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Research Article

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In vitro release kinetic study of ambroxol hydrochloride sustained release matrix tablets using hydrophilic and hydrophobic polymers

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ABSTRACT

The purpose of the present investigation was to design and evaluate sustained release tablets of a sparingly water soluble drug Ambroxol Hydrochloride, employing hydrophilic and hydrophobic polymers and to select the formulation based on pharmacokinetic of Ambroxol Hydrochloride. Two hydrophilic polymers Methocel K15M CR and Methocel K100M CR and hydrophobic Eudragit RL100 were used in tablets prepared by direct compression. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity and drug content. The tablets were subjected to various tests for physical parameters such as thickness, hardness and friability, and in vitro release studies. The in vitro dissolution study was carried out for 12 hours; in 0.1 N hydrochloric acid (pH 1.2) for first 2hrs followed by phosphate buffer at pH 6.8 ±0.2. The results of dissolution studies indicated that formulations containing Methocel K100M CR showed better dissolution properties compared to formulations containing Methocel K15M CR. The drug release data fit well to the Higuchi expression, but a close relationship was also noted with zero order kinetics. Korsmeyer's plot indicated that the drug release mechanism from the matrix tablet followed Fickian mechanism. It was found that Methocel K 15M CR and Methocel K100M CR matrices except one formulation followed first-order kinetics at all proportions whereas Eudragit RL100 matrices followed zero-order kinetics at higher concentration (at 40%). Hydrophilic and hydrophobic matrix tablets (F-3, F-6 and F-9) showed no change in physical appearance, drug content or dissolution pattern after storage at 40°C temperature and relative humidity 75% for 6 months.

Keywords: Ambroxol hydrochloride, Methocel K15M CR, Methocel K100M CR, Eudragit RL 100, Dissolution, Direct compression.

INTRODUCTION

Ambroxol Hydrochloride is an active N-desmethyl metabolite of the mucolytic bromohexine [1]. 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 [2]. It was postulated that Ambroxol HCl decreased airway hyper-reactivity by either increasing lysophosphatidylcholine turnover and/or modifying epithelial secretion where successful treatment needs a constant and uniform supply of drug. Ambroxol HCl is sparingly water solubility. Hence it presents significant formulation challenges. Ambroxol HCl has a half-life of 4 hours and the usual oral dosage regimen is 75 mg [3]. Therefore, it is an ideal candidate to be designed as a controlled release (CR) dosage form, which would result in prolonged clinical efficacy, reduced frequency of dosage and lesser side effects.

The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison to other controlled release systems. It requires fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate [4]. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The purpose of controlled release systems is to maintain drug concentration in the blood or in the target tissues at desired value as long as possible [5].

HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery [6]. While HPMC could potentially (and therefore control) the release of a soluble drug, it could also facilitate the release of sparingly water soluble drugs i.e. Ambroxol Hydrochloride. The net result is controlled drug delivery for a prolonged period of time [7]. HPMC; a semi synthetic derivative of cellulose, a swellable and hydrophilic polymer is very suitable to use a release retardant material in sustained release matrix tablets, as it is nontoxic and easy to handle. Eudragit RL 100 is used as hydrophobic polymer and regarded as nontoxic and non-irritant material.

The present study was designed to formulate matrix tablets of Ambroxol Hydrochloride using various concentrations of Methocel K15M CR, Methocel K100M CR and Eudragit RL 100. To evaluate various pre- and pro-evaluation parameters, to obtain the required release rate of Ambroxol Hydrochloride matrix tablets, to determine the mechanism and kinetics of drug release, to conduct stability studies on optimized formulations.

