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Sustained Release Tablet using combination of Hydrophilic and Hydrophobic Polymers

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ABSTRACT **-** The sustained release tablet of Ambroxol Hydrochloride were prepared and evaluated by emphasizing on the effect of hydrophilic polymer like HPMCK100, Eudragit S100 and hydrophobic polymer Ethyl cellulose which are used as matrices to control the drug release . The polymer were used alone and as in combination. Tablets containing the drug were prepared by direct compression with different drug polymer ratio.The tablet were evaluated for thickness, weightt variation test, drug content, hardness, friability and in-vitro drug release studies. In- vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 hrs using an USP dissolution test apparatus (type II Paddel) at 37±0.50C and 50 rpm. The optimized formulation F11(1:1:1) showed 92.61%drug release in 12 hrs .The release kinetics was analyzed using Korsmeyer- Peppas model which present the maximum regression coefficient value (0.9916)with anamolous release mechanism. The optimized formulation F11 was kept for short term stability study at room temperature and with relative humidity of 75% ,the stability study of formulation F11showed no significant changes

Keywords−Ambroxol Hydrochloride, Sustained release, HPMC K 100, Ethyl cellulose, Eudragit S 100.

I. INTRODUCTION

Oral administration of drugs has been known for decades as the most common and preferred route for delivery of most therapeutic 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].

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. It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders. Its short biological half life (4 hrs) that calls for

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frequent daily dosing (3 to 4 times) and therapeutic use in chronic respiratory diseases necessitates its formulation in to sustained release dosage forms [5],[6] .

II. MATERIALS AND METHODS

Ambroxol Hydrochloride were received as an gift sample from Akhil Healthcare pvt. Ltd., Vadodara. HPMC were obtained from Colorcon, Goa, Ethyl cellulose,Magnesium stearate, Lactose from Aurochem Ltd., Palghar, SD Fine Chemicals, Mumbai, Eudragit S100 and Hydrochloride from Alpha chemika, Mumbai.

Methods

Preparation of Ambroxol Sustained Release Tablet

The requisite quantity of the polymers was weighed and placed in a mortar, which is homogeneously triturated with the help of pestle for two minutes. The required quantity of the Ambroxol Hydrochloride was weighed and uniformly triturated with the homogeneous polymer mixture for further 2 min. Then excipients were added as per requisite quantity to form uniform bulk powder. Bulk .The prepared bulk power were evaluated for preformulation studies.After preformulation studies, the bulk powder were compressed with the 8mm concave punch using a 16 station rotatory tablet compression machine. Compression force was kept constant for all formulations. Each tablet contained 75 mg Ambroxol Hydrochloride [7]. The composition of various formulations given in Table 1.

Table 1: Composition of Tablets

Batch (mg/tab.)	Drug	HPMC K100 M	Ethyl Cellulose	Eudra-gitS100	Lactose	Mag. stearate	Aerosil	Total Weight(mg)
F1	75	37.5	-	-	192	05	0.5	310
F2	75	75	-	-	154.5	05	0.5	310
F3	75	150	-		79.5	05	0.5	310
F4	75	-	37.5	-	192	05	0.5	310
F5	75	-	75	-	154.5	05	0.5	310
F6	75	-	150	-	79.5	05	0.5	310
F7	75	-	-	37.5	192	05	0.5	310
F8	75	-	-	75	154.5	05	0.5	310
F9	75	-	-	150	79.5	05	0.5	310
F10	75	75	37.5	-	117	05	0.5	310
F11	75	75	75	-	79.5	05	0.5	310
F12	75	75	150	-	4.5	05	0.5	310
F13	75	75	-	37.5	117	05	0.5	310
F14	75	75	-	75	79.5	05	0.5	310
F15	75	75	-	150	4.5	05	0.5	310

Each formulation contains 1% Magnesium Stearates

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Micromeritic properties

The physical mixture of the drug with different excipients was prepared by triturating drug and additives in a dried mortar for 5 min and the physical mixture were determine by micrometric properties as angle of repose ,bulk density, tapped density, carr's index, and Hausner's ratio.

