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Research Article

FORMULATION AND EVALUATION OF GUM OLIBANUM-BASED SUSTAINED RELEASE MATRIX TABLETS OF AMBROXOL HYDROCHLORIDE

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ABSTRACT

Ambroxol hydrochloride was designed as a hydrophilic matrix sustained release tablet employing gum olibanum and the sustained release behavior of the fabricated tablets was investigated. Sustained release matrix tablets containing 75mg Ambroxol hydrochloride were formulated using natural polymer like gum olibanum in different drug: polymer ratios, such as F1(1:1), F2(1:1.5), F3(1:2) by wet granulation technique. Microcrystalline cellulose was used as diluent. All the lubricated formulations were compressed using 7mm flat faced punches. The formulation was optimized on the basis of acceptable tablet properties, *in vitro* drug release and similarity with marketed sample. The prepared granules were evaluated for angle of repose, bulk density, compressibility index, Hauser ratio and drug content. The resulting formulations showed optimum hardness, good weight uniformity, uniform thickness and low friability. The results of *in vitro* dissolution studies indicated that all the formulations exhibited good drug release pattern. The data was fitted to various kinetic models to know the mechanism of drug release. The optimized Ambroxol hydrochloride matrix tablets [F2] were packed in glass bottle and subjected to short term stability studies which were carried out at 45°C with 75% RH for 45 days revealed that no considerable differences in drug content, dissolution, $T_{50,}$ and T_{90} were observed. Present work indicates that utility of gum olibanum in the formulations of sustained release dosage forms.

Keywords: Matrix tablets, Ambroxol hydrochloride, Gum olibanum, *In vitro* drug release

INTRODUCTION

There has been a progressive and divergent study on the use of naturally occurring biocompatible polymeric materials in the designing of dosage forms for oral controlled release administration [1-3]. Gums of natural sources are biodegradable and non-toxic, which hydrate and swell on contact with aqueous media; and these have been used for the preparation of single unit dosage forms[4]. Gum Olibanum[5] dried, gummy exudation obtained from various species of Burseraceae trees. Its composition and chemical characteristics depends on its three principal origins : Aden/Somalia, Eritrea, and India which contains approximately 5-9% oil content, 13-17% resin acids, 20-30% polysaccharides, 40-60% boswellic acid. In the classical Indian medicine, gum olibanum is used as an anti-inflammatory remedy and recent studies have found positive influence of olibanum on rheumatism.

Ambroxol a metabolite of bromhexine with similar actions and uses[6] is official in Martindale Extra pharmacopoeia.[7] Chemically it is trans-4-[(2-Amino-3,5-dibromobenzyl) amino]-cyclohexanol. From decades it has been used successfully in its hydrochloride form as a mucolytic and as an expectoration improver for the treatment of acute and chronic diseases characterized by thick or excess mucous. So it is preferred for a variety of respiratory infections like bronchitis and bronchial asthma.[8-9] A short biological half-life of 4hr[10] calls for a frequent daily dose of 30mg 3-4 times a day. [11] Therefore it necessitates for the design of sustained release dosage form to prolong clinical efficacy, minimize side effects and to reduce dosing.

MATERIALS AND METHODS

Ambroxol hydrochloride was a gift sample from Sree Sai Organics Pvt.ltd., Kondapalli, Vijayawada. Gum olibanum, was obtained from Girijan co-operative corporation Ltd, Visakhapatnam. Other materials used were of analytical grade, and procured from commercial sources.

Estimation of Ambroxol hydrochloride

Ambroxol hydrochloride in pure form and in developed formulations were spectrophotometrically estimated using Shimadzu Pharmaspec UV-1700 UV-Visible spectrophotometer at 248 nm in a pH 1.2 buffer, and pH 6.8 phosphate buffers in the present study. [12]

Preparation of Ambroxol hydrochloride matrix tablets

Different matrix embedded formulations of Ambroxol hydrochloride were prepared by wet granulation technique using natural polymer such as gum olibanum. MCC (Avicel pH101) was used as a diluent and starch as a binder. The total weight of tablets varies from 205 to 280mg. The composition of each tablet is shown in **table 1**.

