Formulation and Release Behaviour of Sustained Release Ambroxol Hydrochloride HPMC Matrix Tablet

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Monolithic matrix tablets of ambroxol hydrochloride were formulated as sustained release tablets employing hydroxypropyl methylcellulose polymer, and the sustained release behaviour of the fabricated tablets was investigated. Sustained release matrix tablets containing 75 mg ambroxol hydrochloride were developed using different drug polymer ratios of hydroxypropyl methylcellulose. Tablets were prepared by direct compression. Formulation was optimized on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. All tablets but one exhibited gradual and near-completion sustained release for ambroxol hydrochloride, and 98-101% released at the end of 12 h. The results of dissolution studies indicated that formulation F-V (drug to polymer 1:1.47), the most successful of the study, exhibited drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio. Applying exponential equation, all the formulation tablets (except F-V) showed diffusion-dominated drug release. The mechanism of drug release from F-V was diffusion coupled with erosion (anomalous).

Ambroxol is a metabolite of bromhexine with similar actions and uses[1]. It is chemically described as trans-4-[(2-Amino-3,5-dibromobenzyl)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. It has been successfully used for decades in the form of its hydrochloride as a secretion-releasing expectorant in a variety of respiratory disorders[2]. Its short biological half life (4 h)[3,4] that calls for frequent daily dosing (2 to 3 times) and therapeutic use in chronic respiratory diseases necessitates its formulation into sustained release dosage form.

The development of sustained/controlled release formulations of ambroxol hydrochloride is therefore of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of the drug over time. The simplest and least expensive way to control the release of the drug is to disperse it within an inert polymeric matrix. And hydrophilic matrices are an interesting option when formulating an oral sustained release (SR) of a drug. The dosage release properties of matrix devices may be dependent upon the solubility of the drug in the polymer matrix or, in case of porous matrices, the solubility in the sink solution within the particle's pore network[5]. Hydroxypropylmethylcellulose (HPMC) is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems[6]. Numerous studies have been reported in literature investigating the HPMC matrices to control the release of a variety of drugs from matrices[7-11].

The objective of the present study was to formulate ambroxol hydrochloride SR matrix tablets using HPMC K100 polymer and to elucidate the release kinetics of ambroxol hydrochloride from HPMC matrices. We attempted a systematic approach to develop twice-daily sustained release ambroxol hydrochloride matrix tablets.

MATERIALS AND METHODS

Ambroxol hydrochloride was obtained from New Drug and Chemical Company, Mumbai. HPMC K100M, a grade of HPMC, was procured from Colorcon Asia Pvt. Ltd.,

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Mumbai. Microcrystalline cellulose (MCC) and Aerosil[R]200 were purchased from Coveral and Company, Chennai. Materials and excipients used in preparing tablets were IP grades. All other ingredients used throughout the study were of analytical grade and were used as received.

Calculation of theoretical release profile of ambroxol hydrochloride from SR tablets:

The total dose of ambroxol hydrochloride for twice-daily SR formulation was calculated by Robinson Eriksen equation[12] using available pharmacokinetic data[3,4]. The zero-order drug release rate constant (k^o) was calculated using equation $k^o = DI \times k_e$, where DI is the initial dose (i.e., conventional dose = 30 mg) and k_e is first-order rate constant for overall elimination and was found to be 5.19 mg/h. The loading dose was calculated as 19.42 mg. Hence an oral controlled release formulation of ambroxol hydrochloride should contain a total dose of 76.51 mg ($\cong$ 75 mg) and should release 19.42 mg in first 1 h like conventional tablets, and 5.19 mg/h up to 12 h thereafter.