Evaluation of tablet

Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm2.

Thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier caliper.

Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight was determined.

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

Uniformity of Weight

Weigh 20 tablets at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown and none deviates by more than twice that percentage[8].

Determination of Drug Content:

For determining drug content, 3 tablets were crushed and powder containing 75mg of Ambroxol Hydrochloride was dissolved in 75ml of methanol. Drug content of Ambroxol Hydrochloride was carried out by measuring the absorbance of sample at 248nm using UV-Visible spectrophotometer [9].

Dissolution study

The developed formulations were subjected to release studies using USP type II dissolution apparatus at 100 rpm with a constant temperature water bath at 37 ± 0.5°C. Dissolution medium used was 0.1N HCL (900 ml) for 2 hours . The samples were withdrawn (1 ml) at different time interval and replaced with an equivalent amount of fresh medium .

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IR Spectral analysis

It was used to study interaction between drug and polymer. The drug and polymer must be compatible with one another to produce stable product. Drug and polymer interaction were studied by using FTIR (Shimadzu, model 8400,Japan) as per the method. In IR specrtral analysis, polymers HPMC M100 and EC were produced peaks and pattern were compared with peaks and pattern of pure drug.

Stability study

The optimized formulation was kept for short term stability study. The conditions for stability study were 40°C and relative humidity of 75%. All tablets were suitably packed in aluminum foil. At the end of one month the sealed tablets were opened and evaluated for hardness, friability, uniformity of weight, determination of drug content and dissolution studies [6],[9]. Stability data drug contain and dissolution data is statistically analyzed by using student't' test by using by using Systat Software, Inc. 501 USA[10].

III. RESULT AND DISCUSSION

FTIR study

All the excipients used in the formulation were compatible with each other.(in fig.no.1,2and3)

Micrometrics property

Angle of repose, bulk density, tapped density , Carr's index and Hausner's ratio of physical mixture were determined. All precompression parameters of formulation was showed satisfactory flow properties. (table2)

Physical parameters

The physical parameters of compressed tablet were determined. The results for evaluation of prepared matrix tablets viz. hardness, weight variation, friability, drug content uniformity were found in the range of 5.9±0.20 to 6.4±0.26 kg/cm, 199.12±0.58 to 203.38±1 mg.03, 0.18 to 0.70%, 95.38±1.14 to 98.83±0.61% respectively for all formulations and showed all values within the limit. The friability of the tablets was found to be less than 1% which was considered within the limit. The drug content of the all formulations was found to be within the limits.

Evaluation Of Bulk Powder and Tablet

Table 2. Evaluation of Powder F1to F15

Batch	Angle of Repose	Bulk Density (gms/cm^3)	Tapped Density (gms/cm^3)	Carr's Index (%)	Hausner's Ratio
F1	24.11±0.80	0.369±0.013	0.431±0.015	14.84	1.17
F2	29.42±0.14	0.345±0.017	0.403±0.011	13.89	1.12
F3	24.61±0.08	0.374±0.006	0.399±0.021	11.82	1.13
F4	30.13±0.44	0.378±0.011	0.436±0.017	12.55	1.16
F5	27.14±0.03	0.374±0.006	0.437±0.009	14.84	1.17
F6	25.63±0.08	0.354±0.022	0.416±0.007	15.38	1.18
F7	24.85±0.20	0.356±0.030	0.415±0.027	14.42	1.16

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F8	26.56±0.47	0.342±0.016	0.388±0.013	9.84	1.10
F9	28.61±0.39	0.347±0.005	0.398±0.008	15.75	1.17
F10	27.22±0.22	0.336±0.022	0.387±0.031	13.22	1.15
F11	25.14±0.06	0.374±0.013	0.418±0.011	11.71	1.13
F12	27.46±0.34	0.371±0.011	0.438±0.017	13.90	1.16
F13	25.45±0.32	0.399±0.040	0.462±0.008	11.23	1.16
F14	25.61±0.24	0.339±0.009	0.384±0.019	12.30	1.14
F15	24.50±0.21	0.382±0.008	0.428±0.008	9.21	1.10