EXPERIMENTAL SECTION

Chemicals: Ambroxol Hydrochloride (Dragonfarm Ltd., China), Methocel K15M CR and Methocel K100M CR (Colorcon Asia Pvt. Ltd., India), Microcrystalline Cellulose-PH 101 (Mingtai Chemical Co. Ltd., Taiwan), Colloidal Silicone Dioxide (Deggusa AG, Germany), Magnesium Stearate (Chemical Management Co., Germany), Methanol (Merck, Germany), Disodium Hydrogen Phosphate (Scharlau, Australia), Ortho Phosphoric Acid (Honeywell Riedel-de Haen®, Germany), Hydrochloric acid (Scharlau, Australia) and distilled water. ***Instruments***: Clit-10 Compression Machine, Agilent HPLC 1100 series, Simadzu-1700 UV Spectrophotometer, Digital pH meter (LIDA Instrument, model: OHS-25), Electronic Hardness Tester (PHARMA TEST, Germany), Digital Slide Callipers, Metler Karlfisher Titrator, Electrolab Tablet Dissolution Test Machine, Sartorius Electronic Balance BS-201, 0.45µ Disk Filter.

Preparation of Matrix Tablets

Drug, polymers and other excipients were weighed separately for 200 tablets for each formulation as shown in Table-1. The proposed formulations were coded as F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8 and F-9. The tablets were prepared by direct compression method. Active ingredient (Ambroxol Hydrochloride) and polymers (Methocel K15M CR, Methocel K100M CR and Eudragit RL 100) were passed through #24 sieve and placed in a poly bag. Then these ingredients were blended in a poly bag for 20 minutes. After blending, Aerosil-200 (0.5%) and Magnesium Stearate (0.5%) were passed through #40 sieve and placed in the same poly bag and were blended for another 5 minutes. Blended granules were discharged into the double polythene bags and closed properly. Blended granules were then compressed using Clit Compress machine equipped with 8.0 mm round biconvex punch and die set. After compression, all the preparations were stored in double polythene bags at room temperature for further study.

Evaluation of physical properties of formulation granules

Loose bulk density and tapped bulk density were calculated according to Shah et al [8]. The compressibility index of the granules was determined by Carr's compressibility index [9]. The diameter of the powder cone was measured and angle of repose was calculated according to Cooper and Gunn [10]. Moisture content of granules was determined using Mettler Karl Fischer Titrator. Flow property was predicted from Hausner ratio and angle of repose measurement. Drug content assay of each of nine proposed formulation granules were determined by HPLC analysis.

Table 1: The active ingredient, polymers and excipients used in the proposed formulations coded as F1– F9

Formulation code		Weight (mg)/Tab						
	Ambroxol HCl	Methocel K100MCR	Methocel K15MCR	Eudragit RL 100	Avicel 102	Aerosil 200	Magnesium Stearate	Total
F-1	75	55	-	-	87.88	1.1	1.1	220
F-2	75	44	-	-	98.80	1.1	1.1	220
F-3	75	33	-	-	109.80	1.1	1.1	220
F-4	75	-	55	-	87.88	1.1	1.1	220
F-5	75	-	44	-	98.80	1.1	1.1	220
F-6	75	-	37.4	-	105.60	1.1	1.1	220
F-7	75	-	-	33	109.80	1.1	1.1	220
F-8	75	-	-	44	98.80	1.1	1.1	220
F-9	75	-	-	88	54.80	1.1	1.1	220

Evaluation of physical properties of matrix tablets

Weight variation test, hardness, friability and moisture content of the prepared matrix tablets were determined. Drug content assay of each of nine proposed formulated tablets were determined by UV spectrophotometric analysis.

In vitro dissolution studies were conducted according to USP method [11] using 6 assembly paddle type apparatus II at a speed of 100 rpm and the temperature was maintained at 37.0±0.5°C. The total duration of dissolution was 12 hours in which the tablet matrices were subjected to 0.1 N hydrochloric acid (pH 1.2) for first 2hrs followed by phosphate buffer at pH 6.8 ±0.2 for further 10 hrs.

Preparation of dissolution media

Preparation of 0.1 N HCl: 8.292 gm of 37% HCl (conc) was taken in a 1000 ml volumetric flask and the volume was made up to 1000 ml by adding distilled water.

Preparation of phosphate buffer pH 6.8: 28.8 g of disodium hydrogen orthophosphate and 11.45 g of potassium dihydrogen orthophosphate was taken in a 1000 ml volumetric flask and the volume was made up to 1000 ml by adding distilled water.

