IJPSR (2014), Volume 5, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 March 2014; received in revised form, 19 May 2014; accepted, 05 July 2014; published 01 October 2014

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF AMBROXOL HYDROCHLORIDE USING NATURAL POLYMER

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Keywords:

Ambroxol Hydrochloride, Extracted tamarind seed polysaccharide, Guar gum, Matrix tablet, Sustained release, Wet Granulation

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ABSTRACT: Ambroxol hydrochloride is a potent mucolytic agent capable of inducing bronchial secretions used in the treatment of respiratory disorders. The Sustained release matrix tablets containing 75 mg Ambroxol hydrochloride were developed using different drug: polymer ratios. Sustained release matrix tablets were prepared by wet granulation method. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The prepared tablets were further evaluated for uniformity of weight, hardness, friability, thickness, content uniformity, In-vitro dissolution, drug-excipients interactions, swelling index study also carried out. The FT-IR studies revealed that there was no chemical interaction between drug and excipients. *In-vitro* release studies were carried out using USP XXII type II (paddle method) dissolution apparatus at 50 rpm. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero order to evaluate the kinetics and mechanism of the drug release. Among all the formulations, F4 shows 99.15% better-controlled release at the end of 12 h. The drug release of optimized formulations F-4 follows zero order kinetics. The stability studies were carried out according to ICH guideline, which indicates that the selected formulations were stable.

INTRODUCTION: Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered multiple doses and therefore have several disadvantages [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(10).4225-32

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(10).4225-32

In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered multiple doses and therefore have several disadvantages [1]. Sustained release drug delivery aimed at controlling the rate of release as well as maintains desired drug level in the blood that is therapeutically effective and non-toxic for an extended period, 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 the 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 [2, 3].

The use of polymeric matrix devices to control the release of a variety of therapeutic agents has become increasingly important in the development of the modified release dosage forms [4]. 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 5.

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 the target tissues at the desired value as long as possible [6].

Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used because they are nontoxic and acceptable by the regulating authorities. The various polysaccharides used in drug delivery application are cellulose ethers, xanthan gum, locust bean gum, and guar gum. Another natural polysaccharide Tamarind seed polysaccharide (TSP) obtained from the seed kernel of *Tamarindus indica*, possesses properties like high viscosity, broad pH tolerance, non-carcinogenicity, mucoadhesive nature, and biocompatibility. It is used as stabilizer, thickener, gelling agent and binder in the food and pharmaceutical industries. The tamarind seed polysaccharide constitutes about 65% of the tamarind seed components [7].

Ambroxol is a metabolite of bromhexine with similar actions and uses. It is chemically described as Trans-4-[(2-amino-3, 5-dibromo benzyl) 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. It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders. Adverse effects produced such as gastrointestinal disorder, headache, dizziness, sweating, rhinorrhoea, lacrymation, and allergic reactions [8, 9].

It was postulated that Ambroxol HCl decreased airway hyperreactivity by either increasing lysophosphatidylcholine turnover and modifying epithelial secretion where the successful treatment needs a constant and uniform supply of the drug. Ambroxol HCl is sparingly water solubility. Hence it presents significant formulation challenges. Ambroxol HCl has a half-life of 4 h, and the usual oral dosage regimen is 75 mg [10]. Therefore, it is an ideal candidate to be designed to sustain release dosage form, which would result in prolonged clinical efficacy, reduced frequency of dosage, and lesser side effects. The present study aims to develop sustained release matrix tablets of Ambroxol hydrochloride using natural polymer.

MATERIALS AND METHODS:

Materials: Tamarind kernel powder, collected from a plant source. Ambroxol hydrochloride was obtained from Yarrow chemicals, Mumbai. Guar Gum, Polyvinyl Pyrrolidone K 30, Lactose and Talc were purchased from SD Fine Chem. Limited, Mumbai. Karaya Gum was purchased from Research Lab Fine Chem Industries, Mumbai. Magnesium stearate was purchased from Loba Chemie Pvt. Ltd, Mumbai.

Extraction of Tamarind Seed Polysaccharide: To 20 g of tamarind kernel powder, 200 ml of cold distilled water was added, and the slurry was prepared. The slurry was poured into 800 ml of boiling distilled water. The solution was boiled for 20 min under the stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 min. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The precipitate was washed with absolute ethanol, diethyl ether and then dried at 50-60 ºC under vacuum. The dried material was ground and sieved to obtain granules of the different particle size range. The particle size range of 150-75 microns was used for the preparation of tablets [11].