*All values are expressed as mean± S.D, n=3

Table 3 Characterization of Formulations F1 to F15

Batch	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)*
F1	309.98±0.91	3.08±0.06	6.1±0.26	0.66	96.12±0.90
F2	310.92±1.20	3.14±0.25	6.1±0.15	0.48	95.51±0.99
F3	310.12±1.09	3.09±0.12	6.3±0.20	0.39	95.92±1.28
F4	309.12±0.58	3.19±0.10	6.4±0.26	0.54	98.70±0.85
F5	311.32±1.03	3.25±0.31	6.2±0.15	0.18	97.76±0.47
F6	312.13±0.99	3.20±0.27	6.3±0.30	0.41	97.14±0.27
F7	310.94±1.57	2.97±0.09	6.1±0.20	0.54	98.23±0.96
F8	311.20±1.11	3.28±0.26	6.1±0.23	0.68	96.75±1.51
F9	309.93±0.67	3.15±0.14	6.2±0.20	0.40	95.6±1.21
F10	311.38±1.03	2.99±0.05	6.2±0.25	0.69	98.25±0.36
F11	310.56±0.59	3.19±0.17	6.3±0.15	0.39	96.13±0.43
F12	310.64±1.24	3.33±0.30	6.2±0.15	0.70	95.38±1.14
F13	310.49±1.00	3.34±0.27	5.9±0.20	0.49	98.83±0.61
F14	312.21±0.88	3.19±0.16	6.2±0.35	0.46	97.67±0.40
F15	309.75±0.92	3.24±0.32	6.3±0.15	0.41	98.50±0.97

*All values expressed as mean± are S.D., n=3 except weight variation

FTIR study

The FTIR spectrums of Ambroxol Hydrochloride, and combination with polymer HPMC K 100M ,ethyl cellulose and Edragit S 100 as shown in Fig.1,2,3 and 4

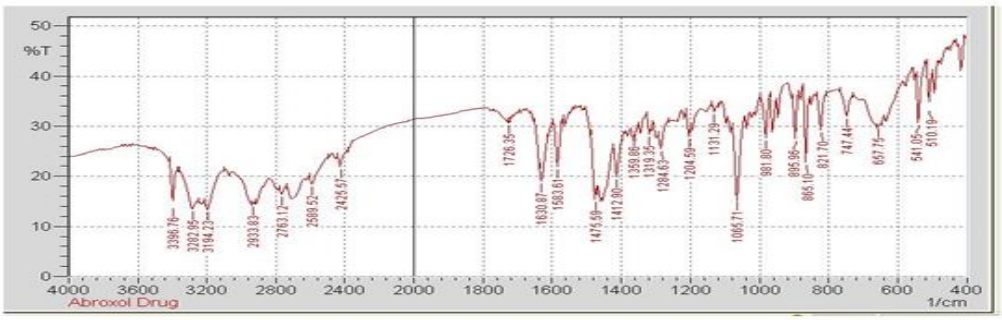

Fig 1.FTIR spectra of Ambroxol Hydrocholride

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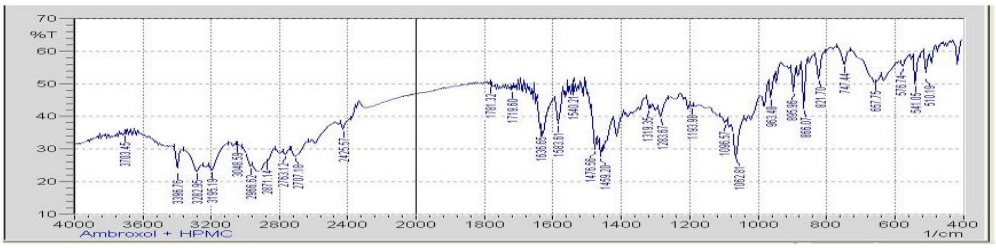

