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Formulation and the effect of channeling agents on the release pattern of ambroxol hydrochloride from HPMC K4M matrix tablets

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ABSTRACT

The present study was undertaken to investigate the effect of channeling agents on the release profile of ambroxol hydrochloride from HPMC (Hydroxypropyl Methylcellulose) K4M based matrix systems. Matrix tablets of ambroxol hydrochloride using HPMC K4M were prepared by direct compression method. Microcrystalline cellulose (MCC) and Sodium chloride (Nacl) were used as channeling agents. Drug release study was evaluated for 12 hours using USP II paddle type dissolution rate test apparatus using pH 1.2 for first two hours and pH 7.4 phosphate buffer for remaining period as the dissolution medium. The obtained dissolution data was fitted into first order release kinetics, Higuchi, Peppas & Koresmeyer's equations. The release rate, extent and mechanisms were found to be governed by channeling agent type and content. Higher channeling agent content in the matrix increased the rate and extent of the drug release, at lower channeling agent level, the rate and extent of drug release was decreased and in absence of channeling agents these were least. Nacl ensures maximum release of drug from low viscosity grade HPMC K4M than MCC. It was found that type and amount of channeling agent significantly affect the time required for 50% of drug release (T50%), percentage drug release at 12 hours, release rate constant (K) and diffusion exponent (n). The release of ambroxol was found to be diffusion controlled and followed first order kinetics. The FT-IR studies were also indicating the absence of strong interactions between the components and suggesting drug-excipient compatibility in all the formulations examined.

INTRODUCTION

The major challenge in the development of new controlled release devices is to achieve optimal drug concentration at the site of action. Development of sustained release oral dosage forms is beneficial for optimal therapy regarding efficacy, safety and patient compliance [1]. Frequently used approaches to achieve adequate control of release include hydrophilic and lipophilic matrix systems, in which the mechanism of drug release is based on a combination of diffusion and erosion processes [2, 3]. Among the numerous hydrophilic carrier materials tested for the development of hydrophilic matrices, the most commonly used is hydroxypropyl methylcellulose (HPMC), which has been used since the early 1960s [4,5]. Their properties as gelling agents are very important in the formulation because they are responsible for the formation, by hydration, of a diffusion and erosion-resistant gel layer which is able to control drug release [6].

Channeling agents are to be soluble in the gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channeling agent, but a water-soluble pharmaceutically accepted solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. The choice will depend on the drug and the desired release characteristics [7]. Based on this, the present work was planned to study the effect of channeling agents on the release pattern of ambroxol hydrochloride from HPMC K4M CR based matrix tablets.

MATERIALS AND METHODS:

MATERIALS

Ambroxol hydrochloride was a gift sample from Darwin Pharmaceuticals, Vijayawada. Hydroxypropyl methylcellulose (Methocel K_4M) was a gift sample from Colorcon Asia pvt-ltd,

Mumbai. Microcrystalline cellulose (MCC) and Nacl were obtained from Loba Cheme Pvt. Ltd., Magnesium stearate and talc was purchased from S.D Fine chemicals Ltd, Mumbai, India.

METHODS

FT-IR Study:

Infrared spectrum was taken (FT-IR, Spectrum RX 1, Perkin Elmer Ltd and Switzerland) by scanning the sample in potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually.

Preparation of matrix tablets of Ambroxol hydrochloride:

Matrix tablets of ambroxol hydrochloride were prepared by direct compression technique as per the composition given in table 1. Ambroxol hydrochloride, HPMC K4M, Micro crystalline cellulose (MCC), sodium chloride, was passed through sieve no # 40. All the above were mixed in geometric proportion in a poly bag for 15 minutes. Talc and magnesium stearate were passed through sieve no # 60. Sifting was performed and the lubricated material was passed through the poly bag and mixed for 2 minutes. The appropriate amounts of the mixture were accurately weighed in an electronic balance for the preparation of each tablet and finally compressed using a Cad mach rotary tablet machine equipped with a 10 mm flat faced punch and die set. The final weight of the tablet was fixed to 500 mg.