Table 1: Composition of Ambroxol hydrochloride matrix tablets

Batch No	Drug	Gum Olibanum	Avicel pH 101	Starch	Talc	Mg stearate	Total weight
F1	75	75	38.75	10.25	4	2	205
F2	75	112.5	35	12.5	5	2.5	242.5
F3	75	150	32.6	14	5.6	2.8	280

*Each quantity in mg

All the powders were screened through 80mesh. Required quantities of drug and polymer were mixed thoroughly and a sufficient volume of granulating agent (propan-2-ol : water) in the ratio of 1:1 was added slowly. After enough cohesiveness was obtained, the mass was passed through sieve no #16 mesh and were dried at 50°C in hot air oven till constant weight was obtained.

The dried granules were then passed through sieve no16#. Talc and magnesium stearate were finally added as glidant and lubricant. Compression was done on 16-station rotary-punch tablet compression machine (Cadmach, Mumbai, India) with an average hardness of 6-8Kg/cm^2 for all the tablets. Prior to compression the granules were evaluated for several tests.

Evaluation of granules

Flow properties of granules

Flow properties of the prepared granules of all the formulations were determined by angle of repose, loose bulk density (LBD) and tapped bulk density (TBD), Compressibility Index, Hauser Ratio.

Drug content in granules

Accurately weighed quantities of powdered granules (75mg) of Ambroxol hydrochloride were extracted with water and the solution was filtered through 0.45-µ membrane. After suitable dilution the absorbance was measured at 248nm.

Loss on drying and moisture content

Loss on drying and Moisture content were measured by placing 1gm of granules in an oven which was maintained at 105°C and dried up to constant weight and were calculated using the formula.

Loss on drying = Initial weight - Final weight/Initial weight x 100

Moisture content = Initial weight - Final weight/Final weight x 100

Table 2: Physical properties of granules formulated with Gum Olibanum*

Batch	Angle of Repose	LBD(g/ml)	TBD(g/ml)	CI (%)	HR	DC (%)	MC (%)	LOD(%)
F1	26.87±0.04	0.40±0.05	0.47±0.04	14.89±0.02	1.17±0.04	97.88±0.04	6.2±0.1	5.8±0.2
F2	27.43±0.03	0.49±0.02	0.55±0.03	10.90±0.02	1.12±0.03	100.09±0.03	6.5±0.5	6.1±0.3
F3	25.15±0.03	0.53±0.03	0.61±0.06	13.11±0.05	1.35±0.05	98.61±0.04	6.9±0.3	6.5±0.4

* All the values are expressed as mean ±SE, n=5

Evaluation of compressed tablets

The evaluations of developed matrix tablets for General appearance, thickness, hardness, weight variation, friability and drug content have been done according to IP specifications. [13]

In weight variation test 20 tablets were selected randomly and average weight was calculated using an electronic balance, then individual tablets were weighed and the weight was compared with the average weight. Tablet hardness was determined for 5 tablets using a Monsanto tablet hardness tester. Friability of the tablets was determined using Roche friabilator. 10 tablets were preweighed and placed in friabilator subjecting for 100 rotations for 4 minutes at 25rpm. Tablets were dedusted using a soft muslin cloth and reweighed and then % friability was calculated. For determining the drug content, three tablets from each of the formulations were crushed and powder containing 75 mg of Ambroxol hydrochloride was dissolved in 75 ml of phosphate buffer pH 6.8. From this 10 µg/ml, equivalent solutions were prepared and drug content of Ambroxol hydrochloride was determined by measuring the absorbance of samples at 248 nm using UV/Visible spectro-photometer. The physicochemical properties of designed tablets are shown in **tables 3.**

