Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2012, 4 (4):1105-1114
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Design and Evaluation of Natural Gum Based Oral Controlled Release Matrix Tablets of Ambroxol Hydrochloride

Ramana G*, Kartik Reddy D and Sravanthi O

Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, AP, India

---

ABSTRACT

The objective of the present investigation was to design and evaluate the oral controlled release matrix tablets of ambroxol hydrochloride by using various natural matrix former gums such as Tara gum and Locust bean gum separately. Tablets were prepared by wet granulation method. 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. Among different formulations, F-3 and F-6 which contain Tara gum and Locust bean gum with drug: polymer ratio as (1:3) and exhibited precise controlled release of drug over a prolonged period of 12 hrs. The in- vitro dissolution data obtained for various formulations were fitted into zero-order, first order, Higuchi's and Peppas kinetic models. The majority of designed formulations displayed zero order release kinetics and Korsmeyer and Peppas equation give release pattern with values of (n = 0.534 – 0.570) indicating non-fickian or Anomalous types of diffusion takes place through matrix of Tara gum and Locust bean gum. The optimized formulations F-3 and F-6 were subjected to stability studies for three months at 25^0C/60%RH and 40^0C/75%RH as per ICH guidelines and result does not shows any change in physical parameters and in-vitro release studies. The result demonstrates the feasibility of natural gums in the development of oral matrix tablets for controlled delivey of ambroxol hydrochloride.

Key words: Ambroxol hydrochloride, Tara gum, Locust bean gum, Swelling studies Matrix tablets.

INTRODUCTION

In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Among the synthetic hydrophilic polymer considered as release retardant but these polymers are quite expensive [1] and biodegradability is questionable when compared with natural polymers [2]. Hence the last two decades have witnessed a mammoth growth in development of drug delivery systems by using natural gum based matrices. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media and these have been used for the preparation of dosage form [3, 4]. The objective of the present investigation was to develop oral controlled release tablets for ambroxol hydrochloride using natural gums such as Tara gum and Locust bean gum. Tara gum is obtained by grinding the endosperm of the seeds of Caesalpinia spinosa consists chiefly of polysaccharides of high molecular weight composed mainly of galactomannans in which the principal component consists of a linear chain of (1, 4)-beta-D-mannopyranose units with alpha-D-galacto-pyranose units attached by (1,6) linkages [5]. Locust bean gum (LBG) is a plant seed galactomannan, composed of a 1-4 linked ß-D-mannan backbone with 1-6-linked α-D-galactose side group. Longer galactose side chain produces a desirable viscosity which retards the release of drug through matrices [6].

Ambroxol is a metabolite of bromohexine with similar actions and uses. It is chemically described as Trans-4-[(2-Amino-3, 5-dibromobenzyl) amino] - cyclohexanol. It is an expectoration improver and a mucolytic agent used in

the treatment of acute and chronic disorders characterized by the production of excess of 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. Its short biological half life (3-4 hrs) that calls for frequent daily dosing (2 to 3 times) and therapeutics use in chronic respiratory disease necessitates its formulation into controlled release dosage form [7].

MATERIALS AND METHODS

MATERIALS:

Ambroxol hydrochloride was obtained from Darwin Laboratories Pvt. Ltd., Vijayawada, Andhra Pradesh, India. Tara gum was obtained from Volga agro products, Mumbai and Locust bean gum was obtained from Food Chem., Chennai. DCP was obtained from Kemphesol, Pharmaceutical Pvt. Ltd., Mumbai. PvpK-30, Magnesium stearate and Talc were obtained from S.D. Fine Chem., Mumbai, India. All other ingredients used throughout the study were of analytical grade.

METHODS:

Calculation of Theoretical Controlled Release profile of Ambroxol Hcl Matrix Tablets:

The total dose of Ambroxol Hcl CR formulation was calculated by Robinson Eriksen equation using available pharmacokinetic data [8]. The zero order drug release rate constant was calculated by the following equation:

$Dt = Dose\ (1+ (0.693\times t)/ t_{1/2})$

Where,

Dt = total dose of drug

t = time (hr) during which the CR is desired (12 hr),

$t_{1/2}$ = half-life of the drug (3 hr).

$Dt = 19.8\ (1+ (0.693\times 12)/ 3) = 75mg$

Hence, the formulation should release 19.8 mg in first hour like conventional tablets and 5.01mg per hour up to 12 hours thereafter.

Drug – Excipients compatibility study:

The compatibility between drug and excipients were tested by Fourier transform infrared spectroscopy (FT-IR) (Parkin Elimer). The pellets were prepared on KBr- press and the spectra were recorded over the wave number range of 4000 to 500 cm-1.

Estimation of Ambroxol hydrochloride:

Ambroxol hydrochloride in pure form and in developed formulations was estimated spectrophotometrically using Elico SL150 UV-Visible Spectrophotometer at 248 nm in 0.1N Hcl and pH 7.4 phosphate buffer [9].

