Original Article

FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE TABLETS USING EUDRAGIT RS-100

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Abstract

The Goal of this study was to design and evaluate the oral controlled release Ambroxol hydrochloride tablets. Controlled release matrix tablets of Ambroxol hydrochloride were prepared by using polymer, Eudragit RS100 (Drug: polymer 1:0.5, 1:0.75, 1:1 ratio) by wet granulation method and Compressed into tablets. The granules were evaluated for the angle of repose, Bulk density, tapped density, bulkiness, Compressibility index, and Hausner ratio. The granules showed satisfactory Flow properties. The tablets were subjected to weight variation test, hardness test, Friability test and drug content test. All the tablets were passed the tests. The invitro release studies were carried out in the phosphate buffer pH 7.4 for 10 hours using an USP type dissolution apparatus. The rate of release data to kinetic analysis, it was observed that the release of all the formulation followed the mechanism of both diffusion and erosion. And all the formulations are stored at 45°±2°C (RH 75±5%) and the stability studies carried out for 45days. It showed that all the formulations are physically and chemically stable.

Keywords: Ambroxol Hydrochloride, Eudragit RS 100, Controlled release, Matrix tablets.

Introduction

Matrix tablets are one of the most widely used dosage forms within controlled release techniques, matrix type systems release the active medicament in a delay and Controlled manner. Oral route has been the commonly adopted and the most convenient route for the drug delivery. In long term therapy for the treatment of chronic diseased Conditions, Conventional formulations are required to be administered as multiple doses and have been several disadvantages. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient Compliance, maintain the uniform drug level, reduce the frequency of dosing and side effects and increase the safety margin for high potency drugs.[1]

Ambroxol hydrochloride is a metabolite of bromhexine and is official in the Martindale Extrapharmacopoeia[2]. It is chemically described as trans-4-[(2-Amino-3,5-dibromobenzyl) amino]-cyclohexanol. It is widely used as a mucolytic agent prescribed in respiratory infections like bronchitis and bronchial asthma[3]. It has a short biological half life of 3–4 hours and is administered in a dose of 30mg 3-4 times a day[4]. Therefore, it is an ideal candidate for design as a Controlled release (CR) dosage form, which would result in prolonged clinical efficacy, reduced frequency of administration and lesser side effects.

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The matrix based controlled release tablets can be prepared by wet granulation method. Many polymers can be used in the Formulation of the matrix based controlled release drug delivery systems, Eudragit as the best acrylic polymer, which has a wide application in the production of matrix tablets with the controlled release. Eudragit is available in many forms. However, in the present work Eudragit RS 100 was selected to prepare controlled release tablets of Ambroxol hydrochloride[5]. It provides pH-independent drug release to oral dosage forms that can be used for formulating the controlled release dosage forms. The aim of this work was to prepare Ambroxol hydrochloride matrix tablets using Eudragit RS100 with three ratios (1:0.5, 1:0.75 and 1:1 each). The Tablets are prepared by wet granulation method, preformulation studies of granules, various tests of evaluation of tablets, IR spectral analysis, dissolution studies, kinetic analysis studies and stability studies were carried out.

Materials and Methods

Ambroxol hydrochloride was obtained as the gift sample from Tablets India (P) Ltd., Chennai and Eudragit RS 100 were obtained as the gift sample from Microlabs, Hosur. All other chemicals and reagents used were of Analytical grade.

Preparation of Ambroxol hydrochloride CR Tablets

Three Formulations of controlled release tablets of Ambroxol hydrochloride using Eudragit RS 100 with three ratios (1:0.5, 1:0.75, 1:1) were prepared by wet granulation method. The details of Composition of each Formulation are shown in table-1.

Ambroxol hydrochloride and the polymer Eudragit RS 100 with three ratios were mixed separately, ethyl cellulose,

lactose was added to the drug and polymer mixed and blended thoroughly for 5minutes. Polyvinyl pyrrolidone (PVP) was dissolved in sufficient quantity of isopropyl alcohol (IPA) until it forms a solution in IPA were added to the drug mixture and mix it thoroughly to form a coherent mass Then the coherent mass was passed through a sieve No.16 to form granules. Then the granules are collected and dried at 40°C ± 2°c for 2 hours. The dried granules were passed through a sieve No. 22, the portion, which was retained on the sieve No. 22 was selected and the fines were rejected. The granules are evaluated for preformulation tests. After preformulation studies, the granules are mixed with magnesium stearate and talc uniformly and finally the granules are compressed into tablets. The same procedure was followed to prepare Ambroxol hydrochloride tablets without polymer.