Preparation of matrix tablets:

Matrix tablets, each containing 75 mg ambroxol hydrochloride, were prepared by direct compression technique. The drug polymer ratio was developed to adjust drug release as per theoretical release profile (Table 1) and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 245 mg with different drug polymer (HPMC) ratios. A batch of 1000 tablets was prepared in each formula. The composition of tablets is shown in Table 1. MCC was incorporated as filler excipient to maintain tablet weight constant. This water-insoluble filler was incorporated also to counterbalance the faster solubility of the drug in presence of hydrophilic polymer and to provide a stable monolithic matrix. The ingredients were passed through sieve no. 30 and thoroughly mixed in a polythene bag. The powder blend was then lubricated with aerosol and magnesium stearate and compressed into tablets on a 16-station single rotary Cadmach machine using 12/32 DC punch.

TABLE 1: FORMULAE OF AMBROXOL HYDROCHLORIDE TABLETS

Ingredients mg/tab.	Formulations*				
	F-I	F-II	F-III	F-IV	F-V
Ambroxol HCl	75	75	75	75	75
HPMC K100M	49	73.5	73.5	98	110.25
MCC	118.6	94.1	94.1	69.6	57.35
Aerosil	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	1.2	1.2	1.2	1.2	1.2
Total	245	245	245	245	245

*The drug: polymer ratios of F-I, F-II, F-III, F-IV and F-V are 1:0.65, 1:0.98, 1:0.98, 1:1.30 and 1:1.47 respectively

Evaluation of tablets:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong-Cobb hardness tester (Tab-machine, Mumbai). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of the tablets was measured by vernier callipers. Weight variation test was performed according to official method[13]. Drug content for ambroxol hydrochloride was carried out by measuring the absorbance of samples at 248 nm using Shimadzu 1201 UV/Vis spectrophotometer and comparing the content from a calibration curve prepared with standard ambroxol hydrochloride in the same medium.

***In vitro* drug release studies:**

The *in vitro* dissolution studies were carried out using USP 24 dissolution apparatus type II[14] (paddle method) at 100 rpm. Dissolution test was carried out for a total period of 12 h using 0.1N HCl (pH 1.2) solution (750 ml) as dissolution medium at 37 ± 0.5° for first 2 h, and pH 6.8 phosphate buffer solution (1000 ml) for the rest of the period. Ten millilitres of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed (37 ± 0.5°) fresh dissolution medium. The samples withdrawn were filtered through 0.45 µ membrane filter, and drug content in each sample was analyzed after suitable dilution by above-mentioned spectrophotometer at 248 nm. The actual content in samples was read from a calibration curve prepared with standard ambroxol hydrochloride.

Kinetic analysis of dissolution data:

The commonly adopted model for understanding release behaviour of a drug from hydrophilic matrix is a simple exponential equation[15]. The *in vitro* drug release data were fitted in the exponential equation (known as Korsmeyer-Peppas equation) $M_t/M_\infty = Kt^n$, where M_t corresponds to the amount of drug release in time t, M_∞ is the total amount of drug released after an infinite time, K is a constant related to the structural and geometric properties of the drug delivery system (tablet) and n is the release exponent related to the mechanism of the release. Table 2 shows an analysis of diffusional release mechanism obtained by various values of n[16]. The n values used for elucidation of the drug release mechanism from the tablets were determined from log

cumulative percentage of drug released versus log time plots [i.e., log ($M_t/M_\infty \times 100$) versus log t].

Stability studies:

One selected fabricated tablet batch was strip packaged and kept at 45° with 75% RH. Samples were withdrawn at 0, 15, 30 and 45 d for evaluation of appearance, drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

The results of hardness and friability of the prepared matrix tablets ranged from 4.5 ± 0.02 to 7.0 ± 0.69 and 0.18 to 0.33 respectively (Table 3). The tablet formulations in all the prepared batches contained ambroxol hydrochloride within 100 ± 5% of labelled content. As such, all the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content. All tablets complied with pharmacopoeial specifications for weight variation and friability. Ambroxol release from tablets was slow and extended over longer periods of time. The results of dissolution studies of formulations F-III, F-IV and F-V are shown in fig. 1. Drug release from the matrix tablets was found to decrease with increase in drug polymer ratio. Formulation F-I, composed of drug polymer ratio of 1:0.65, failed to sustain release beyond 8 h. Between formulation F-II and F-III, formulated employing same drug polymer ratio of 1:0.98, formulation F-III with higher tablet hardness gave slower (t_{50} is 3.1 h) and complete release of ambroxol over a period of 12 h compared to F-II (t_{50} is 2 h). Hence we concluded that there is a direct relationship between tablet hardness and sustaining of the drug release.