Preparation of Matrix Tablets: Tablet formulations were prepared by wet granulation method. The proportion of excipients with the drug was as given in **Table 1**. The drug and all other ingredients were sifted through sieve 60. The sifted ingredients were mixed thoroughly in a mortar with a pestle for 15 min. PVP mixed with Isopropyl alcohol and added into well-mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve 16. The prepared granules were dried at 60 ºC for 1 h in a hot air oven, and then it was sifted through sieve 16 and transferred the granules into a polybag. Magnesium stearate and talc were sifted through sieve 40 and mixed with the prepared granules in a polybag for 5 min. Finally, tablets were compressed at 600 mg weight on a 10 station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 12.1 mm flat-shaped punches.

Evaluation of Granules: The angle of repose was measured by using the funnel method, which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD = weight of the powder/volume of the packing. TBD = weight of the powder/tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100. The physical properties of the granules were shown in **Table 2**.

Evaluation of Tablets: All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability, and thickness according to official methods shown in **Table 3**.

Uniformity of drug content: Accurately weighed quantity of the powder tablet equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of the buffer solution of pH-6.8 was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with the same buffer solution, the mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45 µm. 5 ml of the filtrate was diluted to 100 ml with the same buffer solution and examined under U.V Spectrophotometer at 210 nm.

***In-vitro* Drug Release Studies:** *In-vitro* drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisting of 900 ml of pH 1.2 phosphate buffer for the first two hours and pH 6.8 phosphate buffer for the remaining hour, maintained at 37 ± 0.50 ºC. The drug release at different time intervals was measured using an ultraviolet-visible spectro-photometer (LabIndia, Mumbai, India) at 210 nm.

Drug Release Kinetics: The release kinetics was fitted to different mathematical models like Zero order, First order, Higuchi‘s and Peppas plot. The kinetic treatment of selected optimized formulation F-4 shows that the regression coefficient for zero-order kinetics was found to be higher when compared with those of the first-order kinetics. The slope (n) value of Korsmeyer Peppas plots of optimized formulation F-4 was found to be 0.722, respectively, indicate that the mechanism of release was Anomalous (non-Fickian) diffusion.

Stability Study: Selected formulations were stored at different storage conditions at elevated temperatures such as 25 ºC ± 2 ºC / 60% ± 5% RH, 30 ºC ± 2 ºC / 65% ±5% RH and 40 ºC ± 2 ºC / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes.

TABLE 1: TABLET COMPOSITION OF AMBROXOL HYDROCHLORIDE SUSTAINED-RELEASE MATRIX TABLETS PREPARED WITH DIFFERENT RELEASE RETARDANT (F-1 TO F-8)

Formulation code	Drug	Guar gum	Karaya gum	TSP	PVP	Lactose	Magnesium stearate	Talc
F1	75	75	-	75	30	327	12	6
F2	75	100	-	100	30	277	12	6
F3	75	150	-	150	30	177	12	6
F4	75	200	-	200	30	77	12	6
F5	75	-	75	75	30	327	12	6
F6	75	-	100	100	30	277	12	6
F7	75	-	150	150	30	177	12	6
F8	75	-	200	200	30	77	12	6

TABLE 2: DATA FOR BLEND EVALUATION OF FORMULATION (F-1 TO F-8)

Formulation code	Angle of repose	Loose bulk density (LBD) (g/ml)	Tapped bulk density (TBD) (g/ml)	Compressibility index (%)
F1	30.41 ± 1.47	0.250 ± 0.07	0.289 ± 0.05	13.49 ± 0.21
F2	29.25 ± 1.28	0.232 ± 0.02	0.268 ± 0.04	13.43 ± 0.52
F3	27.69 ± 1.51	0.242 ± 0.03	0.276 ± 0.02	12.31 ± 0.64
F4	26.48 ± 1.67	0.263 ± 0.05	0.295 ± 0.02	10.84 ± 0.75
F5	31.62 ± 1.35	0.275 ± 0.06	0.325 ± 0.02	15.38 ± 0.34
F6	29.14 ± 1.75	0.200 ± 0.05	0.233 ± 0.04	14.16 ± 0.78
F7	30.26 ± 1.45	0.260 ± 0.09	0.299 ± 0.05	13.04 ± 1.52
F8	31.16 ± 1.21	0.281 ± 0.07	0.331 ± 0.06	15.10 ± 1.27