Table - 1
Composition of Matrix Tablet of Ambroxol hydrochloride using Eudragit RS 100

Ingredients (mg/Tablet)	Eudragit RS 100			Control (without polymer)
	1:0.5 (E1)	1:0.75 (E2)	1:1 (E3)	
Ambroxol hydrochloride	75	75	75	75
Ethyl cellulose	20	20	20	20
Eudragit RS 100	37.50	56.25	75	-
Polyvinyl pyrrolidone (PVP K30)	3	3	3	3
Lactose Monohydrate	104.5	85.75	67	142
Talc	6	6	6	6
Magnesium Stearate	4	4	4	4
Isopropyl Alcohol	q.s	q.s	q.s	q.s
Weight of one tablet is 250mg				

Evaluation of granules and tablets

The granules were evaluated for bulk density, tapped density, bulkiness, angle of repose, compressibility index and Hausner ratio to determine for micrometric properties[6] and the results are presented in table-2. The formulated tablets were evaluated for hardness test[7] (using Monsanto Hardness Tester, shital scientific industries, Ahmedabad), Friability (Friabilator, EF- 2 (USP), Roches, (ampbels electronics) thickness and diameter.

For weight variation test, twenty tablets were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation[8]. Drug content was determined as follows: An accurately weighed amount of ambroxol hydrochloride (100mg) was extracted with 0.1N Hcl (pH 1.2) and the solution was filtered through 0.45µ membrane filter. The absorbance was measured by using UV double beam spectrophotometer at 248nm after suitable dilution[9]. The drug Content was determined using the standard calibration curve. All the results are presented in table–3.

Table-2
Evaluations of Ambroxol hydrochloride Granules

Parameter	Ambroxol hydrochloride : Polymers EUDRAGIT RS100 1:0.5	1:0.75	1:1	Control
Bulk density*(gm/cc)	0.43 ± 1.43	0.42 ± 1.24	0.41 ± 1.74	0.42 ± 0.76
Tapped density*(gm/cc)	0.46 ± 0.86	0.46 ± 0.94	0.49 ± 0.68	0.47 ± 0.82
Bulkiness* (cc/gm)	2.35 ± 0.78	2.36 ± 0.69	2.34 ± 0.12	2.38 ± 1.02
Angle of repose*(θ)	28°60′±0.82	26°47′±0.74	26°54′±0.91	29°69′±1.04
Compressibility index*(%)	14.28 ±0.85	11.76 ±0.72	11.82±0.84	11.98±0.41
Hausners ratio*	1.16 ± 0.91	1.10 ± 0.57	1.09 ± 0.64	1.19 ± 0.48

*All values are expressed as mean ± standard deviation (n =5)

Table-3
Evaluation of Ambroxol hydrochloride Tablets

Parameter	Ambroxol hydrochloride : Polymers EUDRAGIT RS100 1:0.5	1:0.75	1:1	Control
Hardness* (kg/cm²)	4.95 ± 0.15	4.93 ± 0.20	4.95 ± 0.21	4.9 ± 0.26
Friability* (%)	0.15 ± 0.05	0.20 ± 0.06	0.15 ± 0.05	0.18 ±0.09
Weight variation* (mg)	198.5±4.07	198.5 ± 3.1	198.2±4.08	199 ± 2.5
Content uniformity* (%)	96.38±0.22	97.1 ± 0.14	98.87±0.29	97.9 ± 0.2
Thickness * (mm)	4.1 ± 0.05	4.1 ± 0.02	4.1 ± 0.01	4.3 ± 0.03
Diameter* (mm)	6.2 ± 0.02	6.1 ± 0.04	6.2 ± 0.05	6.1 ± 0.05

*All values are expressed as mean ± standard deviation (n =5)

IR Spectral Analysis

It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FTIR (shimadzu, model-8400s, Japan) as per the method described by Sharma[10]. IR spectral Analysis, Eudragit RS 100 (1:1) were carried the peaks and patterns produced by the pure drug were compared with the combination of polymer and pure drug.