Preparation of matrix tablets by wet granulation method:

The matrix tablets of Ambroxol hydrochloride were prepared using Tara gum and Locust bean gum as polymers by wet granulation technique by using PVP k-30 as binder, DCP as diluent and mixture of talc and magnesium stearate as lubricant. All the components were screened and then thoroughly mixed for a period of 15 min in a polythene bag . The powder blend was granulated using PVP k-30 (5 % w/v). The wet mass was passed through sieve # 16 and the granules were dried at 50°C for 2 hrs in a hot air oven [10]. The dried granules were passed through sieve # 20 and lubricated with magnesium stearate and talc by further mixing for 5mins. Compression was done on single station (Cadmach, Ahmadabad) tablet compression machine using 8 mm concave punches. The compositions of ambroxol hydrochloride matrix tablets prepared by wet granulation technique were given in Table 1.

Evaluation of granules:

Micromeritic properties of the prepared granules of all the formulations were studied by determining the bulk density, tapped density, Compressibility Index, Hausner's ratio and angle of repose [11].

Evaluation of tablets:

The prepared matrix tablets were evaluated for hardness, thickness, friability, weight variation test and drug content. Hardness of tablets was tested using Monsanto hardness tester (shreeji chemicals, Mumbai). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of tablets was measured by Vernier callipers. Weight variation test was performed according to official method specified in I.P. Drug content for ambroxol hydrochloride was carried out by measuring the absorbance of samples at 248 nm using Elico SL150 UV-Visible Spectrophotometer and comparing the content from a calibration curve prepared with standard ambroxol hydrochloride in the same medium.

Swelling Behaviour Studies of Prepared Matrix tablets:
The extent of swelling was measured in terms of percent weight gain by the tablets. The swelling behaviour of all tablets was studied. One tablet from each formulation was placed in a petridish containing phosphate buffer solution (pH 7.4). At regular time intervals, the tablet was withdrawn, blotted with a tissue paper and weighed. The process was continued for 12 hours and the percent weight gain by the tablets was calculated by using formula [12].

Swelling index (S.I.) = $\{(M_t - M_o)/ M_o\} \times 100$

Where,
M_t = weight of tablet at time't'
M_o = weight of tablet at time t = 0.

***In vitro* drug release studies:**
The prepared matrix tablets were subjected to *in-vitro* dissolution studies using USP type I basket type dissolution rate test apparatus (Labindia, Disso 2000, and Mumbai). The dissolution studies were carried out in pH 1.2 for 2 hrs and in pH 7.4 for next 10 hrs at 37± 0.5°C at 50 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 248 nm for ambroxol hydrochloride against blank using UV Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve [9].

Drug release kinetics:
The rate and mechanism of release of ambroxol hydrochloride from the prepared matrix tablets were analyzed by fitting the dissolution data into the following equations:

Zero-order equation*:*
$Q_t = Q_o + K_o t$

Where,
$Q_{t\ is}$ the initial amount of drug dissolved at time t,
Q_o is the initial amount of drug in the solution, most of the times it is equal to zero, Ko is the zero order release rate constant [13].

First order equation:
$\ln Q_t = \ln Q_o x\ K_1 t$

Where,
Q_t is the initial amount of drug dissolved at time t,
Q_o is the initial amount of drug in the solution; K_1 is the first order release rate constant [14].

Higuchi's equation:
$Q = k_H\ t^{½}$

Where,
Q is the amount of drug released at time t per unit area,
k_H is the Higuchi diffusion rate constant [15].

Korsmeyer- Peppas equation**:**
$M_t/M_\infty = Kt^n$

Where, Mt and M_∞ are the amounts of drug released at time t and infinite time,
k is a constant incorporating structural and geometric characteristics of the device,
'n' is the drug release exponent, indicative of the mechanism of drug release [16].

Stability studies:
An accelerated stability study was conducted for optimized formulations (F-3 and F-6) by storing tablets in amber coloured bottles at 25^0C/60%RH and 40^0C/75%RH. The tablets were evaluated for the physical parameters and *in vitro* drug release from the matrix tablets monthly for three months [17].

Similarity Factor:
The similarity factor (f_2) was used to compare the dissolution profile of each formulation with that of the marketed formulation. In this approach, recommended by the FDA guidance for the industry, when the value is between 50 and 100, the two profiles are nearly identical [18, 19]. The value is determined by the following equation

$$f_2 = 50 + \log \{[1+ (1/n) \Sigma_t=1 * n (R_t - T_t)^2]^{-0.5} *100\},$$

Where, n is the number of dissolution time points,
R_t and T_t are the reference and test dissolution values at time t.

RESULTS AND DISCUSSION

FTIR studies:
Figs. 1 - 3 show the IR spectra of pure drug ambroxol hydrochloride, formulations F3 and F6. The IR spectrum of ambroxol hydrochloride shows peak at3397 due to -OH stretching. The groups of peaks at between 3196, 3281 -NH_2 stretching asymmetric and symmetric. The peak at 3060 may be due to aromatic C-H stretching. The peaks at 2911, 2999 may be due to C-H stretching of CH_2 groups. The peak at 1634 NH bending of -NH_2 groups. The peaks at 1618, 1417, 1450 may be due to C=C ring stretching. The peaks at 1440, 1350 maybe due to C-H bending of CH_2 groups. The peak at 1240 is due to -OH bending. The peak at 890 is due to Substituted benzene ring. The peak at 634 may be due to C-Br. From the result, it was clear that as there were no appreciable shifts in the positions of the bands for drug comparison to the spectra of its formulation, clearly suggesting that there was no interaction of the drug with different excipients used in the present study.