Fig.2 FTIR spectra of Ambroxol tablet and HPMC K 100 M

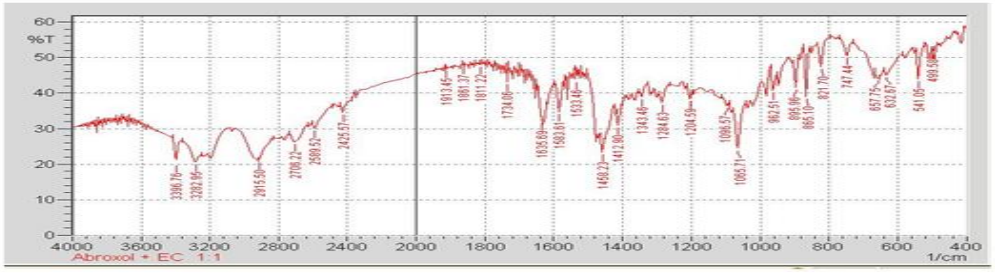

Fig.3 FTIR spectra of Ambroxol hydrochloride and Ethyl cellulose

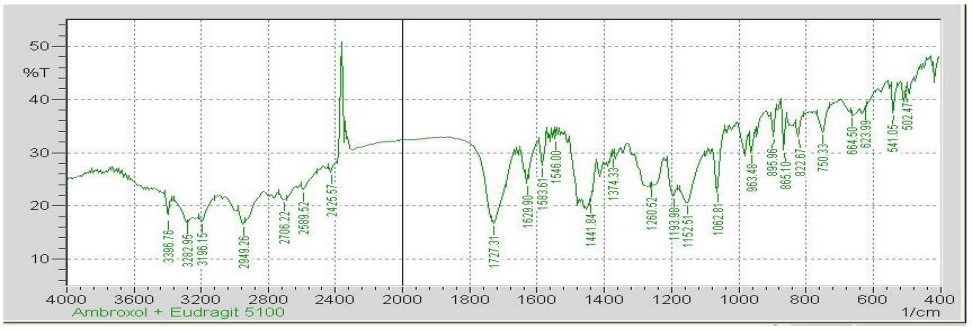

Fig.4 FTIR spectra of Ambroxol hydrochloride and Eudragit S100

Dissolution studies

The sustained release tablet was formulated with different polymers, HPMC K100M, Ethyl cellulose and Eudragit S100 in ratio 0.5%, 1%, 2% .The F1 to F9 and F13 to F15 were unable to retard the release of the drug from the tablet and the formulation release entire drug at the end of 8, 9 and 10 hrs. The polymer individually are not sufficient to prolong the release of drug. Hence addition of polymer HPMC K100M was prolong the release of drug.

In order to study the effect with combination of HPMC K100M and Ethyl Cellulose, the formulation F10, F11 and F12 were prepared in the ratio of 1:1:0.5, 1:1:1 and 1:1:1.5. All these formulations F10 to F12 were subjected to dissolution studies as shown in Fig. 5 and Table 4**.**

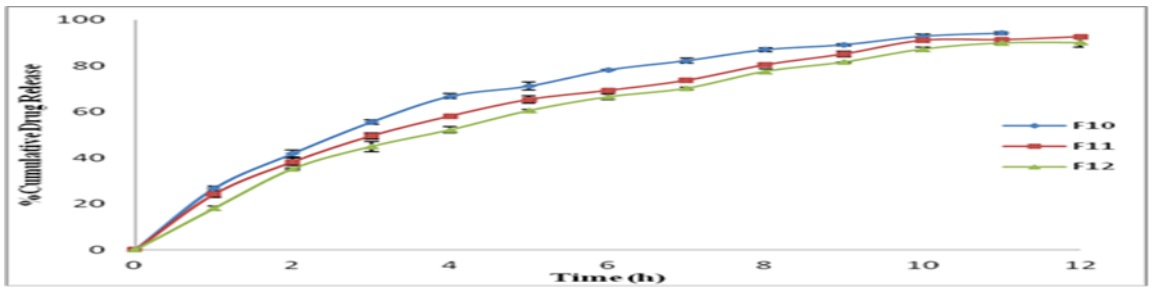

Fig.5 In-vitro drug release of F10 to F12

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Table 4. Cumulative % Drug Release of F10-F12