In vitro dissolution study of the tablet matrix

The release rate of Ambroxol HCl from matrix tablets was determined using USP Dissolution apparatus II (Paddle Method). The dissolution test was performed using 900 ml of 0.1 N HCl of pH 1.2 for first 2hrs and phosphate buffer pH 6.8 from 2-12 hrs at 37 ± 0.5°C at 100 rpm paddle speed. After 2hrs, 4hrs, 8hrs and 12hrs definite volume (15mL) of aliquots were collected for analysis, which were then compensated with equal volume of fresh dissolution medium. The samples were filtered through a 0.45µ disk filter and dilute suitably. Absorbance of these solutions was measured at 248 nm using a Shimadzu-1700 UV-Visible spectrophotometer.

Drug Release Kinetics

To study the release kinetics, data obtained form *in vitro* drug release studies were plotted in various kinetic models: zero order (equation 1), as the cumulative percentage of drug release vs. time, first order (equation 2), as the log of the amount of drug remaining to be released vs. time and Higuchi model (equation 3), as the cumulative percentage of drug release vs. square root of time. [11, 12]

$$C = K_o t \ldots\ldots\ldots\ldots\ldots \text{(equation 1)}$$

$$Log\ C = Log\ C_o - K_1 t / 2.303 \ldots\ldots\ldots\ldots \text{(equation 2)}$$

$$Q = K_h t^{1/2} \ldots\ldots\ldots\ldots \text{(equation 3)}$$

Mechanism of drug release

To evaluate the mechanism of drug release from sustained release tablets, data of drug release was plotted in Korsmeyer et al [13] equation (equation 4), as the log of cumulative % of drug released vs. log time, and the exponent n value was calculated through the slope of the straight line.

$M_t / M_\infty = Kt^n$ … … … … (equation 4)

For a cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n< 0.89 then it is non-Fickian diffusion. An exponent value of 0.89 is indicative of case II transport or typical zero order release [14].

Stability study

The stability studies were carried out at 30±2°C and 65±5% relative humidity (RH) for long term condition and 40±*2°C* & 75±5% RH for accelerated condition in Alu-PVC blister pack for 6 months. The samples were tested initially and the stability test has been completed up to 6 months at accelerated condition and the stability test has been completed up to 9 months at long condition [15].

RESULTS AND DISCUSSION

The main objective of this study was to enhance therapeutic performance of Ambroxol HCl by developing matrix tablets. Methocel K100M CR, Methocel K15M CR and Eudragit RL 100 were selected as the matrix former in this investigation.

The physical attributes (angle of repose, bulk density, tapped density; compressibility index and total porosity) of the prepared powder blend were found to be satisfactory. Results of have been shown in Table 2.

Table 2: Physical properties of Ambroxol Hydrochloride powder blend

Formula	Angle of repose (◦)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Total porosity (%)
F-1	22.1±0.02	0.504±0.03	0.554±0.02	12.25±0.03	29.67±0.02
F-2	21.2±0.02	0.521±0.04	0.578±0.04	12.82±0.02	27.92±0.03
F-3	25.4±0.02	0.284±0.03	0.335±0.03	12.59±0.02	36.71±0.02
F-4	22.95±0.04	0.302±0.02	0.355±0.03	12.86±0.02	34.52±0.02
F-5	25.4±0.03	0.439±0.04	0.586±0.03	13.28±0.02	27.34±0.02
F-6	24.86±0.02	0.291±0.04	0.336±0.03	13.54±0.02	37.34±0.04
F-7	23.52±0.02	0.302±0.02	0.348±0.04	12.98±0.03	32.96±0.03
F-8	25.20±0.01	0.304±0.03	0.352±0.02	13.08±0.02	31.25±0.02
F-9	25.4±0.03	0.439±0.04	0.586±0.03	13.28±0.02	27.34±0.02