Physical tests for compressed tablets :

The standard physical tests for the prepared 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 (Electro lab 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 (Electro lab 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 [8].

In-vitro drug release study:

Release of ambroxol hydrochloride was determined using a USP XXI eight stage Dissolution rate Test Apparatus (Type II) (Lab India 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 period. 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[9].

Drug Release Kinetics:

To study the mechanism of drug release from matrix tablets, the obtained dissolution data were fitted into the following equations:

***Zero order equation* [10]**

$$Q_t = Q_0 + k_{0t} \quad \text{----------} (1)$$

Where, Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug in the solution (more times, $Q_0 = 0$) and k_0 is the zero-order release rate.

First order equation [11]

$$\ln Q_t = \ln Q_0 = k_1 t \quad \text{----------} (2)$$

Where, Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug in the solution and k_1 is the first-order release rate constant.

Table 1: Composition of various formulations of Ambroxol hydrochloride matrix tablets prepared by direct compression method

S.No	Ingredients (mg/tablet)	Formulations						
		F1	F2	F3	F4	F5	F6	F7
1	Ambroxol hydrochloride	75	75	75	75	75	75	75
2	HPMC K4M	225	225	225	225	225	225	225
3	Microcrystalline Cellulose	-	50	100	150	-	-	-
4	Sodium chloride	-	-	-	-	50	100	150
5	Dicalcium Phosphate	194	144	94	44	144	94	44
6	Talc	3	3	3	3	3	3	3
7	Magnesium stearate	3	3	3	3	3	3	3

***Higuchi's equation* [12]**

$$Q = k_H t^{1/2} \quad \text{----------} (3)$$

Where, Q is the amount of drug released at time t, k_H is the Higuchi diffusion rate constant

***Koresmeyer's equation* [13]**

$$M_t / M_\infty = Kt^n \quad \text{----------} (4)$$

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, k is a kinetic constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent of the drug release mechanism .

RESULTS AND DISCUSSION:

The FT-IR spectral studies of ambroxol hydrochloride, 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 excipients shows that the major frequencies of functional groups of pure drug remain intact in blend containing different excipients; hence there is no major interaction between the drug and excipients used in the present study.

The powdered blend was evaluated for various micromeritic properties. The bulk density and the tapped density of various formulations were within the limits. These values indicate 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 blend were further analyzed by determining the angle of repose, it ranged between 23.54 ±1.13^0 to 26.54±0.76 ^{0}. The value indicates good flow properties of all the prepared formulations. The micromeritic properties of these formulations were depicted in the Table no. 2.

All the batches of tablets were produced under similar conditions to avoid processing variables. Mass of the tablets was 500±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 matrix tablets. The drug content uniformity in the prepared matrix tablets was found to be 101±1.8%.

From the drug release profile it was observed that the total percent release of ambroxol from F-1 to F-4 were 70.54%, 78.12%, 89.12%, 93.5% and from F-5 to F-7 were 80.80%, 91.10% and 95.92% respectively at the end of 12 hours. From the Figures 1 & 2, it was observed that without channeling agent, drug release from the F-1 was slow. This effect was due to the characteristic property of HPMC K4M to form gel *in situ*. This type of polymers forms a gel like layer around the matrix system. When HPMC K4M is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscose gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release.

To investigate the effect of channeling agents (MCC and Nacl) on ambroxol hydrochloride release, seven formulations were made (Table 1). The drug release data of matrix tablets were fitted into various kinetic models (zero, first, Higuchi's square root and Peppas equation) to evaluate the kinetics and mechanism of drug release from the matrix tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r^2' value is considered as the best fit of the release data. The 'r^2' values for zero order, first order and Higuchi's models are given in Table 3. The results given in Table 3 indicated that the drug release from the matrix tablets followed first order kinetics. To evaluate drug release mechanism from the tablets, plots of percent released versus square root of time as per higuchi's equation were constructed. These plots were found to be linear with all the tablets with correlation coefficient values in the range of 0.977-0.996 indicating that the drug release from the tablets was diffusion controlled.

