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FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF AMBROXOL HYDROCHLORIDE

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ABSTRACT

Ambroxol hydrochloride has relatively short plasma half life. The need for the administration of the drug for two to three times a day can decrease patient compliance. Sustained release formulations that would maintain plasma level for 8-12 h might be sufficient for daily dosing of Ambroxol Hydrochloride. The overall objective of the present work was to develop an oral sustained release Ambroxol Hydrochloride tablet prepared by direct compression method using hydrophilic Eudragit RSPO and RLPO alone or in combination with hydrophobic ethylcellulose polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, friability and drug content and *in vitro* drug release for 12 h. The *in vitro* drug release study revealed that when Eudragit RSPO, RLPO and Ethylcellulose were used alone as the only retarding polymer, a sustained drug release pattern was not observed while, Combining Eudragit with ethylcellulose, the drug release pattern was observed in a sustained manner for 12 h. F7 formulation sustained the drug release for longer period of time as compared to other formulations. So F7 was selected as the best formulation. Kinetic modeling of *in vitro* dissolution profiles revealed that the drug release mechanism ranges from diffusion controlled to anomalous type. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Keywords: Ambroxol Hydrochloride, Eudragit RSPO, Eudragit RLPO, Ethylcellulose, Sustained release, Release kinetics.

1.INTRODUCTION

Oral administration of drugs has been known for decades as the most common and preferred route for delivery of most therapeutic agents via various pharmaceutical products of different dosage forms. The popularity of oral route is attributed to patient acceptance, ease of

administration, accurate dosing, cost effective manufacturing methods, as well as traditional belief that by oral administration the drug is as well absorbed and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other tablets [1, 2].

Sustained release drug delivery aimed at controlling the rate of release as well as maintains desire drug level in the blood that is therapeutically effective and non toxic for extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. It provides prolonged but not necessarily uniform release of the drug. The rationale for development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition [3, 4, 7, 8].

Ambroxol is a metabolite of bromhexine with similar actions and uses. It is chemically described as Trans-4- [(2-amino-3, 5-dibromobenzyl) amino] -cyclohexanol. Ambroxol hydrochloride is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as, bronchial asthma, chronic bronchitis characterized by the production of excess or thick mucus. Ambroxol Hydrochloride has also been reported to have a cough suppressing effect and anti inflammatory action[9, 10, 11, 12.] It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders. It has short biological half life (4 hrs), that calls for frequent daily dosing (3 to 4 times) and therapeutic use in chronic respiratory diseases necessitates its formulation into sustained release dosage forms[12, 13,14,15].

2.MATERIALS AND METHODS

Ambroxol Hydrochloride was received as a gift sample from Tablet India, Chennai, Eudragit RLPO and RSPO from Evonik industries, Mumbai. Ethylcellulose, Lactose, PVPK-30 was purchased from Yarrow chemicals, Bangalore. Magnesium Stearate and Talc from Karnataka fine chem., Bangalore.

Table 1: Formulation chart of sustained release matrix tablets of Ambroxol Hydrochloride

Sl. no	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7
1	Ambroxol HCl	75	75	75	75	75	75	75
2	Eudragit RLPO	125	-	-	20.87	20.87	83.87	41.87
3	Ethylcellulose	-	-	125	20.87	83.87	20.87	41.87
4	Eudragit RSPO	-	125	-	83.87	20.87	20.87	41.87
5	Lactose	35.5	35.5	35.5	35.5	35.5	35.5	35.5
6	PVPK-30	12.5	12.5	12.5	12.5	12.5	12.5	12.5
7	Magnesium Stearate	1	1	1	1	1	1	1
8	Talc	1	1	1	1	1	1	1

Total weight of each tablet=250mg

2.1.METHOD OF PREPARATION OF SUSTAINED RELEASE TABLETS:

Matrix tablets of Ambroxol Hydrochloride were prepared by direct compression method using Eudragit RLPO, Eudragit RSPO and Ethylcellulose as polymeric matrix materials. Lactose as a diluent for increasing compressibility and PVP-K30 used as binder. In dry state, drug was mixed with other ingredients for the period of 10 min in mortar to get uniform mixture. Powder was lubricated with magnesium stearate and talc. Lubricated powder was compressed to tablets in 9 mm die cavity of tablet punching machine (Mini press-I, Rimek, Karnavati), with a target compression weight of 250 mg containing 75 mg of drug.

2.2.EVALUATION OF PREFORMULATION PARAMETERS:

i) **Micromeritic properties**[40]**:**

a) Angle of repose:

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = \frac{h}{r}$$

Therefore, $\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose, h = height of the pile, r = radius of the pile base.

b) Bulk density[5, 40]**:**

Both loose bulk density (LBD) or bulk density and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using formula:

$$\text{Bulk density} = \frac{Weight\ of\ the\ Powder}{\text{Bulk } volume \text{ of Powder}}$$

$$\text{Tapped density} = \frac{Weight\ of\ the\ Powder}{Tapped\ volume\ of\ the\ Powder}$$

c) Carr's index:-

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by:

Carr's index (%) = [(TBD - LBD) x 100]/TBD Where,

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the Packing

ii) Physicochemical parameters:

a) Tablet hardness [5, 15]:

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.

b) Tablet thickness[5, 15]:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauze on 3 randomly selected samples.

c) Friability[5, 15]:

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined.