Table 3: Physical properties of Ambroxol Hydrochloride matrix tablets

Formula	Average weight (mg)	Weight variation (%)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Drug content (%)	Friability (%)
F-1	220.46	2.83	3.87	8.06	11.08	99.98	0.22
F-2	222.41	1.03	3.71	8.04	8.95	98.78	0.15
F-3	217.5	2.78	3.76	8.01	9.1	99.65	0.055
F-4	217.5	2.98	3.70	8.01	10.62	98.79	0.09
F-5	219.44	2.66	3.64	8.04	11.97	99.86	0.12
F-6	217.9	1.74	3.66	8.03	10.65	98.65	0.31
F-7	220.03	1.57	3.62	8.04	11.01	99.24	0.34
F-8	219.27	1.53	3.71	8.02	8.25	99.36	0.36
F-9	220.35	1.48	3.84	8.00	10.53	99.45	0.47

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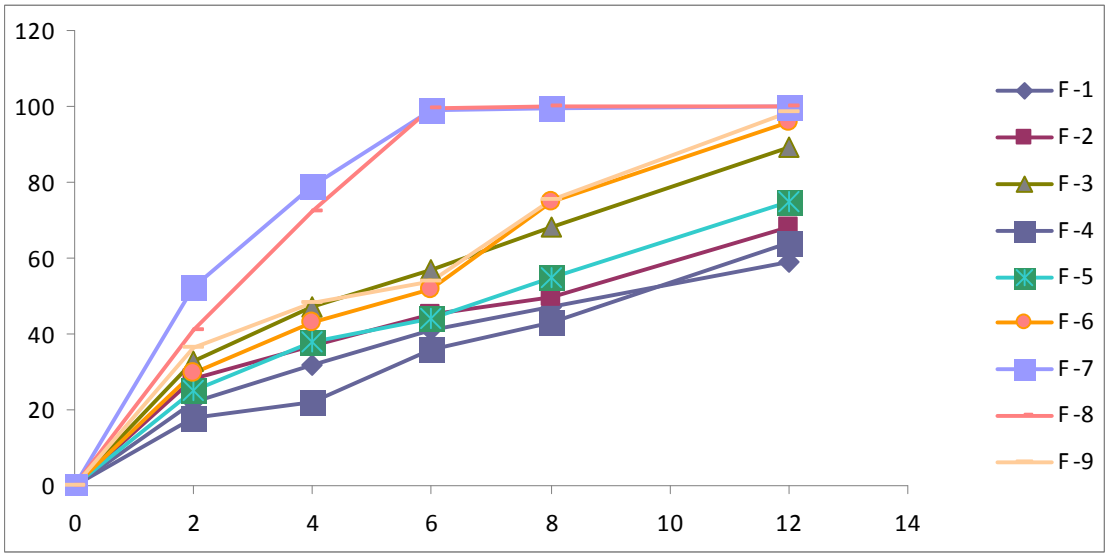

Figure 1: Zero order plot of release kinetics of nine formulations (F-1 to F-9) of Ambroxol Hydrochloride matrix tablets

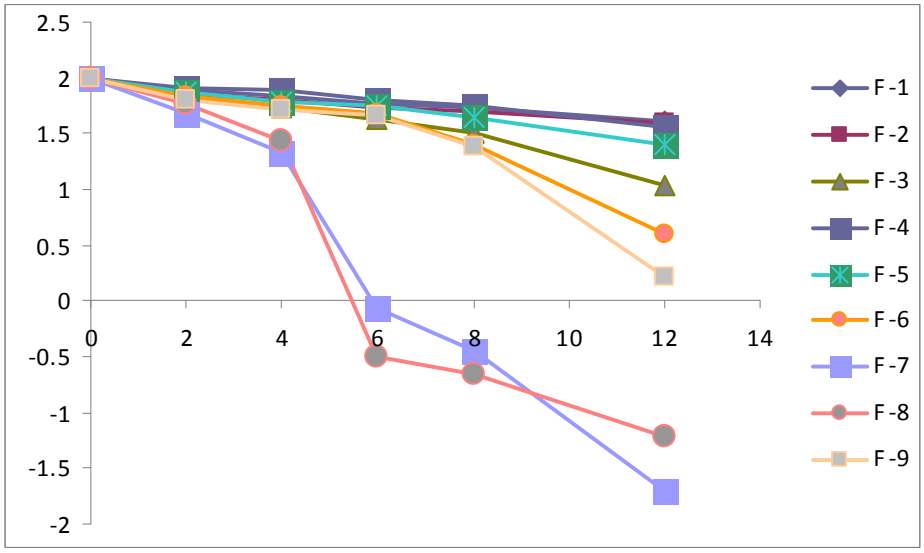

Figure 2: First order plot of release kinetics of nine formulations (F-1 to F-9) of Ambroxol Hydrochloride matrix tablets