Evaluation of granules:
The micromeritic properties of the granules such as bulk density, tapped density, Hausner's ratio and angle of repose for the prepared granules were evaluated and the results were within the limits (Table 2).

Bulk density and tapped density for the granules were within the range of 0.532±0.03-0.689±0.09gm/mL and 0.612±0.01 - 0.776±0.09gm/mL.Compressibility index and Hausner's ratio were in the range of 15.50±0.13% – 17.63±0.19% and 1.14±0.02 - 1.21±0.07. The angle of repose of the formulations was found to be in the range of 21^0±0.42 - 25^0±0.76. Thus, the results obtained confirm that all the formulations exhibited good flow properties and good packing characteristics.

Evaluation of tablets:
The tablets with weight of 350 mg, were obtained and subjected for evaluation of the post compressional parameters such as hardness, friability, weight variation, thickness and drug content uniformity and the results complied with the pharmacopoieal limits of the tablets (Table 3).

The contents of the formulations were found to be uniform, since the amount of the active ingredients in each of the 10 units tested was within the range of 96.15±0.02% - 98.20±0.06% indicating uniform mixing of the drug, binders and other excipients. The mean values for the hardness were found to be in the range of 5.4±0.51 - 5.7±0.46 kg/$cm^2$and all the formulations exhibited friability less than 0.8% during the friability determination.

Evaluation of swelling index of matrix tablets:
The swelling behaviour indicates the rate at which tablets absorb the water from dissolution media and swells. Swelling of matrix tablets increases with respect to time because weight gain by tablets was increased proportionally with rate of hydration up to 4 hrs and matrix appeared swollen almost from the beginning and a viscous gel mass was created after contact with water later on swelling were decreases due to dissolution of outermost gelled layer of tablets. The swelling index of all formulation increases with an increase the concentration of gum in each formulation (Fig.6). Swelling index of tablets prepared from Tara gum and Locust bean gum (F-3 and F-6) with a drug and polymer ratio of 1:3 resulted in better swelling behaviour with respect to concentration. It was observed that drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is the formation of a thick gel layer by matrices around tablets that delays the diffusion and the drug release.

The direct relationship was observed between swelling index and gum concentration, and as gum concentration increases, swelling index was increased. It has observed that swelling index of prepared Matrix tablets F-1 and F-4 contain gum with ratio as (1:1) was less this may attributed to the lower water uptake and less hydrophilicity.

***In- vitro* dissolution studies:**
Ambroxol release from matrix tablets was slow and extended over longer period of time. The results of dissolution studies of formulations F-1 to F-6 are shown in Figs 4 and 5. Drug release from the matrix tablets was found to decrease with increase in drug polymer ratio. Formulation F-1and F-4 composed of drug polymer ratio of 1:1, failed to sustain the drug release over a period of 12 hrs.The formulations F-1 and F-4 were able to sustain the drug release up to 8 hrs. Formulation F-2 and F-5 composed of drug polymer ratio of 1:2 also failed to sustain the drug release over a period of 12 hrs.The formulation F-2 and F-5 were able to sustain the drug release up to 10 hrs.The formulations F3 and F6 containing drug and polymer (Tara gum and Locust bean gum) in the ratios of 1:3, gave slower and complete release of ambroxol over a period of 12 hrs compared to other formulations. It clearly indicates that there is direct relationship between polymer concentration and sustaining of the drug release.

Formulations were prepared from the Tara gum and Locust bean gum as (F-1, F-2 and F-4 , F-5) with ratio as (1:1 & 1:2) was released the drug almost 100% before 12 hrs may be due to rapid swelling and surface erosion of matrix. These gums at this ratio does not develop proper viscous gel layer around tablets hence it allow rapid diffusion of drug in uncontrollable manner which was insignificant to retard the drug release for prolonged period of time.

Matrix tablets were prepared from the Tara gum and Locust bean gum as (F-3 and F-6) with ratio of (1:3) gave slower and complete release of ambroxol over a period of 12 hrs. As the percentage of polymer increased, the kinetics of release decreased. This may be due to changes in the structural reorganization of the polymer and a viscous gel layer is formed, resisting to erosion and the diffusion of the drug is controlled. Failure to generate a uniform and coherent gel may cause rapid drug release.