The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. This may be due to structural reorganization of hydrophilic HPMC polymer. Increase in concentration of HPMC may result in increase in the tortuosity or gel strength of the polymer. When HPMC polymer 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[18].

In vitro release studies demonstrated that the release of ambroxol from all these formulated SR matrix tablets can generally be sustained (fig. 1). According to theoretical sustained release profile (basis of calculation mentioned earlier), an oral controlled release formulation of ambroxol hydrochloride should provide a release of 25.89% in 1 h, 38.81% in 2 h, 46.65% in 4 h, 74.40% in 8 h and 100% in 12 h. Formulation F-V tablet gave release profile close to the theoretical sustained release needed for ambroxol (figs. 1 and 2). The release from the formulation was also comparable to that of a commercially available SR tablet tested (fig. 2).

The mechanism of release of ambroxol from batches F-I to F-III was quasi (Fickian) diffusion, while F-IV showed behaviour of Fickian diffusion (Table 4). As shown in Table 4, the n values increased as the drug polymer ratio of the tablets increased. Formulation F-V showed average linearity (R^2 value 0.9870), with slope (n) value of 0.542. This n value appears to indicate a coupling of diffusion and erosion mechanism (known as anomalous non-Fickian diffusion). Hence, diffusion coupled with erosion may be the mechanism of ambroxol release from F-V. The data for stability studies carried out for F-V batch at 45° with 75% RH for 45 d revealed that no considerable differences in drug content and dissolution rate were observed (Table 5).

TABLE 2: RELEASE MECHANISM WITH VARIATION OF n* VALUES

n value	Mechanism	dM_t/d_t dependence
n<0.5	Quasi-Fickian diffusion	$t^{0.5}$
0.5	Fickian diffusion	$t^{0.5}$
0.5<n<1.0	Anomalous (non-Fickian) diffusion	t^{n-1}
1	Non-Fickian case II	Zero order
n>1.0	Non-Fickian super case II	t^{n-1}

*The diffusional exponent is based on Korsmeyer-Peppas equation, $M_t/M_\infty = kt^n$

TABLE 3: PROPERTIES OF COMPRESSED AMBROXOL MATRIX TABLETS

Formulation	Weight mg ± SD (n=20)	Hardness kg/cm² ± SD (n=5)	Thickness mm ± SD (n=5)	Friability %	Drug content (%) ± SD (n=3)
F-I	246.0 (1.52)	4.5 (0.21)	3.61 (0.04)	0.33	101.80 (1.13)
F-II	246.2 (1.75)	5.1 (0.35)	3.67 (0.06)	0.40	99.60 (0.95)
F-III	246.4 (1.55)	7.0 (0.69)	3.52 (0.07)	0.18	98.37 (0.82)
F-IV	247.3 (1.69)	4.7 (0.40)	3.72 (0.08)	0.13	99.50 (0.72)
F-V	247.0 (1.20)	4.8 (0.37)	3.73 (0.03)	0.22	99.90 (1.15)

Note: All figures in the parentheses represent ±SD; n is specified in each column head

TABLE 4: MATHEMATICAL MODELLING AND DRUG RELEASE MECHANISMS OF AMBROXOL SR TABLETS (FORMULATED AND COMMERCIAL)

Formulations	n	R	Mechanism
F-I	0.336	0.9859	Quasi-Fickian diffusion
F-II	0.386	0.9973	Quasi-Fickian diffusion
F-III	0.402	0.9874	Quasi-Fickian diffusion
F-IV	0.497	0.9851	Fickian diffusion
F-V	0.542	0.9870	Anomalous (Non-Fickian)
CAS*	0.573	0.9621	Anomalous (Non-Fickian)