Dissolution Studies

Drug release studies were carried out using an USP XXIV dissolution apparatus type-II[11], with 900ml of the dissolution medium maintained at 37±1°C for 10h, at 50rpm, 0.1N hydrochloric acid (pH 1.2) was used as a dissolution medium for first 2h followed by pH 7.4 ± 0.2 phosphate buffer for further 8h. 5ml of sample was

withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug content in each sample were analyzed after suitable dilution by UV/Vis Spectrophotometer at 248 nm, and cumulative percent drug release was calculated. The commercial Ambroxol conventional tablets were used as the reference formulation.

Kinetic analysis

In order to analyze the drug release mechanism rate kinetics of all the formulations, the results of invitro release profile were fitted into the first order kinetic model, Higuchi model, Zero order kinetic model and korsmeyer model the results of invitro drug release profile of all parameters are plotted in models of data as follows.

1. Log cumulative percent drug remaining versus time (first order kinetic model)[12]
2. Cumulative percent drug release versus square root of time (Higuchis model)[13].
3. Log cumulative percent drug release versus time (zero order kinetic model)[14].
4. Log cumulative percent drug release versus time (Korsmeyers model)[15]

Table-4
Curve fitting analysis for different formulations

Formulations	Regression Coefficient (R^2)			Korsmeyer's Plot	
	Zero order Plot	First order Plot	Higuchi's Plot	R^2	Slope (n)
E1	0.9939	0.9410	0.9675	0.6614	0.465
E2	0.9953	0.9375	0.9527	0.6909	0.458
E3	0.9949	0.9576	0.9481	0.7206	0.554

Stability Studies

The stability study was carried out on the optimized formulation. The stability of all formulated controlled release tablets as per the method of yeok et al [16] the stability studies were performed storing at a temperature at of $45^0 \pm 2^0$C and (75%±5% RH) for 45days. At 15 days intervals the tablets were evaluated for all physical parameters. The invitro drug release and the percentage of drug content were also determined.

Results

Evaluation of granules and tablets

The granules prepared for compression of matrix tablets were evaluated for their flow properties. The bulk density was within the range of 0.41 to 0.43 gm/cm^3. Tapped density ranged from between 0.46 – 0.49 gm/cm^3. Bulkiness was found to be 2.22-2.52 cm^3/gm. Angle of repose was within the range of $26^0$54' to $29^0$96'. Compressibility index was found to be 11.50-14.28 and Hausner ratio ranged from 1.09 – 1.19 for granules of different formulations (Table–2). These values indicate that the prepared granules exhibited good flow properties. The formulated matrix tablets met the pharmacopoeial requirements of hardness, friability, uniformity of weight and the percentage of drug content complying with as per pharmacopoeial specifications[8]. The result of tablet evaluation tests was presented in Table-3.

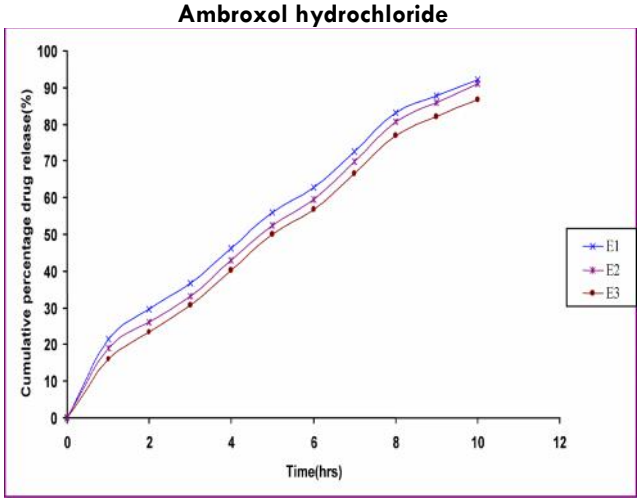
IR spectral Analysis

In the spectral analysis of pure Ambroxol hydrochloride and in combinations of Ambroxol hydrochloride with Eudragit RS 100 (1:1) were carried out to study the interaction between the drug and polymer used. N-H stretching of primary amine, C-H stretching, C-5 stretching, C-H deformation, N-H out of plain bending of pure Ambroxol hydrochloride and the Ambroxol hydrochloride with polymer was almost in the same region of the wave number ranging from 608 cm^{-1} to 3402 cm^{-1}. It showed that there was no significant interaction between the drug and polymers compatible with each other.