TABLE 3: PHYSICAL PROPERTIES OF TABLET FORMULATION (F-1 TO F- 8)

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Weight variation
F1	4.17 ± 0.07	4.6 ± 0.25	0.52 ± 0.32	98.52 ± 0.23	600.5
F2	4.25 ± 0.05	4.6 ± 0.27	0.47 ± 0.51	99.26 ± 0.27	600.4
F3	4.30 ± 0.0.04	4.8 ± 0.23	0.46 ± 0.37	99.45 ± 0.17	600.5
F4	4.40 ± 0.02	4.9 ± 0.21	0.42 ± 0.44	99.67 ± 0.14	600.3
F5	4.20 ± 0.05	4.7 ± 0.24	0.54 ± 0.42	97.62 ± 0.25	600.5
F6	4.27 ± 0.04	4.7 ± 0.29	0.51 ± 0.46	98.27 ± 0.19	600.4
F7	4.45 ± 0.02	4.9 ± 0.27	0.49 ± 0.39	99.15 ± 0.12	600.4
F8	4.50 ± 0.03	5.0 ± 0.26	0.48 ± 0.43	99.31 ± 0.15	600.3

RESULT AND DISCUSSION:

Differential Scanning Calorimetry: Thermogram of Ambroxol hydrochloride is shown in **Fig. 1** which indicates the melting point of the pure drug is 240 ºC and the melting peak of optimized formulation (F-4) is at 206 ºC was observed in **Fig. 2**. Change in temperature is due to drug and polymer mixture. DSC studies revealed that there was no much shift in the melting point of the drug in the physical mixture compared to the pure drug; this indicates that there is no interaction between drug and matrix materials.

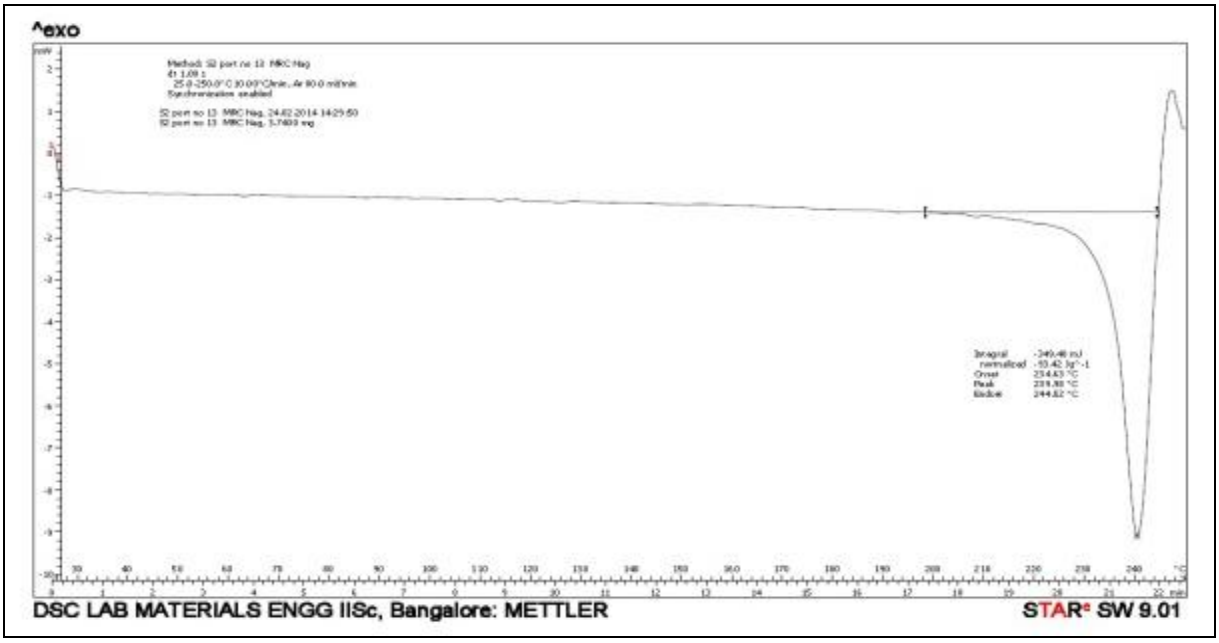

FIG. 1: DSC THERMOGRAM OF PURE AMBROXOL HYDROCHLORIDE

FTIR Spectroscopy: FTIR spectrum of Ambroxol hydrochloride showed in scan in **Fig. 3**. A physical mixture of drug and polymers are shown in **Fig. 4**. The characteristic peaks of the drug were observed in the spectra of drug and polymer mixture, indicates that there is no interaction between the drug and polymer mixtures. Hence, these release retarding materials were selected for the formulation of sustained-release tablets.