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

d) Weight variation[5, 15]:

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the (Table 7) and none deviates by more than twice that percentage.

e) Uniformity of drug content[5, 15]**:**

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder weight equivalent to 100 mg drug was dissolved in methanol and the volume was made upto 100 ml with methanol. From the stock solution, 1 ml solution was taken in 10 ml volumetric flask and the volume was made with methanol. Further 0.5 ml was pipetted and volume was made up to 10 ml with methanol. The solution was filtered through Whatmann filter paper and absorbance was measured spectrophotometrically at 248 nm against methanol as a blank. Amount of drug present in one tablet was calculated.

f) Dissolution studies[5, 15]**:**

The release rate of Ambroxol Hydrochloride from sustained release tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm. The dissolution test was performed using 750 ml of 0.1 N HCl (pH 1.2) for 2 h at 37±0.5 °C and then 250 ml of 0.2M tri sodium phosphate was added and pH is adjusted to 6.8 as described in the USP 26/NF monograph and dissolution is carried out for further 10 h. 1ml of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

2.3.KINETICS MODELLING OF DRUG DISSOLUTION PROFILE[39, 40]**:**

The dissolution profile of most satisfactory formulation was fitted to zero order, first order and Higuchi model to ascertain the kinetic modeling of the drug release. The methods were adopted for deciding the most appropriate model.

1. Cumulative percent drug released versus time (Zero order kinetic model)
2. Log cumulative percent drug remaining versus time (First order kinetic model)
3. Cumulative percent drug released versus square root of time (Higuchi's model).

- **Zero order:**

In many of the modified release dosage forms, particularly sustained or controlled release dosage

forms (those dosage forms that release the drug in planned, predictable and slower than the normal manner) is zero order kinetic. The plot of cumulative percent drug released versus time is the linear.

- **First order:**

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparation, particularly prolonged release formulations, adheres to this type of dissolution pattern. It assumes that the drug molecules, diffuses out through a gel like layer formed around the drug during the dissolution process. A plot of log cumulative percent drug remaining versus time is the linear.

- **Higuchi model:**

A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled). In Higuchi model, a plot of cumulative percent drug released versus square root of time is linear.

2.4.STABILITY STUDIES FOR THE MOST SATISFACTORY FORMULATION OF SUSTAINED RELEASE MATRIX TABLETS OF LORNOXICAM[47]**:**

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C / 65 ± 5 % RH and 40 ± 2 °C / 75 ± 5 % RH for two months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, sustained behavior and other physicochemical parameters.

3.RESULTS

FTIR OF PURE AMBROXOL HCl DRUG AND DRUG+POLYMER MIXTURE

Table 2:Characteristic peak of Ambroxol Hydrochloride and polymer mixtures in FTIR spectra

Frequency (cm^{-1}) Pure drug	Frequency (cm^{-1}) Pure drug + mixture	Description
3397	3397	NH_2 stretch
3282	3285	N-H stretch
2947	2947	CH_2 stretch
3196	3197	O-H stretch
3057	3057	HC=CH stretch
1457	1458	C-N stretch