When the release data were analyzed as per Peppas equation, the values of release exponent of 'n' for F-1 and F-2 were 0.598 and 0.573 respectively, which indicate that the drug was released by anomalous transport (coupling of the diffusion and erosion

Table 2: Micromeritic properties of powder blends of various formulations.

Formulations	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (0)	Percentage compressibility	Hausner's ratio
F1	0.53±0.08	0.79±0.32	23.54±1.13	14.51±0.14	1.170±0.04
F2	0.57±0.04	0.65±0.44	26.24±0.65	14.06±0.18	1.164±0.09
F3	0.58±0.01	0.59±0.07	25.32±0.38	14.42±1.10	1.163±0.05
F4	0.52±0.05	0.64±0.01	26.23±1.14	14.25±0.85	1.201±0.01
F5	0.51±0.04	0.67±0.57	25.45±0.48	13.24±0.95	1.152±0.05
F6	0.56±0.03	0.68±0.24	26.42±0.95	15.00 ±0.75	1.102±0.12
F7	0.57±0.08	0.65±0.15	26.54±0.76	14.41±0.64	1.142±0.07

mechanism). The values of 'n' for F-3 and F-4 were 0.418 and 0.386 respectively. This value indicates that the drug was released by following Fickian release pattern, more specifically diffusion controlled release mechanism. The values of 'n' for F-5, F-6 and F-7 were 0.542, 0.402 and 0.331 respectively. This clearly shows that the diffusion exponent (n) was reduced with the increase of channeling agent. The shifting of release mechanism from non-Fickian transport to Fickian transport in case of MCC. and Nacl were observed. This effect is due to the formation of channels on the surface of matrix that facilitated the diffusion mechanism [14].

From the table 3, it was also clear that $T_{50\%}$ values were changed due to the change of the amount of channeling agents in the matrix tablets. In all these formulations the values of $T_{50\%}$ were larger for those formulations which contained smaller quantities or absence of channeling agents. The $T_{50\%}$ values for F-1, F-2, F-3 and F-4 were 8.5 hours, 6.4 hours, 5.3 hours and 3.4 hours respectively. This reduction of the magnitude of $T_{50\%}$ indicated that the increment of MCC enhanced the channeling effect on the surface of the matrix to facilitate the drug release. Similar behavior was also observed in case of F-5, F-6 and F-7 where Nacl was used as channeling agent. The rate and extent of ambroxol

Table 3: In-vitro dissolution kinetic data of ambroxol hydrochloride matrix tablets by direct compression method.

Formulation code	Correlation co-efficient (R^2)				Fractional Dissolution Time (hrs)
	Zero order	First order	Higuchi	Peppas	
	R^2 value	R^2 value	R^2 value	'n' value	$T_{50\%}$
F1	0.869	0.975	0.977	0.598	8.5
F2	0.876	0.978	0.986	0.573	6.4
F3	0.845	0.988	0.988	0.418	5.3
F4	0.869	0.986	0.981	0.386	3.4
F5	0.872	0.990	0.996	0.542	5.4
F6	0.911	0.987	0.983	0.402	4.2
F7	0.892	0.982	0.987	0.331	3.1