Table 3: Physical properties of tablets formulated with Gum Olibanum*

Batch No	Wt in mg	Hardness(Kg/cm^2)	Thickness(mm)	Friability (%)	DC (%)
F1	204.2±0.07	7.1±0.6	3.46±0.02	0.49±0.02	99.32±0.07
F2	241.8±0.09	6.8±0.8	3.75±0.08	0.53±0.08	98.43±0.03
F3	277.1±0.04	6.9±0.4	3.95±0.05	0.57±0.05	96.78±0.09

* All the values are expressed as mean ±SE, n=5

***In vitro* drug release studies**[14]

The *in vitro* dissolution studies for the formulated matrix tablets were conducted for a period using USP apparatus type II (paddle) at 100 rpm. The dissolution medium (900 ml) consisted of 0.1N hydrochloric acid for the first 2 hours and the phosphate buffer pH 6.8 up to 12 hours, maintained at 37± 0.2°C. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain sink conditions. After filtration and appropriate dilution, the samples were analyzed spectro-photometrically at 248 nm using a UV-visible spectro-photometer and cumulative percent drug release was calculated. The study was performed in triplicate. The commercial Ambroxol SR capsules were used as the reference formulation, and were also subjected to *in vitro* drug release studies.

Calculation of similarity factor (f_2) [15]

Similarity factor (f_2) is the measurement of similarity of two different dissolution curves. When f_2 value is greater than 50, the curves are similar. The value is determined by the equation $f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} *100\}$, where n is the number of dissolution sampling times, and R_t and T_t are the individual or mean percent dissolved at each time point for the reference and test dissolution profiles respectively.

Swelling or water uptake studies[16]

The rate of test medium uptake by the polymer was determined by equilibrium weight gain method. The swelling behaviour of the optimized formulation was studied. Initially tablet was accurately weighed (W_0), At predetermined time intervals (15,30,45,60,90,120,180,240min) tablets were removed from the petridish and lightly blotted with tissue paper to remove excess test liquid and then reweighed on an analytical balance (W_1).The experiment was performed in triplicate for each time point and fresh samples were replaced for each individual time point. The % increase in weight due to absorbed liquid or water uptake was estimated at each time point from the following equation:

$$\% \text{ Weight change} = W_1 - W_0 / W_0 \times 100$$

Stability studies [17]

To determine any change in *in vitro* drug release profile on storage, short term stability study was performed at 45^{0}C over a period of 45 days on the matrix tablet formulation (F2). Sufficient number of tablets (20) were packed in amber-colored screw capped bottles and kept in oven maintained at 45^{0}C. At the end of 45 days period, tablets were also evaluated for change in hardness, drug content and *in vitro* release pattern.

RESULTS AND DISCUSSION

FTIR studies

The FTIR studies of pure Ambroxol hydrochloride, pure gum olibanum, and optimized formulation F2 were carried out to study the interaction between the drug and polymer used. The results are shown in **figures 1.** The comparision of IR spectra of the pure drug and its formulation F2 revealed that there is no shift of positions of the bands in both the spectra which clearly indicate that there is no interaction between the drug, polymer and any other excipients used for the study.