According to theoretical sustained release profile, an oral controlled release formulation of ambroxol hydrochloride should provide a release of 25.89% in 1 h, 38.81 % in 2 h, 46.65% in 4 h, 74.40 % in 8 h and 100 % in 12 h. The formulations F3 and F6 gave release profile close to the theoretical sustained release needed for ambroxol. The release from the formulations (F-3 and F-6) was also comparable to that of a commercially available SR tablet tested. Initially, a small burst effect in the release of the drug was observed, which was probably sufficient for quick build up of plasma concentration. This burst effect could be due to the highly water soluble drug present in the periphery of the matrix. Subsequently, the release was more uniformly controlled by diffusion from the swelling core of the matrix.

Kinetics and mechanism of drug release:
To ascertain the mechanism of drug release, the *in vitro* drug release data was fitted into various release kinetic models such as Zero order, First order, Higuchi's and Peppas models.

The zero order plots obtained for formulations F1-F6 were linear compared with that of the first order plots and the regression coefficients (r^2) obtained for zero order kinetics were found to be superior when compared with those of first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics(Table 4).

Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. To evaluate the drug release mechanism from the matrix tablets, plots of percent drug released versus square root of time as per Higuchi's equation were constructed and the plot shows linearity indicating that the drug release from the tablets was diffusion controlled. Further, to under stand the drug release mechanism, the data were fitted into to Korsmeyer peppas equation Q = Ktn. In the present study it was observed that the "n" value obtained between (0.534 – 0.570) for all formulations. Therefore both diffusion and erosion mechanism play major role for release of drug from natural gums.

Similarity factor:
The similarity factor (f_2) was calculated in order to compare the release profiles of formulations F3 and F6 with that of the reference formulation. The formulations F3 and F6 had a profile similar to the commercial formulation with similarity factors f_2 = 51.5 and 51.3 respectively, hence these formulations were comparable with that of the marketed formulation.

Stability study:
The optimized formulations such as (F-3 and F-6) were further evaluated for stability studies. It was suggested that there was no changes in physical parameters like hardness, thickness, weight variation and content uniformity. *In vitro* release profile of optimized formulations such as (F-3 and F-6) were shown in Figs.7 and 8.The release of drug from matrix tablets were not affected by storing of tablets for 3 months. Thus the formulations were stable at given conditions of temperature and humidity for 3 month period of time.

Table 1. Composition of Controlled Release Formulations of Ambroxol Hcl Matrix Tablets

S.No.	Ingredients (mg/tab)	Formulations					
		F1	F2	F3	F4	F5	F6
1	AmbroxolHcL	75	75	75	75	75	75
2	Tara gum	75	150	225	--	--	--
3	Locust bean gum	--	--	--	75	150	225
4	DCP	186	111	36	186	111	36
5	PVP k-30	10	10	10	10	10	10
6	Talc	2	2	2	2	2	2
7	Mg Stearate	2	2	2	2	2	2
8	Drug: Gum ratio	1:1	1:2	1:3	1:1	1:2	1:3
Total Weight		350	350	350	350	350	350

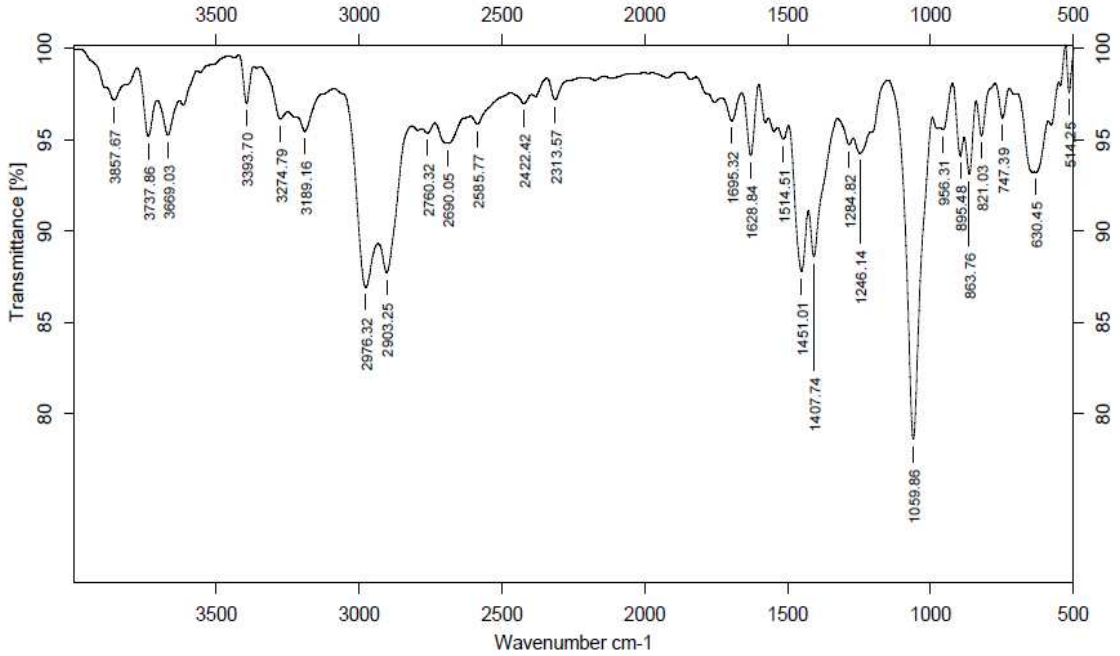
Table 2. Precompressional Parameters of Various Controlled Release Matrix Tablet Formulations by Wet Granulation Technique