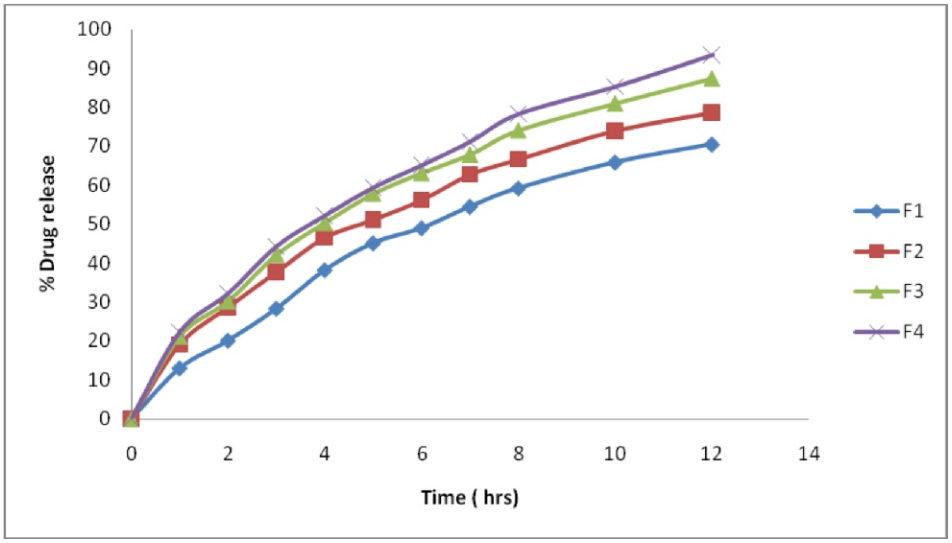

Fig 1: Drug release profile of Ambroxol matrix tablets containing MCC as channeling agent. F1 used as control with no channeling agents

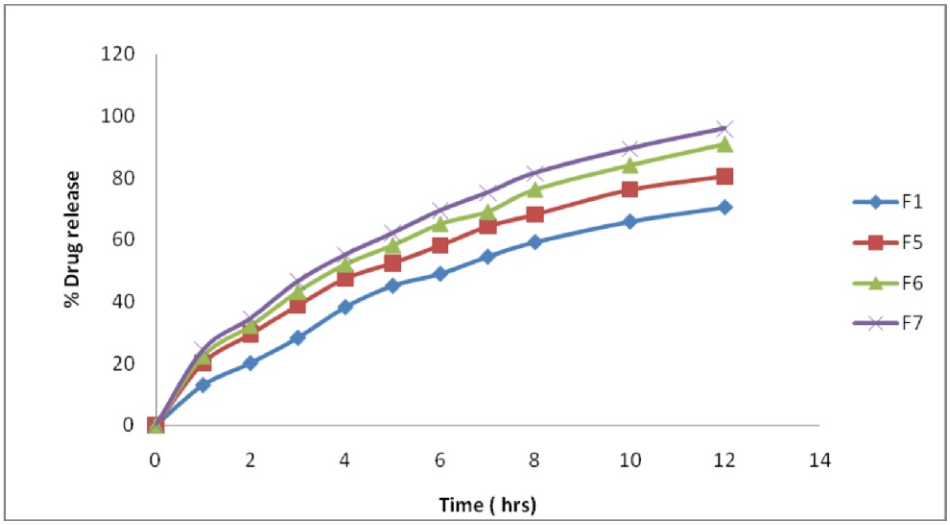

Fig 2: Drug release profile of Ambroxol matrix tablets containing Nacl as channeling agent. F1 used as control with no channeling agents.

release increases from the matrices with increasing the amount of MCC in the F- 2, F- 3 and F- 4 (Figure 1) and the amount of Nacl in the F-5, F- 6 and F- 7 (Figure 2). Among the two channeling agents investigated (MCC and Nacl), Nacl showed greater degree of drug release than MCC

CONCLUSION:

Channeling agents significantly affected the drug release kinetics from prepared matrix tablets in our study. In all cases the increase of the channeling agent content caused a lowering of the magnitude of release exponent (n) which indicates the shifting of release mechanism from non-Fickian to Fickian mechanism. In case of release rate MCC and Nacl exert almost same effect but Nacl offered greater release than MCC from HPMC K4M hydrophilic polymer. It was concluded that by using the both channeling agents can increase the rate of drug release from HPMC K4M based matrix tablets of ambroxol hydrochloride.

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