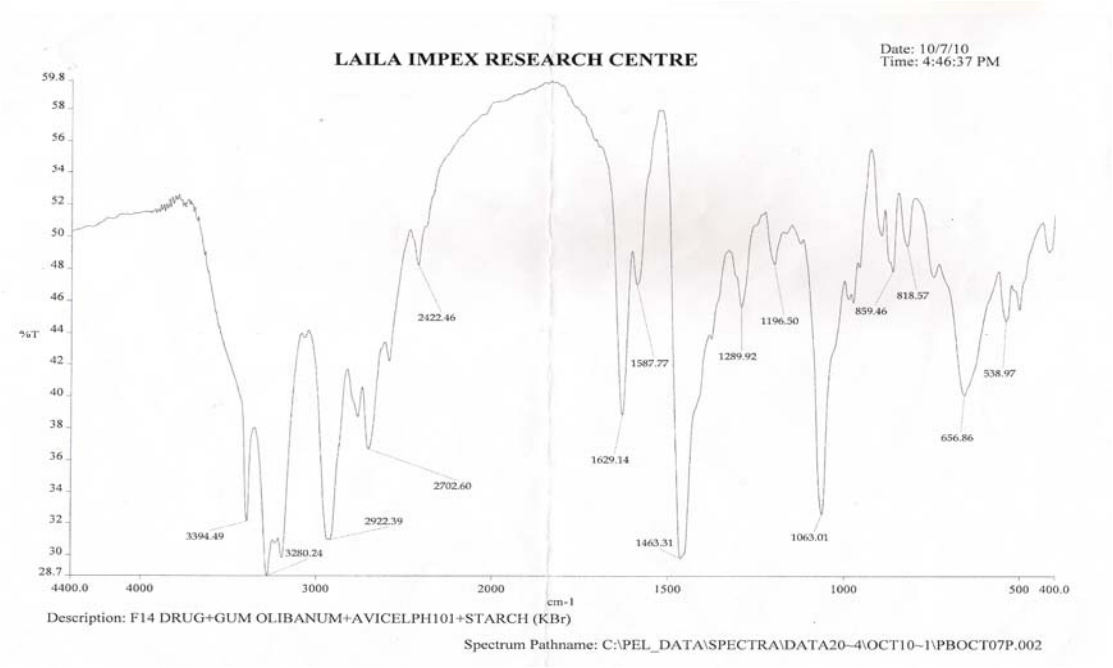

Fig. 1: IR Spectra for F2 matrix tablets

Physical properties of granules

The prepared granules of the different formulations were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD) and compressibility index (CI), Hauser ratio given in **table 2**. For all the formulations angle of repose for the granules was found to be in the range of 25-30° for which the flow was found to be excellent. Based on the CI for the formulations F1, F2 and F3 the flow was good. Based on the Hauser ratio for the formulations F1, F2 the flow was good and for F3 the flow of granules was poor.

Physical properties of tablets

The prepared tablets were tested for physical parameters like weight variation, hardness, friability, content of active ingredient. The results of all these evaluation are tabulated in the **table 3.** The results obtained were within the prescribed limits.

***In-vitro* release studies**

The release of Ambroxol hydrochloride from the matrix tablets was sustained up to 12hrs. F2 was optimized among the three formulations as it showed 99.30% drug release for 12th hour and it was found that the % drug release was maximum with 1:1.5 drug: polymer concentration and also F2 gave the release profile close to the commercially available marketed sample of Ambroxol HCl (MS) which has a similarity factor of 78.58 shown in **table 5.**

The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. This may be due to changes in the structural reorganization tortuosity or gel strength of hydrophilic gum polymers. Failure to generate a uniform and coherent gel may cause rapid drug release.

The release data of matrix tablets were fitted into various mathematical models (Zero order, First order, Higuchi equation and Korsmeyers equation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation co-efficient(r) value in various models. The model that gives high "r" value is considered as the best fit of the release data. The "r" values for zero order, first order, Higuchi model and Korsmeyers plot are given in the **table 4.** These results indicate that the drug release from F1 and F3 matrix tablets followed first order kinetics but the formulation F2 followed Zero order kinetics.

To evaluate drug release mechanism from the tablets, plots of percent released versus square root of time as per Higuchi's equation were constructed. F1 and F3 formulations show better linearity for Higuchi release kinetics with (r^2>0.97) which indicates that the drug release is by diffusion mechanism. But F2 with (r^2<0.97) which indicates that the drug release is by erosion mechanism.

The dissolution data was fitted to Korsmeyer equation which is used to describe the drug release behaviour from polymeric systems. Plots of Log cumulative percent drug release versus log time gives r^2 values. The values of n<0.45 indicates Fickian release, >0.45 but <0.85 indicates Non-Fickian release. All the formulations showed diffusion co-efficient value (n) greater than 0.45 but less than 0.85 after fitting to the Korsmeyer equation as shown in the **table 4.** So, it indicates Non-Fickian transport mechanism. Therefore the drug release is by diffusion and erosion mechanism.