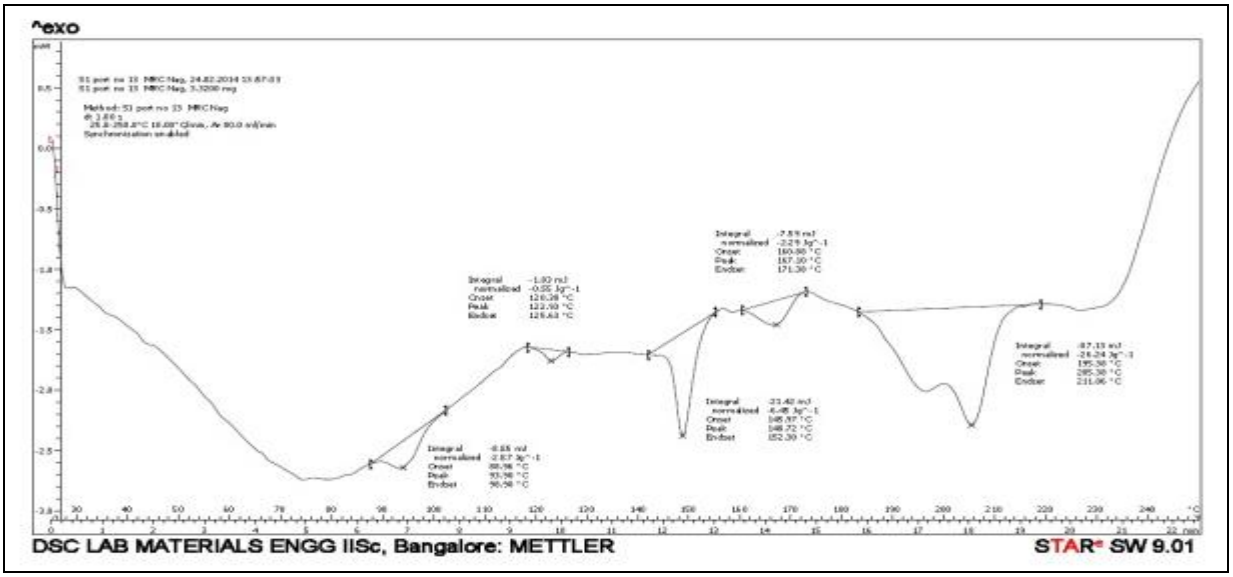

FIG. 2: DSC THERMOGRAM OF OPTIMISED FORMULA F-4

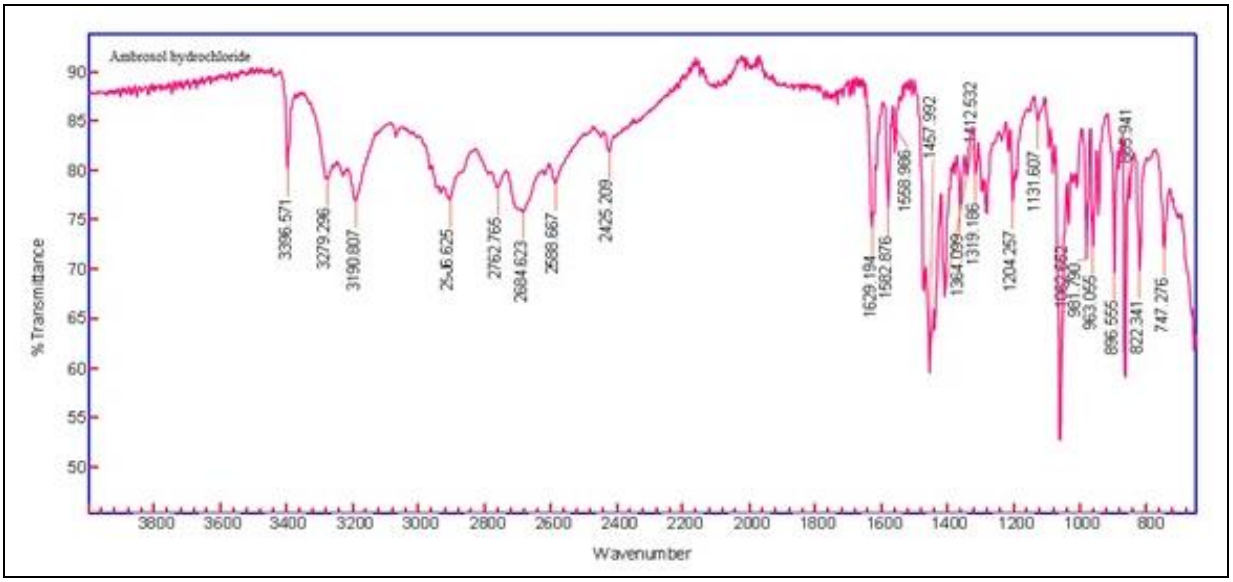

FIG. 3: FTIR SPECTROSCOPY OF PURE DRUG AMBROXOL HYDROCHLORIDE

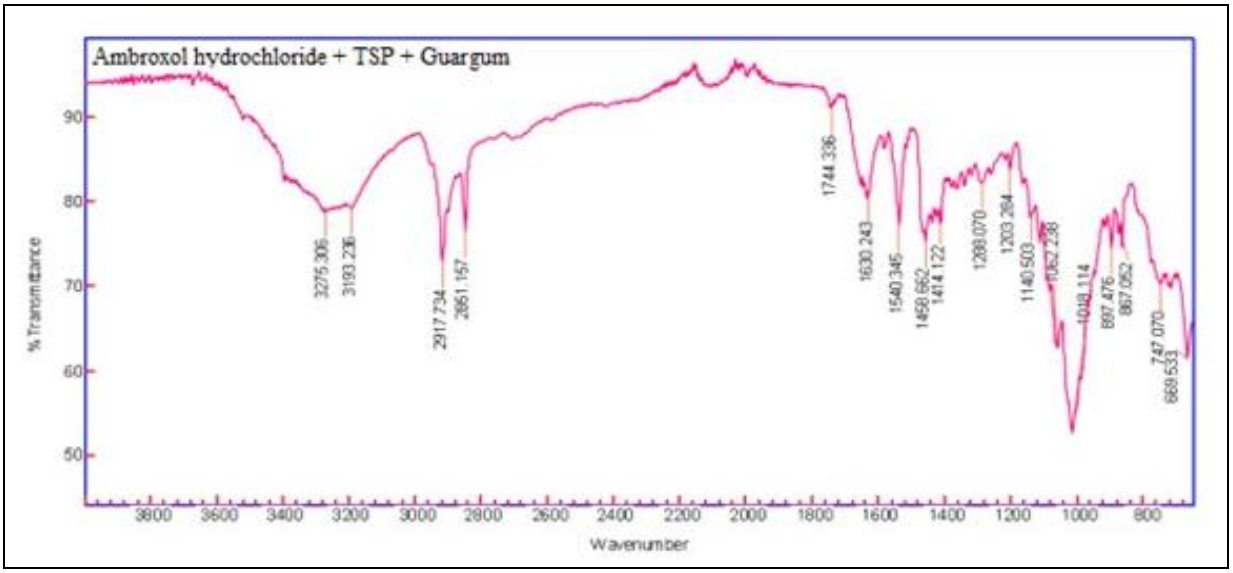

FIG. 4: FTIR SPECTROSCOPY OF FORMULATION 4

Scanning Electron Microscopy (SEM) of the Optimized Formulation: The Scanning Electron Microscopic (SEM) Analysis was conducted using a JOEL (Model - JSM 840A) Scanning Microscope for the optimized formulations in three states involving Dry tablet surface, Tablet after swelling for 2 ho and Tablet after swelling for 6 h and 12 h, so as to determine particle size distribution, surface topography, and texture and to examine the morphology of fractured or sectioned surfaces.

As with SEM high vacuum is required for image formation and samples must be thoroughly desiccated before entering the vacuum chamber. Therefore samples were thoroughly dried after swelling for analysis. The dried samples were mounted on a sample holder using double-sided adhesive carbon tape.

The condenser lens position was maintained at a constant level. SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet (F-4). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix.