Note: Based on Korsmeyer-Peppas equation, $M_t/M_\infty = kt^n$; *CAS - Commercially available sample SR tablet

TABLE 5: STABILITY STUDIES ON FORMULATED F-V BATCH TABLET

Parameter	Initial tablets	Strip pack at 45° with 75% RH		
		15 d	30 d	45 d
Drug content (%)	99.90 (1.10)	99.60 (1.76)	99.55 (1.45)	99.25 (1.01)
t_{50} (h)	5.10	5.15	5.10	5.05
t_{90} (h)	10.00	10.05	10.05	9.55

Note: Figures in the parentheses represent ±SD, (n = 3); other each value represents an average of two values

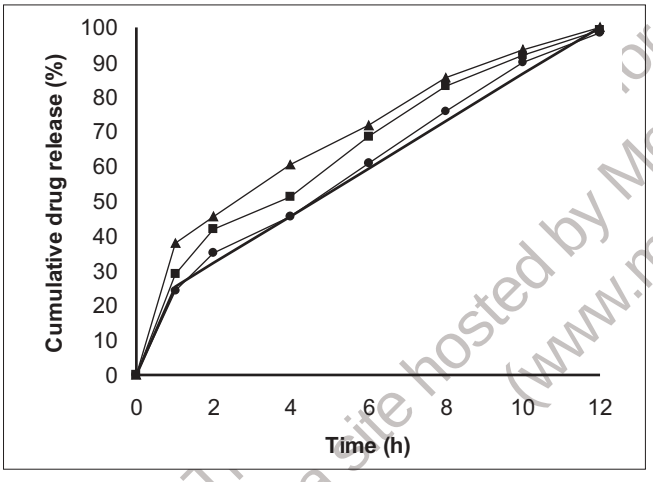

Fig. 1: Comparison of *in vitro* release profiles of ambroxol from tablets of batches F-III, F-IV and F-V and theoretical dissolution profile
***In vitro* cumulative release of ambroxol from formulation F-III (▲), F-IV (■), F-V (●) and theoretical release profile (-)**

It may be concluded from the present study that slow, controlled and complete release of ambroxol over a period of 12 h was obtained from matrix tablets (F-V) formulated employing drug polymer ratio of 1:1.47. It is also evident from the results that formulation F-V is a better system for twice-daily SR of ambroxol hydrochloride. Formulation F-I to F-IV exhibited diffusion to quasi diffusion mechanism of drug release, whereas the mechanism of drug release from F-V was anomalous.

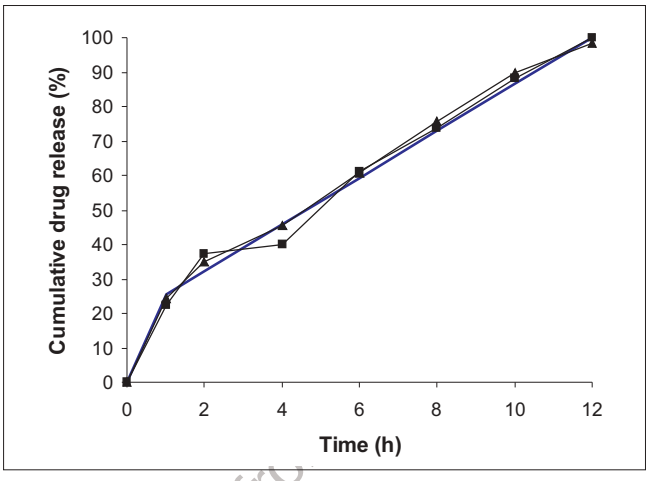

Fig. 2: *In vitro* release profiles of ambroxol from formulated matrix tablets (batch F-V), commercial SR tablets and theoretical dissolution profile
***In vitro* cumulative release of ambroxol from formulation F-V (▲), commercial SR tablets (■) and theoretical release profile (-)**

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