Table 4: Release kinetics of Ambroxol hydrochloride matrix tablets formulated with gum Olibanum

Batch No	Release model								T_{50} (hrs)	T_{90} (hrs)
	Zero order		Firstorder	Higuchi			Koresmeyer-Peppas			
	r	k	r	r	k	n	r	k		
F1	0.9436	7.0605	0.9958	0.9861	20.3690	0.6940	0.9967	13.9380	5.8	14.8
F2	0.9800	9.2730	0.9886	0.9678	26.3936	0.7959	0.9981	14.5517	4.7	10.0
F3	0.9703	7.8168	0.9953	0.9787	21.5137	0.7256	0.9990	13.7014	5.8	13.2

Table 5: Similarity factor of Ambroxol hydrochloride matrix tablets formulated with Gum olibanum (F2) and MS (f_2=78.58)

S.no	Time	Average	% Drug release	Reference	Test	f_2	MDT(T) / MDT(R)	AUC(T) /AUC(R)
1	0	0.000	0.000	0.000	0.000	0.000		
2	0.5	6.25	8.76	84.59	1.000	1.400		
3	1	13.59	14.28	87.21	0.853	1.218		
4	1.5	18.72	19.16	89.08	0.901	1.117		
5	2	22.69	23.02	90.45	0.926	1.076		
6	3	33.35	36.60	85.11	1.029	1.070		
7	4	39.79	45.15	77.94	1.051	1.089		
8	5	56.02	52.28	76.71	0.865	1.064		
9	6	58.78	63.26	75.07	1.033	1.047		
10	7	76.42	73.36	75.02	0.922	1.038		
11	8	79.39	78.97	75.93	0.966	1.024		
12	9	85.35	84.25	76.64	0.962	1.018		
13	10	90.35	89.19	77.27	0.967	1.012		
14	11	93.86	94.42	77.94	0.994	1.010		
15	12	99.06	99.31	78.58	0.991	1.009		

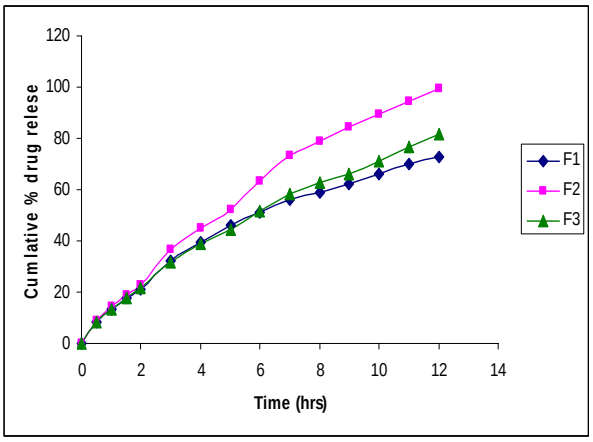

Fig. 2: Dissolution profiles of Ambroxol hydrochloride matrix tablets formulated with gum Olibanum

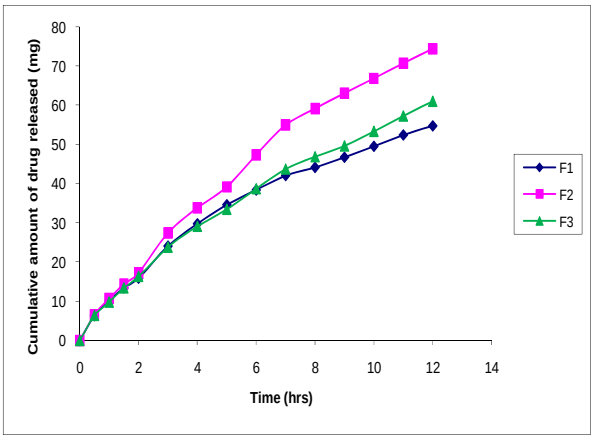

Fig. 3: Zero order plot of Ambroxol hydrochloride matrix tablets formulated with gum Olibanum