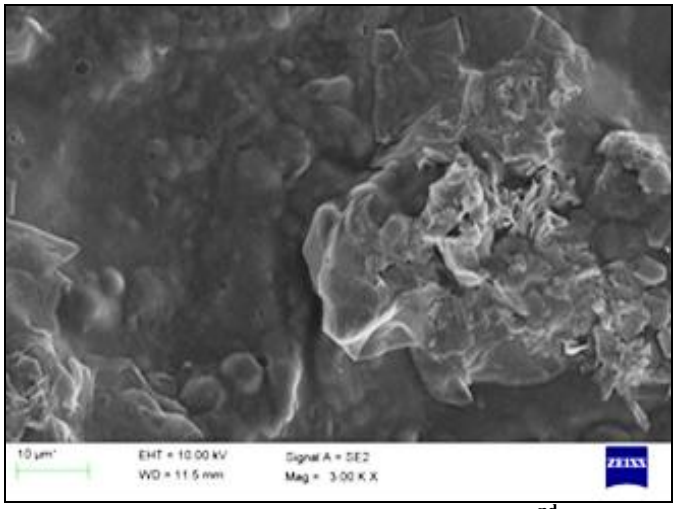

FIG. 5: SEM PHOTOMICROGRAPH AT 2nd HOUR

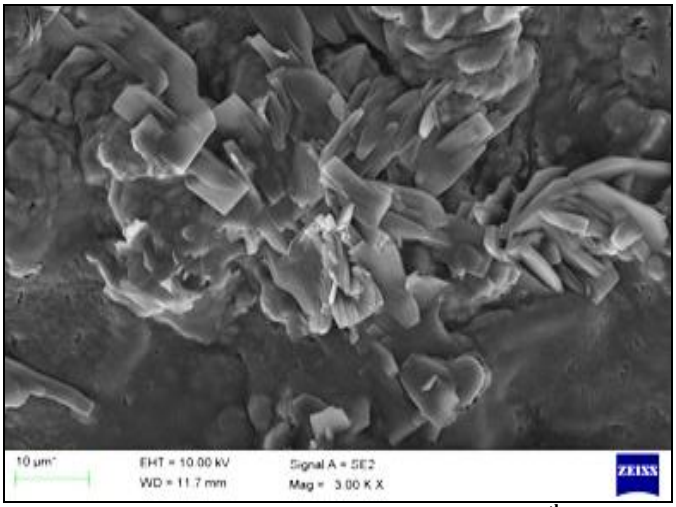

FIG. 6: SEM PHOTOMICROGRAPH AT 6th HOUR

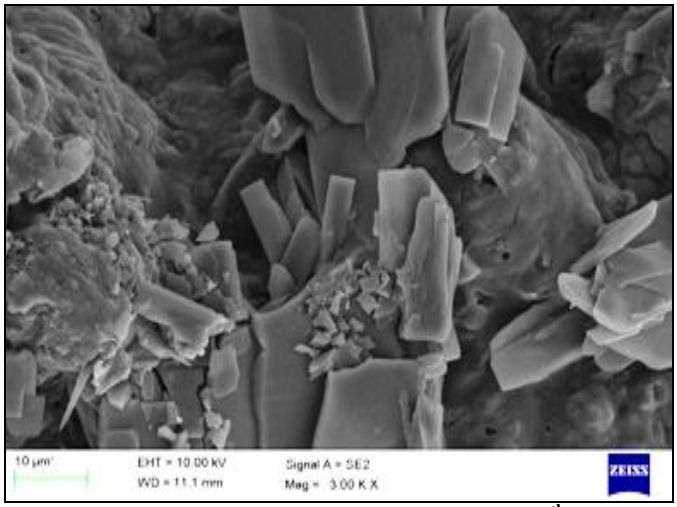

FIG. 7: SEM PHOTOMICROGRAPH AT 12th HOUR

Characterization of Granular Properties: Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table 2. The angle of repose was in the range 26.48 ± 1.67º to 31.62 ± 1.35º, which indicates the excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.200 ± 0.005 to 0.281 ± 0.007 gm/ml; the tapped density was in the range of 0.233 ± 0.04 to 0.331 ± 0.06 gm/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the

range of 10.84 ± 0.75 to 15.38 ± 0.34; indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical Evaluation of Matrix Tablets: Tablets with a weight of 600 mg were obtained and subjected to quality control tests such as hardness, friability, and drug content **Table 3**. The hardness of the tablets was found to be in the range of 4.6 ± 0.25 to 5.0 ± 0.26 Kg/cm^2. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 4.17 ± 0.07 to 4.50 ± 0.03 mm.