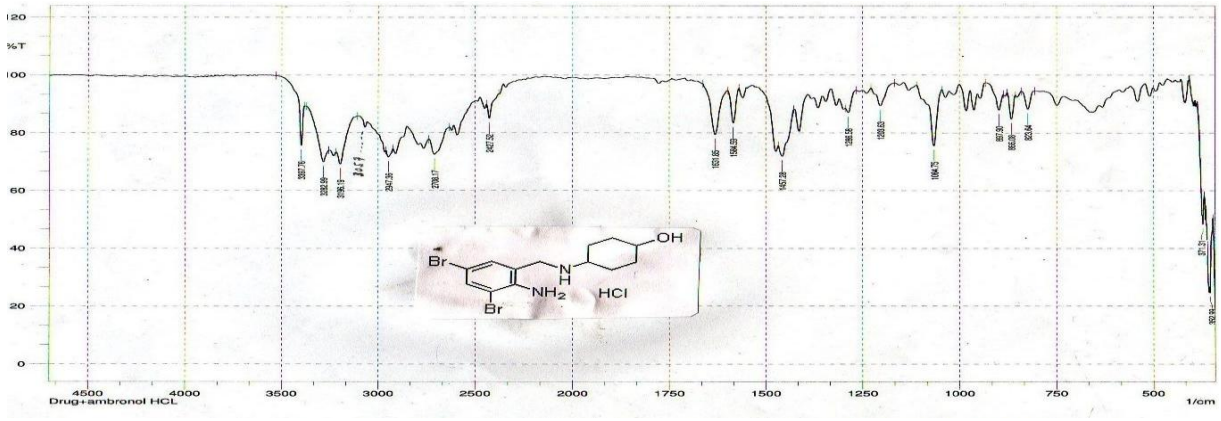

Fig1: FTIR (ATR) spectrum of Ambroxol Hydrochloride

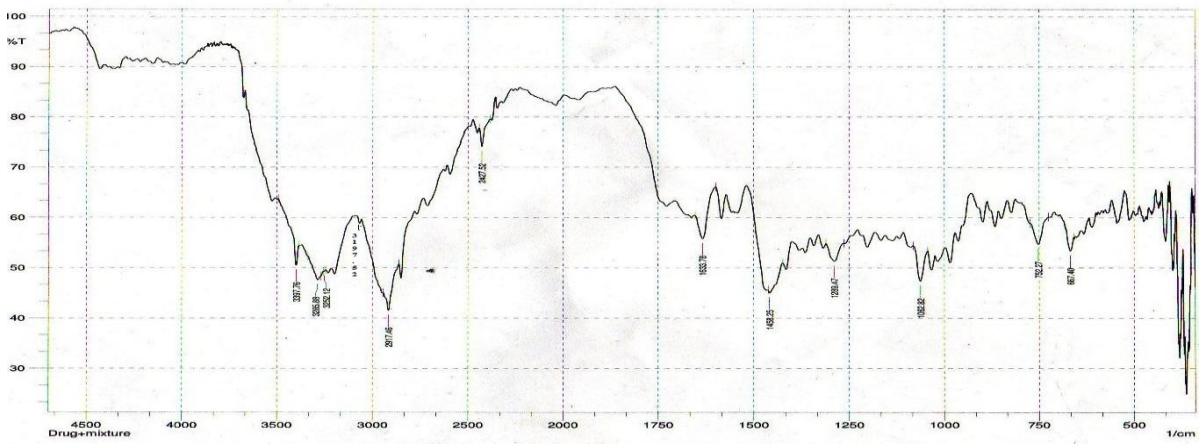

Fig 2: FTIR (ATR) spectra of physical mixture of Ambroxol Hydrochloride with Polymers

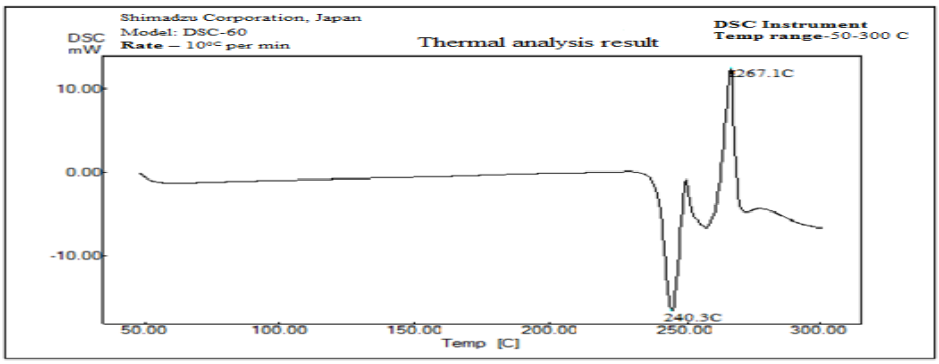

Fig 3: Differential Scanning Calorimeter of Ambroxol Hydrochloride (Drug)

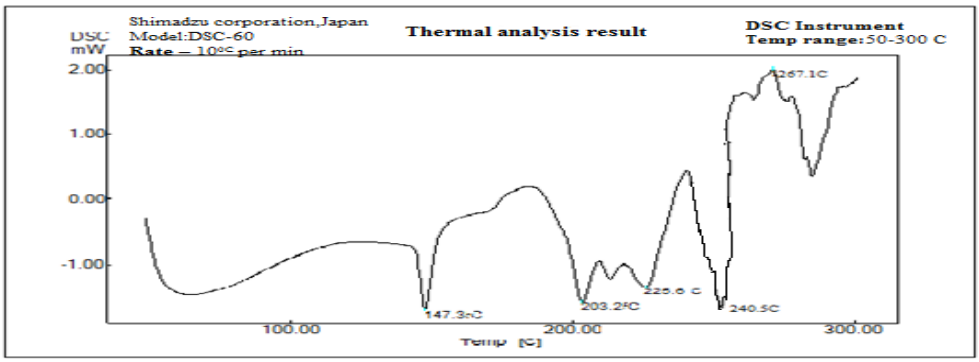

Fig 4: Differential Scanning Calorimetry of formulation F7

EVALUATION OF PREFORMULATION PARAMETERS:

Table 3: Micromeritic properties of sustained release matrix tablets of Ambroxol HCl

Formulation code	Angle of repose (º)*±SD	Carr's index (%)*±SD	Hausner Ratio*±SD
F1	36.30±0.5	14.52± 0.56	1.21±0.03
F2	33.77± 0.31	16.31 ± 0.68	1.19±0.01
F3	36.66± 0.10	16.76 ± 0.27	1.17±0.02
F4	32.76± 0.30	12.50± 1.07	1.13±0.02
F5	33.05± 0.29	13.15 ± 0.09	1.13±0.02
F6	32.82 ± 0.81	12.47 ± 1.18	1.12±0.03
F7	31.54±0.27	11.5±1.08	1.12±0.02