Formulation	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.576 ±0.08	0.654 ±0.05	16.07 ±0.14	1.18 ±0.01	21.5 ±0.27
F2	0.532 ±0.03	0.612 ±0.01	15.90 ±0.11	1.17 ±0.12	25 ±0.76
F3	0.569 ±0.01	0.636 ±0.01	15.50 ±0.13	1.19 ±0.05	21 ±0.42
F4	0.592 ±0.07	0.664 ±0.06	16.67 ± 0.09	1.21 ±0.07	22 ±0.95
F5	0.657 ±0.05	0.743 ±0.05	16.07 ±0.13	1.16 ±0.03	23 ±0.63
F6	0.689 ±0.09	0.776 ±0.09	17.63 ±0.19	1.14 ±0.02	24 ±0.44

Table 3. Post Compression Parameters of Matrix Tablets of Ambroxol Hcl by Wet Granulation Technique

Formulations mg/tab	Hardness (Kg/cm^2)	Friability (%wt. loss)	Weight variation (mean ± SD)	Thickness (mm)	Drug content (mg/tab)
F1	5.5±0.95	0.62±0.04	348.02±2.4	3.46±.01	96.15±0.02
F2	5.6±0.63	0.66±0.02	346.02±3.2	3.35±.12	97.23±0.06
F3	5.4±0.51	0.64±0.01	348.04±1.2	3.58±.05	97.14±0.04
F4	5.5±0.45	0.59±0.03	344.08±2.4	3.44±.07	96.54±0.04
F5	5.7±0.46	0.59±0.04	346.05±2.3	3.96±.03	97.26±0.02
F6	5.4±0.51	0.62±0.02	348.05±2.1	3.38±.02	98.20±0.06