The physical attributes (weight variation, thickness, hardness, and friability) of the prepared tablets were found to be satisfactory. Typical tablet defects such as capping, chipping and picking were not observed. All these properties compiled with the official limit as shown in Table 3.

Ideally, an extended release tablets should release the required quantity with pre-determined kinetic pattern in order to maintain an effective drug plasma concentration. To achieve this, the tablet should be formulated so that it releases the drug in a pre-determined and reproducible manner. By considering the biopharmaceutics and pharmacokinetic profile of the drug, one can determine the required amount of drug release from the tablets [16].

Based on dissolution profiles of various tablet formulations, an inverse relationship between the amount of polymers and the release rate of medicament was observed by increasing the concentration of hydrophilic polymers within the formulation F-1 to F-6 from 15% to 25%, a slow rate and significant decrease in the amount of drug release from

different tablet formulation was noted. In case of hydrophobic polymer an inverse result of hydrophilic polymer was observed. In formulation F-1, F-2 and F-3 (which contained 25%, 20% and 15% w/w polymer), 59.27%, 61.14% and 89.07% of drug was released after 12 hrs. In formulations F-4, F-5 and F-6 which contained 25%, 20% and 17% w/w polymer; 64.47%, 75.09% and 96.02% of drug content was released after 12 hrs. However, in formulation F-7 and F-8 containing 15% and 20% of polymer, failed to generate sustained action of drug up to 12 hrs and drug was completely released at 8 Hrs. F-9 contained 40% of polymer gave satisfactory release profile in a sustained manner (Figure 1).

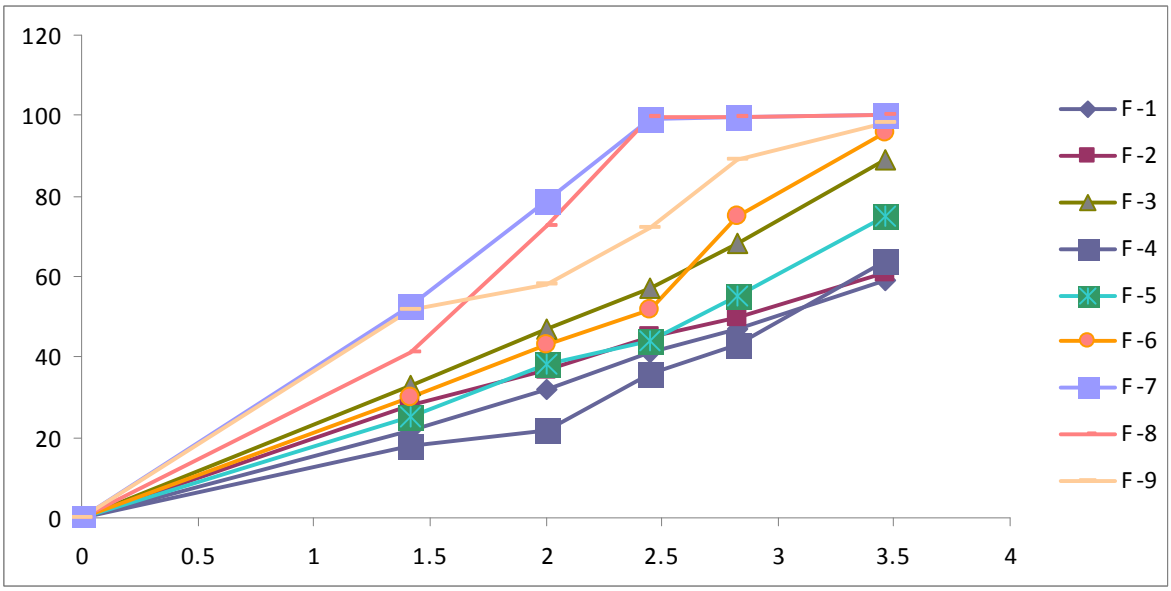

Figure 3: Higuchi plot of release kinetics of nine formulations (F-1 to F-9) of Ambroxol Hydrochloride matrix tablets