*All values are mean of 3 readings ± SD

Table 4: Physicochemical parameters of SRDDS of Ambroxol Hydrochloride tablets

Formulation Code	Hardness * (kg/cm^2) ±SD	Thickness *(mm) ±SD	Friability (%)	Weight variation *(% deviation)±SD	Drug content (%)
F1	5.7 ± 0.55	4.76 ± 0.048	0.680	250.6 ± 0.95	99.09
F2	5.6 ±0.45	4.84 ± 0.051	0.661	250.6 ± 0.81	98.78
F3	5.5 ± 0.37	4.88 ± 0.052	0.648	251.8± 0.47	97.87
F4	6.0 ± 0.42	4.92 ± 0.042	0.647	251.5 ± 0.99	98.18
F5	6.1 ± 0.38	4.98 ± 0.042	0.584	249.8±0.52	98.48
F6	7.0 ± 0.29	4.96 ± 0.042	0.623	249.8 ± 0.88	99.08
F7	6.7 ± 0.33	4.98 ± 0.011	0.587	251.4 ± 0.63	99.39

*All values are mean of 3 readings ± SD

Table 5: *In vitro* drug release study: Percentage (%) drug released

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
1	34.58 ± 0.48	32.21 ± 0.72	11.64 ± 0.24	29.12± 0.24	13.83±0.48	30.85±0.49	22.90±0.37
2	44.99± 0.47	43.53 ± 0.96	18.03± 0.12	35.34±1.21	18.21±1.21	37.16±0.53	32.42 ± 0.48
3	56.33± 1.72	54.87 ± 0.48	24.42 ±1.24	51.03±0.25	27.70±0.24	53.22±1.23	41.19 ± 0.33
4	69.50± 0.19	67.49 ± 1.24	31.54± 0.48	61.10±0.32	33.19±0.74	62.93±0.81	46.15± 0.24
5	75.94±0.12	76.12 ± 0.53	39.95± 0.39	68.27±0.24	41.78±0.25	69.36±0.26	53.67 ± 0.21
6	86.22± 0.12	84.03± 0.24	43.21± 0.52	73.26±0.48	45.29±0.97	73.81±0.24	63.19 ± 0.48
7	93.60± 0.25	90.13 ± 0.23	46.78± 1.28	77.71±0.86	50.80±0.48	78.81±0.75	71.09 ±0.97

8	98.07± 0.48	97.69 ± 0.75	53.20± 0.72	87.62±0.26	57.77±0.32	88.62±0.98	76.81± 0.72
9	-	-	57.81± 0.28	90.45±1.22	62.57±1.13	92.56±0.48	83.08 ± 0.47
10	-	-	68.98 ± 0.20	97.72±0.96	71.74±0.24	98.56±0.66	88.45 ± 0.22
11	-	-	73.24 ± 0.48	-	79.28±1.29	-	93.10 ± 0.48
12	-	-	80.42± 0.49	-	87.56±0.41	-	97.75± 0.24

*All values are mean of 3 readings ± SD

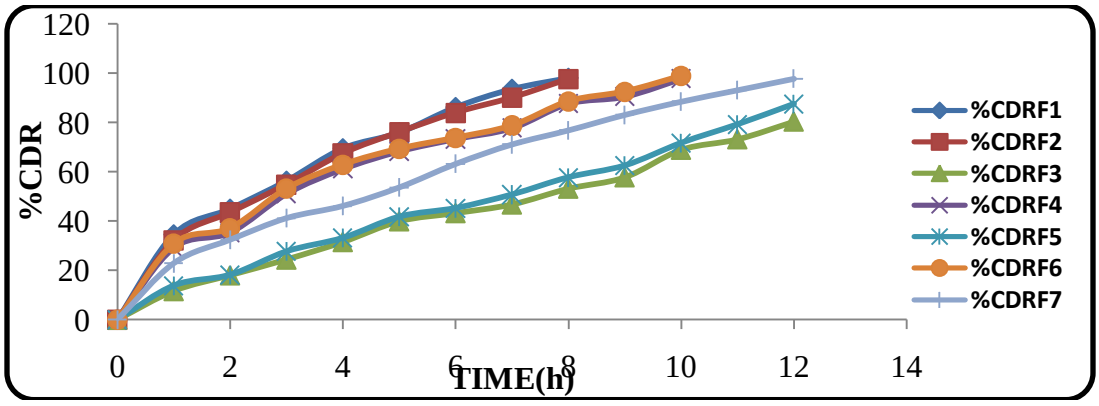

Fig 5: Comparative drug release profile of SRDDS F1 – F7

KINETIC MODELING OF DRUG DISSOLUTION PROFILES:

Table 6: Kinetic modeling of drug dissolution profiles

Formulation code	**Zero order**		**First order**		**Higuchi Model**		**Peppas Model**	
	r^2	*k*	r^2	*k*	r^2	*k*	r^2	*N*
F7	0.995	6.868	0.908	0.123	0.986	31.73	0.990	0.607

STABILITY STUDIES:

Table 7: Physicochemical characterization of most satisfactory formulation F7 during stability studies