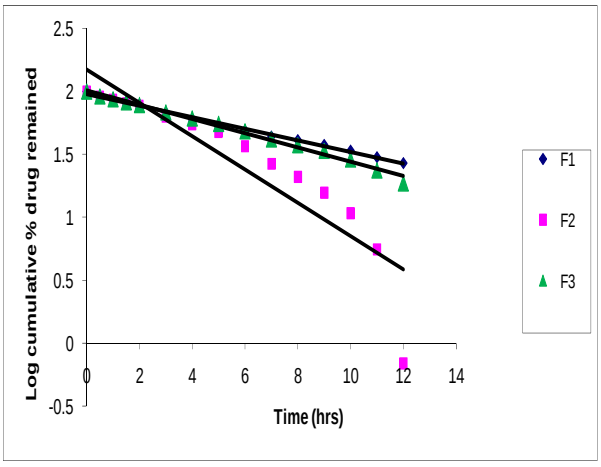

Fig. 4: First order plot of Ambroxol hydrochloride matrix tablets formulated with gum Olibanum

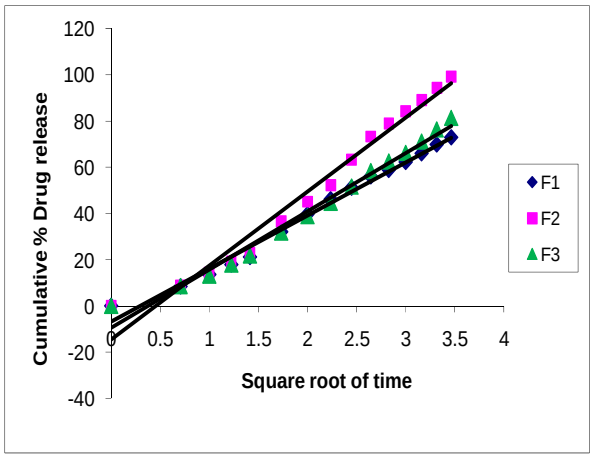

Fig. 5: Higuchi plot of Ambroxol hydrochloride matrix tablets formulated with gum Olibanum

Swelling index

The swelling index of the optimized formulation F2 was found to be 73.45%. Plastic viscosity was found to be 0.35.

Stability studies

The short term stability studies were carried out for F2 formulation at 45°C with 75% RH for 45 days revealed that no considerable

differences in drug content, dissolution, T_{50}, and T_{90} were observed. The results were shown in **table 6.**

Table 6: Stability studies of optimized formulation

Time(hrs)	% drug release from F2				
	Before storage	After storage	T_{50}(hrs)	T_{90}(hrs)	DC (%)
0	0.000	0.000			
0.5	8.75±0.7	8.36±0.3			
1	14.28±0.8	13.64±0.6			
1.5	19.15±0.4	18.76±0.2			
2	23.01±0.4	23.32±0.6			
3	36.60±0.6	37.13±0.6			
4	45.14±0.8	45.46±0.1			
5	52.28±0.2	53.72±0.7	4.6	10.1	99.85
6	63.26±0.5	62.99±0.5			
7	73.35±0.2	74.06±0.8			
8	78.97±0.1	79.02±0.3			
9	84.25±0.7	85.74±0.9			
10	89.19±0.9	88.78±0.8			
11	94.42±0.5	94.44±0.3			
12	99.30±0.2	98.92±0.5			

CONCLUSION

The approach of the present study was to make an evaluation of gum olibanum based matrix tablets of Ambroxol hydrochloride for sustained delivery and to assess the kinetics of drug release mechanism. The study reveals that, the release of exhibited diffusion and erosion mechanism. The ratio of drug and polymer plays an important role in overall release of the drug and the formulated gum olibanum matrix tablets with drug: polymer 1:1.5 offered comparative release profile with that of marketed formulation.

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