Fig 1. FTIR Spectrum of Pure Drug Ambroxol Hydrochloride



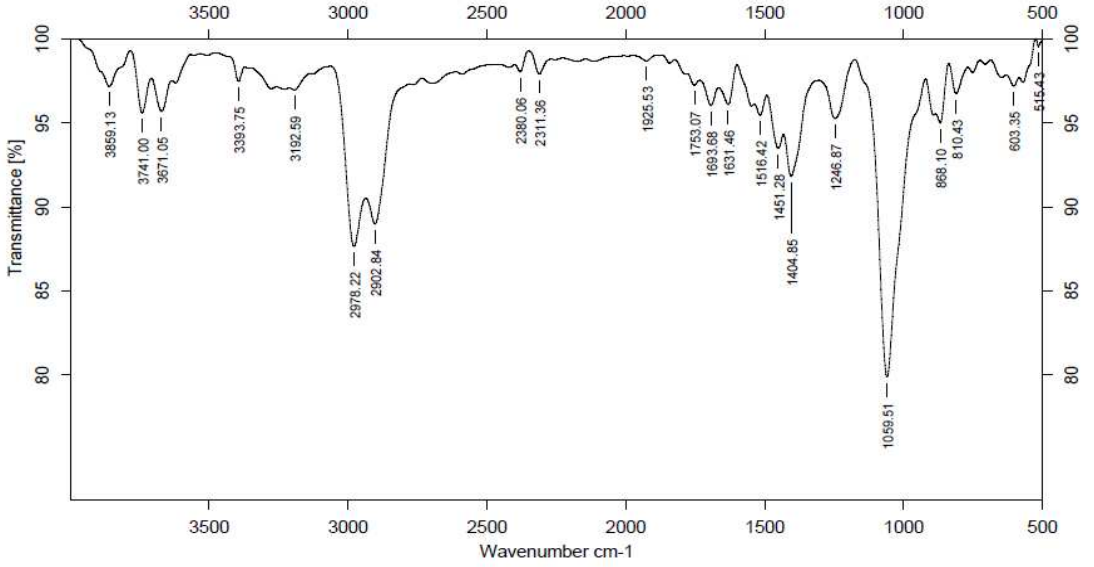


Fig 2. FTIR Spectrum of Formulation F3

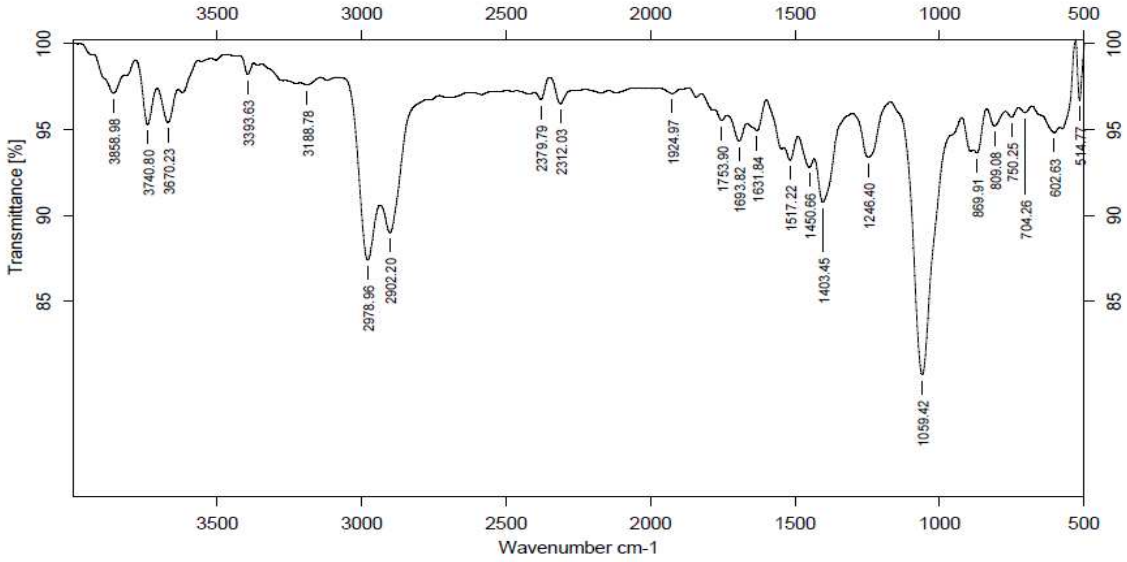


Fig 3. FTIR Spectrum of Formulation F6

Table 4. In-***vitro*** **Drug Release Kinetics:**

Formulation	Zero order r^2	First order r^2	Higuchi r^2	Peppas 'n'
F1	0.949	0.921	0.995	0.534
F2	0.962	0.840	0.981	0.567
F3	0.983	0.866	0.981	0.561
F4	0.968	0.899	0.991	0.568
F5	0.971	0.834	0.992	0.570
F6	0.991	0.844	0.984	0.557

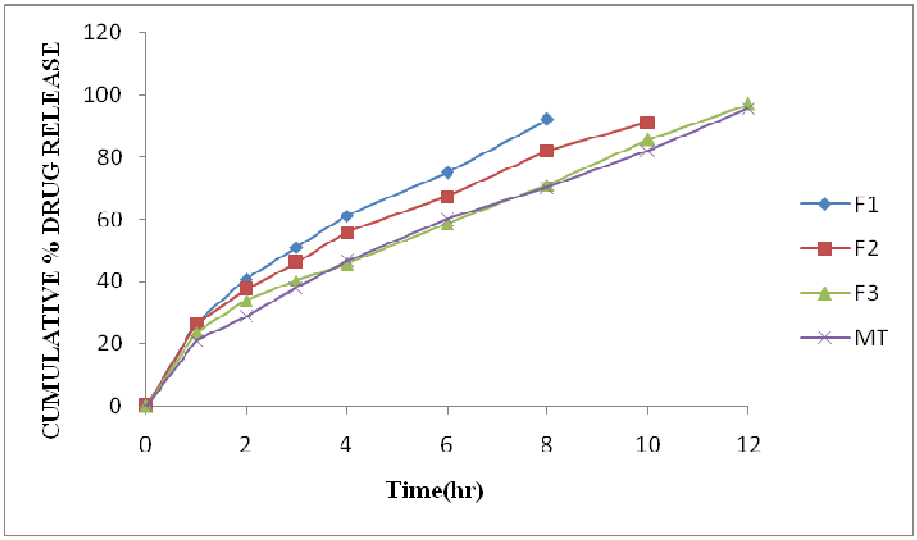


Fig 4. Cumulative Percent Drug Release Profiles of Formulations Prepared F1, F2, F3 and Marketed Product (n=3)

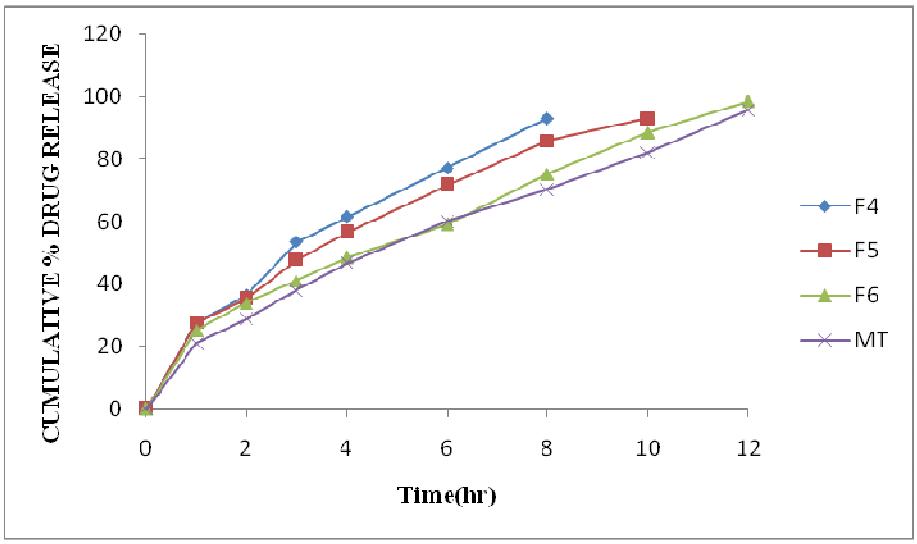


Fig 5. Cumulative Percent Drug Release Profiles of Formulations F4, F5, F6 and Marketed Product (n=3)