Time (Days)		Hardness (kg/cm^2)*± SD	Drug content (%)*± SD
		F7	
0		6.7±0.33	99.39
30	**A**	6.5±0.21	99.08
	B	6.4±0.33	98.18
60	**C**	6.3±0.11	98.78
	D	6.2±0.32	98.16

*All values are mean of 3 readings ±SD

A, C = 30 ± 2°C / 65 ± 5% RH
B, D = 40 ± 2°C / 75 ± 5% RH

Table 8: Drug release profile for most satisfactory formulation F7 during stability studies

TIME (h)	AFTER 30 DAYS		AFTER 60 DAYS	
	A	**B**	**C**	**D**
	F7 (%)* ±SD	F7 (%)* ±SD	F7 (%)* ±SD	F7(%)* ±SD
1	21.29±0.55	20.93±0.32	21.12±0.11	20.64±0.87
2	31.51±0.31	30.23±0.34	31.24 ±0.23	30.24±0.28
3	40.28±0.32	39.55±0.32	40.08 ±0.58	39.16±0.28
4	46.15±0.63	46.15±0.63	45.64 ±0.28	45.97±1.16
5	52.57±0.46	52.20±0.36	52.10 ±0.58	51.68±0.88
6	61.73±0.63	61.91±0.95	61.26 ±0.58	60.87±2.05
7	69.81±0.63	69.44±0.64	68.95 ±0.29	68.98±1.77
8	75.71±0.55	75.71±0.24	75.42 ±0.59	75.12±1.20
9	82.16±0.32	80.70±0.46	81.78 ±0.59	80.17±1.79
10	87.72±0.33	87.16±0.31	87.13 ± 0.59	86.96±1.51
11	92.003±0.31	91.45±0.32	91.90 ±0.27	90.75±0.64
12	97.56±0.34	97.19±0.61	97.09±0.60	96.50±0.52

*****All values are mean of 3 readings ± SD

A, C = 30 ± 2°C / 65 ± 5% RH
B, D = 40 ± 2°C / 75 ± 5% RH

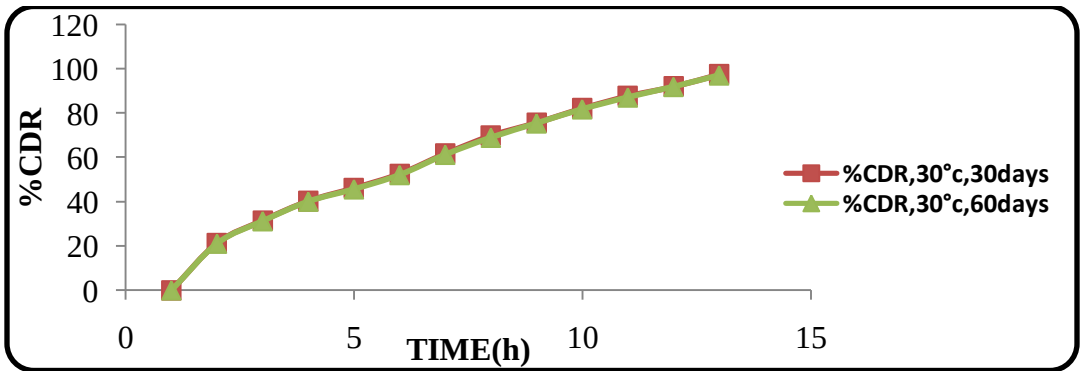

Fig 6: Comparison of *in vitro* dissolution profile of formulation F7 for 30, 60 days of 30°C ± 2°C / 65 ± 5 % RH

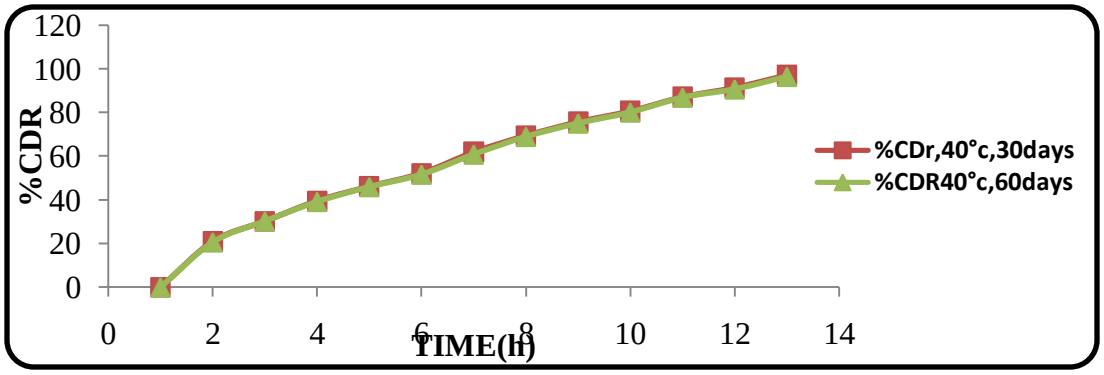

Fig 7: Comparison of *in vitro* dissolution profile of formulation F7 for 30, 60 days of 40^{0}C ± 2^{o}C / 75 ± 5 % RH

4.DISCUSSION

In the present study, Ambroxol Hydrochloride Sustained release tablets were prepared by using Eudragit RLPO, RSPO as hydrophilic polymers and Ethylcellulose as hydrophobic polymer. A total of 7 formulations were prepared by direct compression technique. The preformulation studies such as bulk density, tapped density, angle of repose, compressibility index and Hausner ratio were evaluated which were found to be within prescribed limits and indicated good to fair flow properties. The data obtained from physicochemical parameters such as hardness, friability, weight variation, drug content and *in vitro* drug dissolution are shown in Table (15, 16, 17, 18 and 19).