The friability of the tablets was found to be less than 1%, and it was within the range of standard specification. The drug content for all the batches was found to be in the range of 97.62 ± 0.25 to 99.67 ± 0.14. The results are given in **Table 3**. The punches used to compress the tablets were 12.1 mm flat-shaped punches.

***In-vitro* Release Study:** *In-vitro* drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consist of 900 ml of pH 1.2 phosphate buffer for the first two hours and pH 6.8 phosphate buffer for the remaining hour, maintained at 37 ± 0.5 ºC. The drug release at different time intervals was measured using a visible-ultraviolet spectro-photometer (LabIndia, Mumbai, India) at 210 nm.

The results were evaluated for 12 h. As per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7 and F- 8 showed 96.72, 95.49, 98.42, 99.15, 92.87, 94.38, 95.74 and 95.23 % respectively. The drug release from the tablet was sustained for 8 to 12 h. Formulation F4 found to be most promising formulation as they showed sustained release (99.15% to 12 h) as well as maintained excellent matrix integrity during the period of 12 h study. Hence, formulation F4 was selected as the optimized formulation.

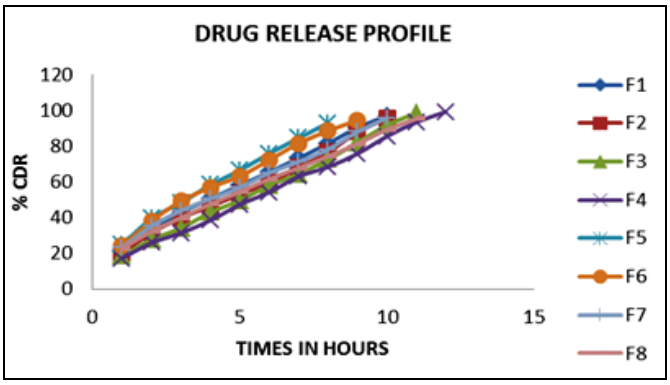

FIG. 8: *IN-VITRO* DISSOLUTION PROFILE OF F1 TO F8 FORMULATIONS

Determination of the Release Kinetics: The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-8 could be best expressed by zero order equation as the plots showed the highest linearity (R2: 0.989 to 0.998) then first order release kinetics (R2: 0.698 to 0.919). The n values obtained from Korsmeyer Peppas plots range from (0.598 to 0.722) indicate that the mechanism of release of formulations F-1 to F-8 was Anomalous (non-Fickian) diffusion.

TABLE 4: RELEASE KINETICS PARAMETERS OF SUSTAINED RELEASE MATRIX TABLETS OF AMBROXOL HYDROCHLORIDE

Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope n
F1	0.996	0.811	0.99	0.998	0.659
F2	0.994	0.820	0.970	0.990	0.658
F3	0.998	0.732	0.971	0.988	0.703
F4	0.998	0.698	0.972	0.987	0.722
F5	0.994	0.919	0.994	0.998	0.625
F6	0.989	0.902	0.995	0.998	0.610
F7	0.995	0.830	0.984	0.994	0.598
F8	0.998	0.870	0.987	0.993	0.602

CONCLUSION: The matrix tablets were found to be effective in sustaining the drug release up to 12 h. This is mainly due to the formation of a thick gel structure that delays drug release from tablet matrix; Drug release was found to be diffusion coupled with erosion. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. DSC and FTIR

studies revealed that there was no shift in peaks, indicating there is no interaction between Ambroxol hydrochloride and other ingredients used. SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that the matrix was intact, pores had formed throughout the matrix and also found the formation of gelling structure. It can be concluded that stable formulation could be developed by incorporating hydrophilic polymer Tamarind seed polysaccharide and Guar gum in a definite proportion so that the controlled released profile is maintained for an extended period.

ACKNOWLEDGEMENT: The authors are thankful to the Management, Sree Siddaganga College of Pharmacy, Tumkur, for providing necessary facilities to carry out this work.

CONFLICT OF INTEREST: Nil

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How to cite this article:
Kumar S, Rao BS and Kulkarni SV: Formulation and evaluation of sustained release matrix tablets of ambroxol hydrochloride using natural polymer. Int J Pharm Sci & Res 2014; 5(10): 4225-32. doi: 10.13040/IJPSR.0975-8232.5(10).4225-32.