15	30	45
Microcrystalline cellulose	157.5	130	102.5	75	47.5	20	41.5	36.5	21.5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

Table.3 IN-VITRO DISSOLUTION KINETIC DATA OF AMBROXOL HYDROCHLORIDE BI-LAYERED MATRIX TABLETS BY DIRECT COMPRESSION

S.NO	Formulations	Zero order constant µg/ml/hr		First order constant (hr^{-1})		Higuchi constant ($mg/hr^{1/2}$)		Peppas constant		
		K_0	R^2	K_1	R^2	K	R^2	K	R^2	n
1	**F1**	4.66	0.943	0.17	0.987	21.77	0.99	0.04	0.98	0.78
2	**F2**	4.62	0.962	0.13	0.989	21.31	0.98	0.04	0.90	O.88
3	**F3**	4.12	0.965	0.11	0.978	19.03	0.98	0.02	0.97	0.71
4	**F4**	2.71	0.945	0.10	0.981	16.78	0.98	0.01	0.98	0.61
5	**F5**	3.51	0.953	0.08	0.991	16.32	0.99	0.01	0.99	0.64
6	**F6**	3.37	0.952	0.07	0.987	15.71	0.99	0.01	0.99	0.64
7	**F7**	4.74	0.941	0.25	0.967	22.15	0.99	0.05	0.97	0.88
8	**F8**	4.61	0.952	0.19	0.985	21.48	0.99	0.03	0.98	0.81
9	**F9**	4.39	0.963	0.16	0.982	20.33	0.99	0.03	0.98	0.75

The FT-IR spectrum of Ambroxol hydrochloride, shown in Fig.3a and 3b, revealed the presence of peaks at 3283.7 cm^{-1} due to the presence of hydroxyl group, peaks at 3397.18 cm^{-1} due to the presence of aliphatic amino group. The FT-IR spectrum of Ambroxol hydrochloride tablet blend containing different polymers shows that the major frequencies of functional groups of pure drug remain intact in blend containing different polymers; hence, there is no major interaction between the drug and polymers used in the study.

The release of Ambroxol hydrochloride from the prepared formulations was analyzed by plotting the cumulative percent drug released versus time as shown in

Figs 1 and 2. Simple visual observation of the plot shows an initial burst effect. From all the formulations, over 33% of the Ambroxol hydrochloride was released quickly. This initial high amount of ambroxol hydrochloride release can be attributed to the immediate release layer of the formulation and also from the peripheral parts of the CR layer. Further release of Ambroxol hydrochloride was studied for 12 hrs.

Figure.1 Drug release profile of bilayered matrix tablet formulations of Ambroxol hydrochloride

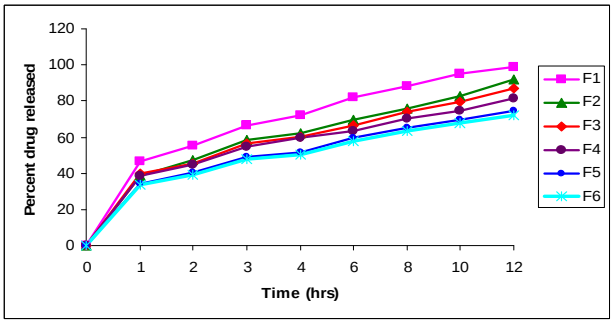


Figure.2 Drug release profile of bilayered matrix tablet formulations of Ambroxol hydrochloride

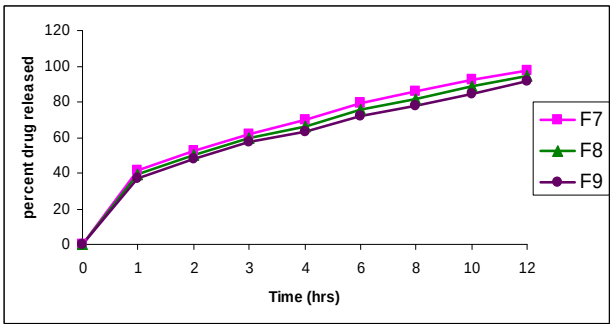
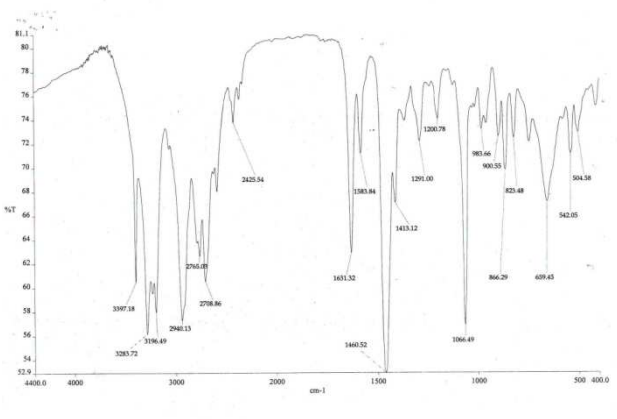