PREFORMULATION STUDIES:

Estimation of Ambroxol Hydrochloride was carried out by using SHIMADZU-1700 UV spectrophotometer at λ_{max} 248 nm in 0.1N HCl and in Phosphate buffer (pH6.8) at 248nm. The linear coefficients were found closer to 1. By using the regression coefficient equation, the drug content and % CDR were calculated.

UV spectrum analysis of Ambroxol Hydrochloride:

Ambroxol Hydrochloride showed maximum absorption at a wavelength of 248 nm in 0.1 N HCl and Phosphate buffer (pH 6.8). Standard calibration curve when subjected to regression analysis, the value of regression coefficient was found to be 0.999 and 0.998 respectively, which showed linear relationship between concentration and absorbance.

Melting Point:

Melting point of Ambroxol Hydrochloride was determined by capillary tube method and it was found to be 235-240°C. The value is same as that of IP.

Drug- polymers Compatibility Studies:

FTIR and DSC studies showed that there was no interaction between drug and polymer. So, the drug and polymers were found to be compatible.

FORMULATION STUDIES:

Various formulations of Sustained release Ambroxol Hydrochloride tablets were prepared by using Eudragit RLPO, RSPO and Ethylcellulose as polymers. Lactose was used as diluent, PVPK-30 as binder, Talc and Magnesium Stearate as lubricants by direct compression method using 9 mm flat punches to an average weight of 250 mg.

MICROMERITIC PROPERTIES:

Angle of repose:

The results of angle of repose ranged between 31.54° ±0.27 to 36.66º ±0.10 (Table 3) which indicates good to fair flow properties of Powder.

Compressibility index and Hausner ratio:

The compressibility index values were found to be in the range of 11.5 ±1.08% to 16.7 ±0.27% and the Hausner ratio was found to be in the range of 1.12 ±0.02 to 1.21 ±0.03 (Table 3). These findings indicated that the mixture of all batches of formulation exhibited good to fair flow characters and hence, were suitable for compression into sustained release tablets.

EVALUATION OF PHYSICOCHEMICAL PARAMETERS:

Tablet hardness:

Hardness of the developed formulations varied from 5.5 ±0.37 to 7.2 ±0.29 kg/cm^2 (Table 4) in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling.

Tablet thickness:

Thickness of the developed formulations varied from 4.76 ±0.048 mm to 3.58 ±0.01mm (Table 4) each sample was analyzed in triplicate.

Friability**:**

The loss in total weight of the tablets due to friability was in the range of 0.58 to 0.68% (Table 4) in all the formulation and the friability value was less than 1% which ensured that formulated tablets were mechanically stable.

Weight variation:

The maximum % deviation of all the formulations is shown in Table 4. As none of the formulation showed a deviation of more than ± 7.5% (IP limit) for any of the tablets tested, the prepared formulations comply with the weight variation test, thus it fulfills the IP requirements.

Uniformity of drug content:

The drug content in different tablet formulations was uniform and in the range of 97.8 to 99.3 (Table 4). The drug content was found within the limits specified by IP.

In vitro drug dissolution studies:

The *in vitro* release study of Ambroxol Hydrochloride from sustained release tablets of all formulations were carried out in 0.1 N HCl for first 2 h and in phosphate buffer (pH 6.8). From these studies, it was found that the formulation F1 containing Eudragit RLPO (50%) and F2 containing Eudragit RSPO (50%) exhibited the following release pattern. F1 showed initial burst drug release of 34.58±0.48% within 1 h and total amount of drug (98.07±0.48) released within 8 h. Similarly F2 showed initial burst drug release of 32.21±0.72% within 1h and total amount of drug 97.57%±0.24, released within 8 h. This is due to the use of hydrophilic polymers, Eudragit RLPO and RSPO, which causes rapid diffusion of the dissolved drug through the hydrophilic gel network. Formulation F3 containing EC (50%), exhibited a very low drug release pattern, 80.42% at the end of 12 h. This is due to the use of hydrophobic polymer, ethylcellulose, which showed more retardation in the release of the drug. These data clearly establishes, that the formulation containing respectively Eudragit RLPO, RSPO and ethylcellulose used alone, have not exhibited any sustained drug release pattern. In view of these results, a combination of

hydrophilic polymers, Eudragit RLPO and RSPO and hydrophobic polymer, ethylcellulose has been tried out.