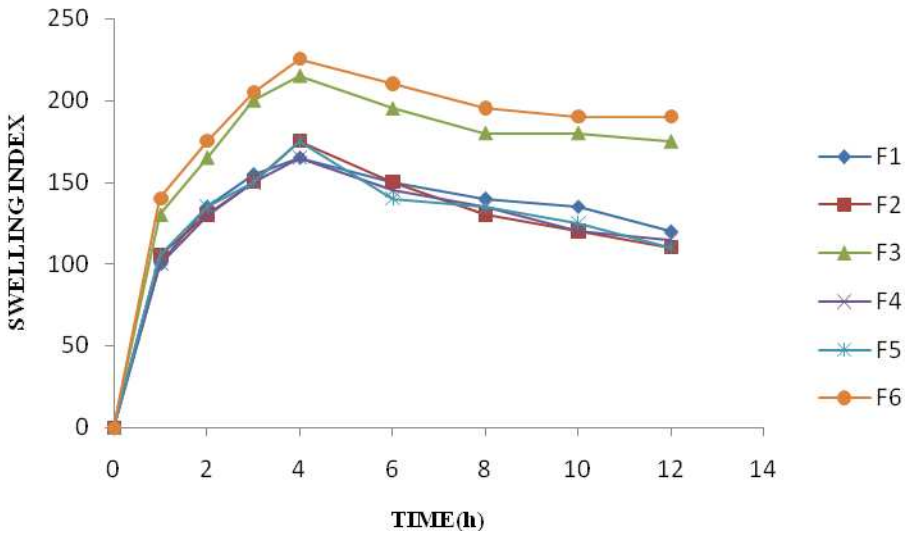
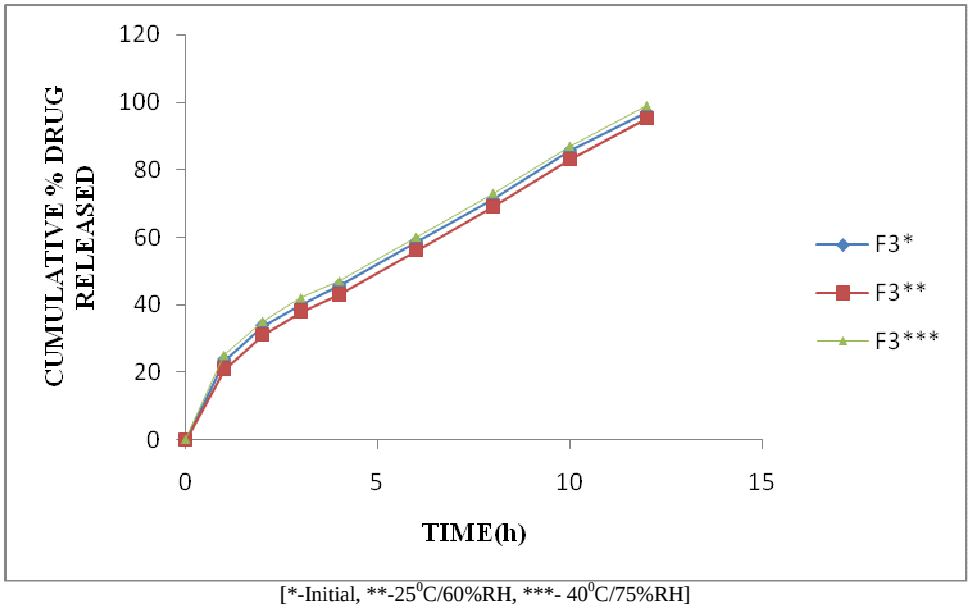
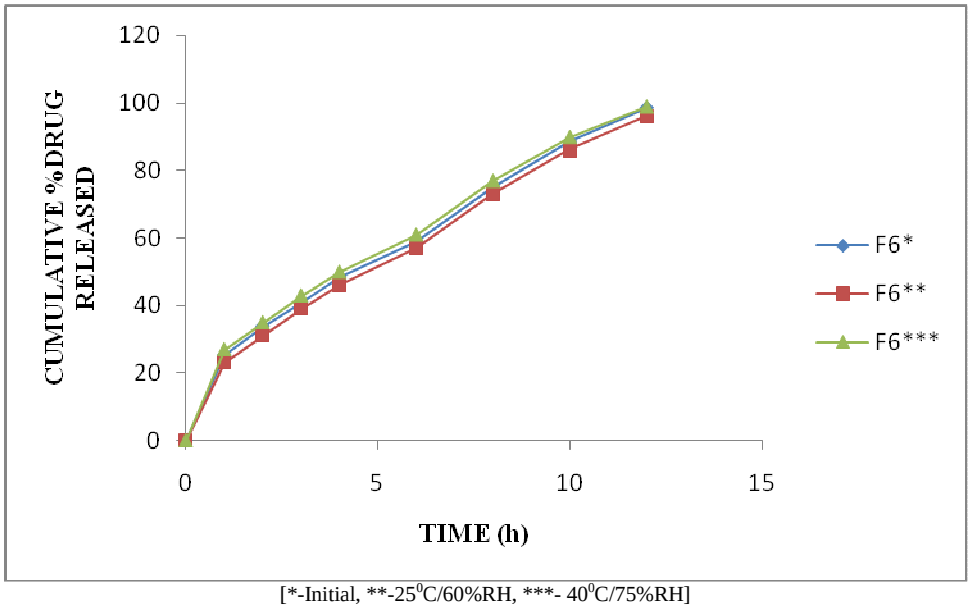