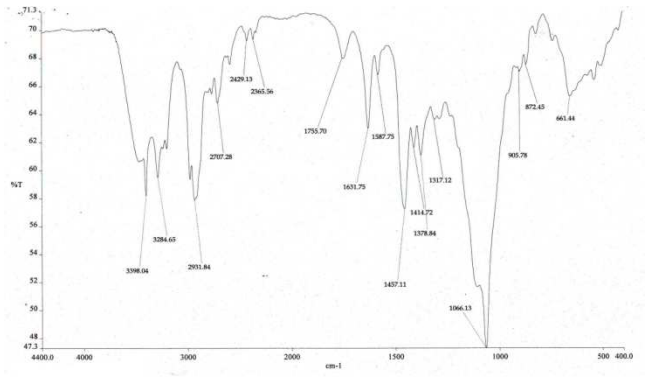
Figure.3a FT-IR spectrum of Ambroxol hydrochloride



The release of Ambroxol from the CR layer of the matrix tablets was found to be slow and extended up to a period of 12 hrs. The results of drug release were shown in figures 1 and 2. It was seen that more than 99%drug was released in the case of matrix tablet formulation F_1(containing 1:0.5%of drug :polymer HPMC K_4M alone). As the proportion of the polymer increased, the release rate of Ambroxol decreased (F_2 to F_6). The initial high amount of drug release from the CR layer can be retarded to some extent by the incorporation of hydrophobic polymer like ethyl cellulose (EC). Various formulations (F_7, F_8 and F_9) were made with varying proportions of ethyl cellulose. Ethyl cellulose has been used as release retardant polymer in controlled release dosage forms. EC reduces the drug release due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethyl cellulose present on the surface of the tablet i.e, the rate of release is controlled by the permeability of matrix structure. As the proportion of ethyl cellulose increases, the release process of Ambroxol hydrochloride decreases. So, the formulations prepared, F_9 (containing 1:0.5:30% of drug: HPMC K_4M: EC) gave Ambroxol release close to the theoretical CR release. Initially, burst effect in the release of the drug was observed, which was probably sufficient for quick buildup of plasma concentration.

The rate and mechanism of release of Ambroxol hydrochloride from the prepared bilayer tablets were analyzed by fitting the dissolution data into the zero-order, first-order, Higuchi's and Korsmeyer-Peppas equation. All the formulations (F_1 to F_9) followed first order release mechanism and r^2 values were also linear. Higuchi plots for all the formulations were linear indicating the drug release by diffusion controlled. To explore the release pattern, results of the in- vitro dissolution data were fitted to the Korsmeyer peppas equation, which characterizes the transport mechanism. The value of release exponent (n) for all the formulations were in between 0.60 to 0.88 indicates the anomalous transport with slow erosion of the polymer matrix followed by diffusion of drug resulted in linear drug release over a prolonged period of time. The values were depicted in Table.3.

Figure.3b FT-IR spectrum of combination of Ambroxol hydrochloride, Methocel K4M and Ethyl cellulose



CONCLUSION

The present study was carried out to develop bilayered matrix tablets of Ambroxol hydrochloride using super disintegrant sodium starch glycolate for the fast release layer and Methocel K_4M, ethyl cellulose for the sustaining layer by direct compression method. Bilayer tablets showed an initial burst effect to provide the loading dose of the drug, followed by sustained release for 12 hrs, indicating a promising potential of the

Ambroxol hydrochloride bilayer tablets an alternative to the conventional dosage form.

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