The formulation F4 was prepared with a combination of (8.34% RLPO+33.54% RSPO+8.34% EC), showed drug release of 97.72%±0.92 within 10 h. The formulation F5 containing (8.34% RLPO+33.54% RSPO+8.34% EC), showed very low drug release pattern of 87.56%±0.41 at the end of 12 h and the formulation F6 containing (8.34% RLPO+33.54% RSPO+8.34% EC), showed drug release of 98.94%±0.66 within 10 h. This is due to the use of higher concentration of both hydrophilic and hydrophobic polymers. As can be seen even this combination has not yielded the desired extent of sustained drug release pattern. This prompted me to work out further options of the formulation changing the proportion of polymers. Thus formulation F7 formulated using both hydrophilic polymers and hydrophobic polymer in equal proportion. The formulation F7 contains (16.74% RLPO+16.74% RSPO+16.74% EC). This showed a good sustained drug release pattern of 97.75%±0.24 at the end of 12 h.

KINETIC MODELLING OF DRUG DISSOLUTION PROFILES:

The *in vitro* release data obtained were fitted into various kinetic models. Correlation coefficients of formulation F7 batch showed higher correlation with zero order plots than First order, Higuchi model and Peppas model. The 'n' value from the Peppas model was found to be 0.607 which corresponds to Non-Fickian release. So, predominant drug release mechanism was found to be of controlled and Non-Fickian type due to diffusion followed by erosion mechanism of drug release.

STABILITY STUDIES:

Stability studies were carried out for the most satisfactory formulation F7 at 30 ± 2°C / 65 ± 5% RH and 40 ± 2°C / 75 ± 5% RH for 60 days to assess their long term stability.

A various time intervals of 30 days and 60 days, samples were evaluated. There was no significant difference in the physicochemical parameters evaluated like hardness, drug content and *in vitro* dissolution pattern at the various sampling points. There was no difference between the initial values and the results obtained during stability studies.

5.CONCLUSION

The objective of the present study was to formulate Sustained release dosage form of Ambroxol Hydrochloride. The results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers in equal proportion could be successfully employed for formulating sustained release tablets of Ambroxol hydrochloride. Diffusion coupled with erosion might be the mechanism for the drug release from hydrophilic and hydrophobic polymer based matrix tablets which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional Ambroxol Hydrochloride tablets.

6. REFERENCES

[1]. Vyas SP, Khar RK. Controlled drug delivery: concepts and advances. 1st ed. Delhi: Vallabh Prakashan; 2002.

[2]. Verma RK, Garg S. Current status of drug delivery technologies and future directions. Pharma Techno 2001; 25(2):1-13

[3]. Darshana HD, Mangal NS, Sudhakar GD. Design and evaluation of an extended release tablets of prochlorperazine maleate. Ind Drugs 2000; 38: 64-9.

[4]. James MA, Sung W. Advances in drug delivery systems. Controlled release series-1. New York: Elsevier-Amsterdom Oxford; 1980.

[5]. Lachman L, Liberman A, Kanig J. The theory and practice of industrial pharmacy.3rd ed. Mumbai: Varghese publishing house; 1990.p.430-31,297-99,300-01,302-3.
[6]. Banker GS, Rhodes CT. Modern Pharmaceutics. 4th ed. New York: Marcel Dekker Inc; 2002. vol 12-1. p. 501-04, 505-13.
[7]. Gendle R, Kaushik B, Verma L. Parameters required for sustained release drug delivery system. Pharmainfo.net; 2009.
[8].Robinson JR, Lee HL. Controlled drug delivery fundamentals and applications. 2nd ed. New York: Marcel Dekker Inc; 1987. p. 395-403.
[9]. Tripathi KD. Essentials of medical pharmacology. JP. Brothers, medical publisher. 6th ed. New Delhi: p.214-5.
[10].Jayachandran DL, Jeganath S, Krishnamoorthy RM. formulation and evaluation of ambroxol hydrochloride tablets using eudragit rs-100. Int. J. Pharm and Ind Res 2011; 1(2):71-5.
[11].Sweetman CS. Martindale: the complete drug reference. 35th ed. London: The pharmaceutical press; 2007. vol I. p.1395-6.
[12].Ambroxol HCl drug profile [online] 2006. [Cited 6/8/2010]; Available from URL: http://www.pharmainfo.net/reviews/ Ambroxol HCl-potent-Mucolytic-drug.
[13].Indian Pharmacopoeia. 6th ed. Ghaziabad: The Indian pharmacopoeia commission; 2010. vol II. p. 792-93, 185-95, 392, 559.
[14]. Eudragit polymer profile [online] 2008. [Cited 4/9/2010]; Available from URL: http://eudragit.evonik.com/product/eudragit/en/downloads.
[15].Raymond RC, Paul SJ, Sian OC. Handbook of pharmaceutical excipients. 5th ed. USA: Pharmaceutical press; 2006.p.553-60.
\[16].Rowe RC, Sheshkey PJ, Quinn ME. Hand book of pharmaceutical excipients. 6thed.London: Pharmaceutical press and American pharmaceutical association; 2009. p. 143, 364,404,581,728.
[17].Kamlesh JW, Rajendra BK, Milind JU. Development of a sustained release tablet of metformin hydrochloride containing hydrophilic eudragit and ethyl cellulose polymer. Int J comp pharm 2011; 2 (5):1-6.
[18].Rajesh GJ, Rama RT, Vanaja A. Formulation and *in vitro* evaluation of sustained release matrix tablets of losartan potassium. Int J Pharm Sci 2011; 2 (1):31-6.
[19]. Pandya HV, Patel AR, Bodiwala JB. Formulation, development and evaluation of doxophylline sustained release matrix tablet. Int res J pharm 2011; 2(12): 204-7.
[20].Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and *In Vitro, In Vivo* Evaluation of Extended release Matrix Tablet of Zidovudine: Influence of Combination of Hydrophilic and Hydrophobic Matrix Formers. AAPS Pharm Sci Tech 2006; 7(1):1-6.
[21].Apurba SA, Atiqul HP, Golam K, Reza UJ. *In vitro* Release Kinetic Study of Theophylline from Eudragit RSPO and Eudragit RLPO Matrix Tablets. Dhaka Univ J Pharm Sci 2009; 8(1):1-6.
[22].Hosseinali T, Seyed AM, Tina BG. Preparation of sustained release matrix tablets of aspirin with EC, Eudragit RS100 and studying the release profiles and their sensitivity to tablets hardness. Iranian J Pharm Res 2003:201-6.
[23].Indiran PS, Irina RA, James ASA, Steven H, Neau B. Formulation and *in vitro* testing of sustained release theophylline tablets by direct compression. Int J Pharm 1998; 164:1-10.
[24].Akhil S, Shweta S, Kamal KJ. The study of salbutamol matrix tablets using different polymers as release retarding agent. Pharm Res 2009; 1:15-22.