Table 4: Dissolution kinetics of Ambroxol Hydrochloride matrix tablets

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas		Best fit model
	K_o	R^2	K_1	R^2	K_h	R^2	n	R^2	
F-1	8.928	0.932	-0.031	0.981	17.04	0.997	0.551	0.999	Peppas
F-2	10.91	0.912	-0.031	0.951	17.47	0.996	0.433	0.998	Peppas
F-3	12.49	0.936	-0.075	0.963	25.13	0.993	0.545	0.994	Peppas
F-4	3.30	0.984	-0.035	0.974	17.66	0.932	0.726	0.946	Zero order
F-5	8.528	0.955	-0.047	0.979	20.93	0.981	0.595	0.987	Peppas
F-6	8.383	0.968	-0.110	0.893	27.23	0.961	0.657	0.972	Peppas
F-7	11.71	0.944	-0.617	0.739	26.84	0.974	0.380	0.830	Higuchi
F-8	14.29	0.926	-0.390	0.784	27.79	0.982	0.510	0.853	Higuchi
F-9	11.56	0.947	-0.136	0.838	27.33	0.970	0.381	0.936	Higuchi

Kinetic analysis of dissolution data

The drug release data obtained were analyzed by zero order (Figure 1), first order (Figure 2), Higuchi (Figure 3) and Korsmeyer-Peppas to know the mechanism of drug release from these formulations (Table 4). In this study, the *in vitro* release profiles of drugs from the formulations F -1 to F -3 showed good fit in the Korsmeyer-Peppas model (R^2 : 0.999 to 0.994) compared to other kinetics model (zero order, first order and Higuchi). Formulation F-4 showed highest linearity with the zero order kinetics. Formulation F-7 to F-9 followed Higuchi model. This indicates that the release rate of drug from the swelling matrix tablets is proportional to the square root of time (Figure 3).

The data were plotted into Korsmeyer-Peppas equation to know the confirmed diffusion mechanism. The formulations F-1 to F-3 showed good linearity (R^2: 0.9994 to 0.9949) with slope (n) values ranging from 0.433 to 0.551. Kinetic study of formulation F-2 showed aberrant type of release exponent (n<0.45) indicating a Fickian type of release. The release exponent (n) of other two formulations (F-1 and F-3) containing Methocel K100M CR 0.551 and 0.545 respectively indicate a so called anomalous transport (non-Fickian). That is, F-1 and F-3 showed both diffusion and dissolution controlled drug release. On the other hand, formulations containing Methocel K15M CR (F-4 to F-6) showed release exponent ranging from 0.595 to 0.726 indicating anomalous transport (non-Fickian) as that of F-1 and F-3. On the other hand, formulations containing Eudragit RL100 F-9 showed release exponent 0.381. Formulation F-9 (n< 0.45) indicates Fickian type of release.

CONCLUSION

The use of polymeric matrix devices to control the release of variety of therapeutic agents has become increasingly important in development of the modified release dosage forms [17]. The current study indicates that the hydrophilic matrix tablet Ambroxol Hydrochloride prepared using Methocel K15M CR and Methocel K100M CR can successfully be employed as twice-a-day oral controlled release dosage form. The study reveals that the mechanism of release changed with the nature and contents of polymers in the matrix. The type of polymers used was found to induce a conspicuous effect on release rate and mechanism. Based on the *in vitro* drug release the formulation F-6 was concluded as best formulation, although Eudragit RL 100 also showed desired release pattern at higher concentration of polymer. In conclusion, the present study demonstrates the successful preparation of sustained release matrix tablet of Ambroxol Hydrochloride.

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