Fig 6. Swelling Behaviour of Formulations F1 – F6 (n=3)



[*-Initial, **-25^{0}C/60%RH, ***- 40^{0}C/75%RH]

Fig 7. In vitro release profile of Ambroxol hydrochloride from the matrix tablets (F3) after stability studies (n=3)



[*-Initial, **-25^{0}C/60%RH, ***- 40^{0}C/75%RH]

Fig 8. In vitro release profile of Ambroxol hydrochloride from the matrix tablets (F6) after stability studies (n=3)

CONCLUSION

The aim of the present study was to design and evaluate gum based matrix tablets of ambroxol hydrochloride with Tara gum and Locust bean gum for controlled delivery and to assess the kinetics of drug release mechanism. The study revealed that the release followed Non-Fickian diffusion (anomalous transport) which includes coupling of diffusion and erosion mechanisms. The ratio of drug and polymer played an important role in overall release of the drug and the formulations prepared by wet granulation technique containing drug and polymer in the ratio 1:3 showed drug release profiles similar to that of the marketed formulation and they were stable after storage at 25^{0}C/60%RH and 40^{0}C/75%RH conditions for a period of three months. Results of the present study demonstrate that both the Tara gum and Locust bean gum could be suitable candidates for formulating controlled release matrix tablets of ambroxol hydrochloride.

Acknowledgements
The authors are thankful to the Principal and management of Siddhartha Academy of General And Technical Education, Vijayawada, for their support and cooperation in carrying out the research work.

REFERENCES

[1] Saleh M. Yellela SR. Krishnaiah YS. *AAPS PharmSciTech* .**2005**, 6 (1), E14- E21.
[2] Khullar P, Khar RK, Agarwal SP. *Drug Dev Ind Pharm*. **1998**,24, 1095-9.
[3] Nokano M, Ogata A. *Ind. J. Pharm. Sc.* **2006**, 68(6), 824- 826.
[4] Colombo P, Bettini R, Peppas NA. *J.pharm sci*.**1985, 84,991**-997.
[5] Amelia M. Avachat, Rakesh R. Dash and Shilpa N. Shrotriya. Indi*an Journal of Pharmaceutical Education and Research*.**2010**, 90.
[6] Choudary KPR, Mohapatra P. *Indian J.Pharm.Sci*.**2006**, 68(4), 497-500.
[7] Sweetman C, Eds., In; Martindale, The complete drug reference, The Pharmaceutical press, **London**. **2006**, 1084.
[8] Robinson JR, Eriksen S.P. *Journal of pharmaceutical sciences*. **1966**, 55, 1254-1263.
[9] Ganesan V, Jayachandran D. L. *Research J. Pharm. and Tech*. **2008**, 1, 507-512.
[10] Gupta A.K Introduction to pharmaceutics, 2nd edition, CBS publications; New Delhi **1991**,270
[11] Leon Lachman, Herbert A. Lieberman, Joseph L.Kanig. The Theory and Practice of Industrial pharmacy, 3rd Edition, Varghese publishing house, **1987**, 296-300.
[12] Shah V.P, Tsong Y, Sathe P, Liu *J. Pharm. Res*. **1998**, 15,889-896.
[13] Brazel C.S, Peppas N.A. *Eur.J.Pharm.Biopharm*. **2000**, 49, 47-58.
[14] Lapidus H, Lordi N. G. *J.Pharm.Sci*. **1966**,55,840-843.
[15] Higuchi T, *J.Pharm.Sci*. **1963**,52,1145-1148.
[16] Korsmeyer R.W, Gurny R, Doelker E, Buri P, Peppas N.A, Mechanism of solute release from porous hydrophilic polymers, *Int. J. Pharm*. **1983**,15, 25-35.
[17] Mathews BR. Regulatory aspects of stability testing in Europe. *Drug DevInd Pharm*. **1999**, 25,831-856.
[18] Shah V.P, Tsong Y, Sathe P, Liu J . *Pharm. Res*. **1998** 15,889-896.
[19] Moore J.W, Flanner H. H. *Pharm. Technol*. **1996**, 20, 64-74.