[25].Sourabh J, Yadav SK, Patil UK. Preparation and evaluation of sustained release matrix tablets of furosemide using natural polymers. Res J Pharm Tech 2008; 1(4):374-6.
[26].Margret C, sandip, Muruganantham V, Debjit, kumudhavalli, Jayakar B. formulation and evaluation of sustained release matrix tablets of zidovudine. Int J Cur Pharm Res 2009; 1(1):14-31
[27].Ganesh GNK, Sureshkumar R, Jawahar N, Senthil V, Nagasamy VD, Shanmukha SM. Preparation and evaluation of sustained release tablet formulation of diclofenac sodium using natural polymer. J Pharm Sci Res 2010; 2(6):360-8.
[28].Kamlesh JW, Rajendra BK, Milind JU. Formulation of sustained release metformin hydrochloride tablet using combination of lipophilic waxes by granulation technique. African J Pharm 2010; 4(8):555-61.
[29].Raghavendra RNG, Gandhi S, Patel T. Formulation and evaluation of sustained release matrix tablets of tramadol hydrochloride. Int J Pharm Sci 2009; 60-70.
[30].Dhirendra K, Vivek D, Shaila L, Brajesh P, Kavita RG, Sarvesh P. Design and evaluation of sustained-release matrix once daily formulation of stavudine. Int J Drug Del 2010:125-34.
[31].Anton SA, Kottai MA, Wagh BPR, Manavalan R. Formulation development & evaluation of Ondansetron hydrochloride sustained release matrix tablets. J Pharm Sci Res 2009; 1(4):48-54.
[32].Raghuram RK, Srinivas M, Srinivas R. Once-daily sustained release matrix tablets of nicorandil: formulation and *in vitro* evaluation. AAPS Pharm Sci Tech 2003; 4(4):61-4.
[33].Syed NU, Anup KR, Martand K, Vinod KSM. Formulation and Evaluation of Sustained Release Matrix Tablets of Lornoxicam. Int J Drug Dev and Res 2011; 3 (1):31-44.
[34].Mohammed MR, Mohammed QA, Mithilesh KJ, Ishtiaq A. Development and in-vitro evaluation of sustained release matrix tablets of salbutamol sulphate using methocel k100M cr polymer. Int J Pharm Res and Dev.2011; 2(11):104 -5.
[35].Radhika pr, Dedeepya k, Sivakumar T. Fabrication of sustained release matrix tablets of venlafaxine hydrochloride using eudragits. Int j res ayur and pharm 2011; 2(4):1386-9.
[36].Kumar BS, Tajnin A, Afia F, Riaz U. Formulation and comparison of in vitro release profile of hydrophilic and hydrophobic polymer based Naproxen matrix tablets. J Appl Pharm Sci 2011; 01 (05): 155-9.
[37].Ashutosh KS, vijayakumar S, Karthikeyan M, Manidipa S. Formulation and evaluation of sustained release tablets of metoprolol succinate. Int J Pharm and Bio Arch 2010; 1(5): 416-20.
[38].United States Pharmacopeia 31 and National Formulary 26, Rockville, MD: United States pharmacopeial convention; 2008; vol I .p.813-14.
[39]Gosh TK, Jasti BR. Theory and Practice of contemporary pharmaceutics. London: CRC press; 2005. p. 333-58.
[40]Shoaib MN, Tazeen J, Hamid AM, Rabia IY. Evaluation of drug release kinetics from ibuprofen matrix tablets using hpmc. Pak J Pharm Sci 2006; 19(2):119-24.