Hour	F10	F11	F12
1	26.64±1.01	24.16±1.51	18.01±1.08
2	41.84±1.54	38.24±1.62	35.24±0.36
3	55.56±0.99	49.54±1.36	44.91±2.19
4	66.76±1.11	58.14±0.36	52.14±1.30
5	71.18±1.76	65.35±1.60	60.49±0.40
6	78.15±0.21	69.24±0.10	66.43±1.22
7	82.25±1.19	73.66±0.81	70.16±0.44
8	87.02±0.95	80.40±1.01	77.52±1.21
9	89.19±0.51	85.12±1.22	81.57±0.16
10	92.90±1.02	91.03±1.01	87.18±1.02
11	94.21±0.70	91.31±0.22	89.88±0.51
12	-	92.61±0.19	90.01±1.79

Mean, ± S.D., n=3

From the Fig. 5 and Table 6.10, it was observed that the formulation F10, F11 and F12 showed maximum drug release rate of 94.21 % in 11 h, 92.61 % and 90.01 % in 12 h respectively. The formulation F11 showed better retardation of drug release 92.61 % in 12 h. Hence, the formulation prepared with HPMC K100 and Ethyl Cellulose in combination can be used as an aid to sustain desired drug release rate up to 12 h.

Release Kinetics

The release kinetics of the optimized formulation F11 were found to release the drug by non-Fickian transport (anomalous). The drug release data fit well to the Korsmeyer Peppas model which gave the highest r2 value 0.9916 and release exponent 0.5662 (Fig 6).

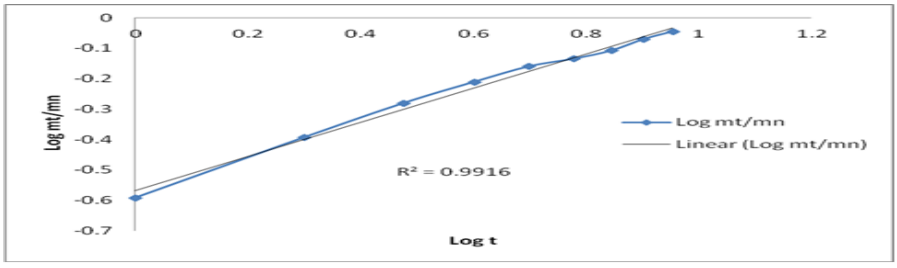

Fig.6 Korsmeyer- Peppas graph of optimize batch F11

Stability Study

The optimized formulation were subjected to stability studies and showed no significant changes in the physical parameters , drug content, in vitro drug release.

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Table 5. Results of Stability Study

Parameters	Before the stability study	After the stability study
Hardness (kg/cm^2)	6.3±0.15	6.3±0.19
% Friability (%w/w)	0.19	0.45
Weight Variation (mg)	200.56±0.59	200.45±1.67
Drug content (%)	96.13±0.43	96.03±0.98
Dissolution Study	92.61±1.19	91.78±2.01

Mean, ± S.D., n=3

IV. CONCLUSION

The present study was aimed to develop sustained release tablet of Ambroxol Hydrochloride for treating of acute and chronic respiratory diseases. The tablet prepared showed the sustained release of Ambroxol hydrochloride by using hydrophilic and hydrophobic polymer. The prepared formulation showed 92.61% release in 12hrs by using drug :polymer1:polymer2 ratio 1:1:0.5.

V. ACKNOWLEDGEMENT

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