Dissolution Studies

The invitro release study of Ambroxol hydrochloride matrix tablets were studied in the phosphate buffer pH 7.4. The invitro release study performance over Ambroxol hydrochloride matrix tablet formulations with polymer, marketed conventional tablet and Ambroxol hydrochloride tablet formulation without polymer. The results of the invitro release studies of all formulations are presented in Figure I and II.

Figure-I
Percentage Drug Release of Matrix Tablet Formulations of Ambroxol hydrochloride



The percentage drug release of all formulations after 10 hours using Eudragit RS 100 was 92.1% (Ambroxol hydrochloride: Eudragit RS 100 1:0.5), 91.1% (1:0.75) and 86.8% (1:1) respectively.

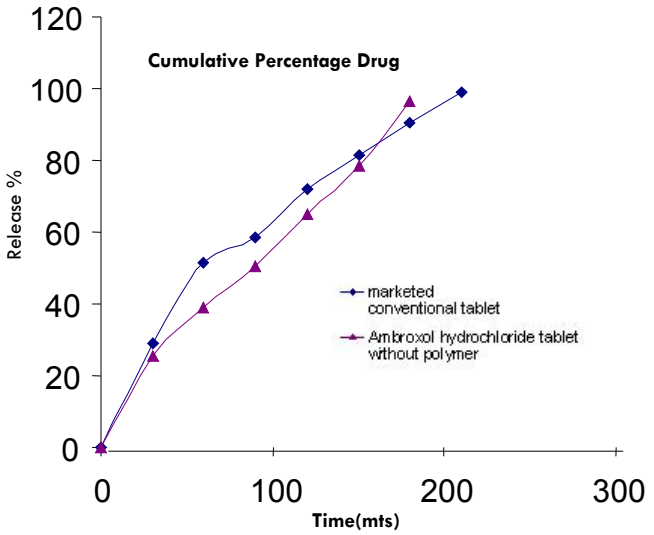
The cumulative percentage of drug release of the formulation E1 (92.1%) was more than E2 (91.1%) and F_3

(86.8%). The result revealed that the formulation E3 showed controlled release than the formulation E1 and E2[17]. When the ratio of polymer was increased, and the percentage release of Ambroxol hydrochloride was decreased from controlled release dosage form[18].

The invitro drug release profile of Ambroxol hydrochloride from the formulation without polymer was found to be 96.7% is 3 hours were as the release of Ambroxol hydrochloride from the conventional marketed tablet was 90.3% in 3 hours (figure-II).

The concentration of polymer plays an important role in drug release. When the polymer concentration is high, the drug release was prolonged than the lower concentration of the polymer[19].

Figure-II
Percentage Drug Release of marketed sample (conventional tablet) & Ambroxol hydrochloride tablet without polymer (Control)



Kinetic Analysis

The release rate kinetic data for all the formulations is shown is Table-4. When the data plotted according to zero order, the formulations showed high linearity regression co-efficient values (R^2) between 0.9939 and 0.9949. Diffusion is released to transport of drug from the matrix dosage form into the Invitro fluid depending on the concentration. This is explained by Higuchi's model the release profile of the drug all formulations could be regression co-efficient values (R^2) between 0.9481 and 0.9675. By using korsmeyers model, if n=0.45 it is fickian diffusion, if n=0.45-0.89 it is non fickian transport. Here all the formulation showed 'n' values between 0.458-0.554. So all the formulations followed non-fickian transport mechanism[15]. The results proved that all the formulations followed mechanism of both diffusion and erosion[20].

Stability Studies

The stability studies were performed for all the formulations stored at $45^0 \pm 2^0$C (Rh 75±2%) tablet evaluation test was also carried out there were no significant changes. Hardness, friability, drug content, and dissolution profile. Hence the formulations are stable[21].

Conclusion

Controlled Release Matrix tablets of Ambroxol hydrochloride were prepared using natural polymer (Eudragit RS100) with three different ratios. The following Evaluations were performed for the powder blends & tablets: IR spectral studies, dissolution studies and stability. The result of powder blends and evaluation of tablets tests showed that all the parameters are within the limits. IR spectroscopic studies indicated that the drug is compatible with the highest proportion of polymer. When comparing all formulations, E3 showed the controlled drug release of 86.8% at the end of 10th hour. Kinetic analysis showed that all the formulations followed zero order release and follows the mechanism of both diffusion and erosion. The stability studies proved that there was no significant change in drug content and invitro drug release. From the above study, it was concluded that Ambroxol hydrochloride can be formulated as matrix tablet using Eudragit RS100 for its CR property.

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