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DESIGN AND EVALUATION OF ORAL CONTROLLED RELEASE MATRIX TABLETS OF AMBROXOL HYDROCHLORIDE BY USING ALMOND GUM AS RETARDING POLYMER

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ABSTRACT

The objective of the present investigation was to design and evaluate the oral controlled release matrix tablets of Ambroxol hydrochloride by using hydrophilic natural polymer such as Almond Gum. Almond gum is a polysaccharide exudate obtained from the trunk of the tree *Prunusamygdalus* (Family: Rosaceae). After purification, the yield of the hydrogel was 71.64% w/w. The total microbial load of the selected polysaccharide hydrogel (Almond gum) is within specified limits for natural excipients and the pathogenic organisms were found to be absent. Hence, the selected hydrogel had promising properties for application as multifunctional excipient. The almond gum up to 1000 mg/kg did not cause any mortality in mice. 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 and DSC studies revealed that there was no chemical interaction between drug and excipients. Among different formulations, F4 which contain Almond gum with drug: polymer ratio as (1:2) 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 first order release kinetics and Korsmeyer and Peppas equation gave release pattern with values of (n = 0.520 – 0.735) indicating non-fickian or Anomalous type of diffusion takes place through matrix of Almond gum. These studies show Almond gum is the best natural binder used as a release modifier.

KEY WORDS

Controlled Release, Almond Gum, Acute toxicity studies and Ambroxol Hcl.

INTRODUCTION:

When addressing the need for novel oral controlled release technologies, the time and costs associated with the process of drug development should be taken into account today, the total time of the drug discovery and development process of a new NCE drug generally exceeds 10 years and the development costs have rapidly increased over the last decade. Therefore, line extensions of successful first-generation products form an interesting alternative for the pharmaceutical industry. The development costs and risks associated with the development of line extensions are substantially lower as compared to NCE drugs. For the generic industry, controlled release technologies based on cheap excipients and cost-effective manufacturing processes provide an interesting option as generic products bioequivalent to high priced originators may be produced at low costs. From this point of view, new excipients of natural origin or synthetic materials with proven biological safety form an interesting class of materials. Among the synthetic hydrophilic polymer considered as release retardant but these polymers are

quite expensive, and biodegradability is questionable when compared with natural polymers[1]. 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[2].

Almond gum is a polysaccharide exudate obtained from the trunk of the tree *Prunusamygdalus* (Family: Rosaceae). This gum hydrolyzes into L-arabinose (4 parts), D-xylose (2 parts), D-galactose (3 parts) and D-glucouronic acid (1 part). Aldobiouronic acid is also present in this gum[3]. The gum is non- toxic and is used in pharmaceutical and food industries as an alternative to gum tragacanth. It is reported as a release modifier in sustained release spheroids.

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 inthe 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[4].

MATERIALS AND METHODS

MATERIALS:

Ambroxol hydrochloride was obtained from Darwin Laboratories Pvt. Ltd., Vijayawada and Andhra Pradesh, India. Almond gum was obtained from Girijan Corporation Ltd., Vizag. PVP K-30, DCP, Magnesium Stearate, Talc was obtained from S.D. Fine Chem. Ltd., Mumbai. All other ingredients used throughout the study were of analytical grade.

METHODS:

PURIFICATION OF ALMOND GUM

The crude almond gum was cleaned by removing extraneous materials by hand pricking, breaking and sieving. The gum was dried in an oven at 60ºC for about 10 hours until it became sufficiently brittle. The dried gum was then sorted into two grades, light coloured grade and dark coloured grade. The light coloured grade was selected for further processing by grinding in a porcelain mortar into fine powder.To purify the gum 500 g of the crude gum powder was dissolved in 1000 ml of hot distilled water and allowed to stand for 24 hours with intermittent stirring as the gum was very soluble in water. Mucilage was re-filtered to ensure that all debris was removed. The filtered mucilage was purified by precipitating the gum out with 96 % ethanol. About 1200 ml of 96 % ethanol was used to precipitate 500 g of the gum, the precipitated gum was filtered and washed with diethyl ether and dried in the hot air oven at 60ºC for about 8 hr. The dried purified gum was milled and sieved through sieve number 80. The powdered gum was used in subsequent test and analysis as purified almond gum[3].

MICROBIAL LIMIT TESTS FOR ALMOND GUM

As almond gum which is used in the present research work is of natural origin, it should have microbial load within specified limits. For assessing the safety of excipients of natural origin compliance with GACP (General approach- compliance with good practice guidelines) and GMP is crucial. So, following tests were performed to assess that whether almond gum is within microbial limits or not according to Indian Pharmacopoeia[5, 6].

Total viable count (TVC):

In this test, microbial test in terms of cfu/g of bacteria and fungi for the almond gum was carried out. Here pour plate method was followed using phosphate buffer pH 7.2 or buffered sodium chloride-peptone solution pH 7.0. Usually a maximum permitted level is set where; TVC does not exceed the limit level.

PROCEDURE:

A. Pre-treatment of test material:

1mg/ml concentration of 10ml almond gum solution was suspended in lactose broth and diluted to 100ml with same medium (Almond gum was insoluble in water). A suitable surfactant, such as a solution of polysorbate20R (1mg/ml) was added to aid dissolution.

B. Plate count method (pour plate method):

For bacteria:

Using petri dish of 9-10cm diameter and to each dish, a mixture of 1ml of pre-treated material and about 15ml of liquefied *soya bean casein digest medium* was added at temperature not exceeding 45^{0}C and incubated at 30-35^{0}C for 48-72hrs.The number of colonies formed were counted and results were calculated using plate with

largest number of colonies up toa maximum of 300 colonies.

For fungi:

Here Petri dish of 9-10cm diameter was used. To one dish, a mixture of 1ml of pre-treated material and about 15ml of liquefied *sabouraud dextrose agar medium* was added at temperature not exceeding 45^{0}C and incubated at 20-25^{0}C for 5 days. The number of colonies formed was counted and results were calculated using petridish with not more than 100 colonies.

Acceptance criteria:

Total aerobic count→ NMT 300cfu/g

Total fungal count→ NMT 100cfu/g

Test for presence of specific microorganisms:

The substances like almond gum which is to be used as excipient in dosage form need to be free from *E. coli, S.typhii, P.aeruginosa, S.aureus* according to I.P.

Acceptance criteria:

Salmonella, P.aeruginosa, S.aureus should not be present.

E. coli→ maximum of 10 per gram of material (Almond gum)

E. coli:

Almond gum of few ml was transferred to lactose broth and incubated at 43-45^{0}C for 18-24hrs.Asub culture was made on a plate with *mac conkey agar* and incubated at 43-45^{0}C for 18-24hrs, observed for growth.

Salmonella species:

10ml of almond gum was taken into 100ml of tetrathionate bile brilliant green broth and incubated at 42-43^{0}C for 18-24 hrs. Subcultures was made on *deoxycholate citrate agar* and incubated at 35-37^{0}C for 24-48 hrs, observed for growth.

Pseudomonas aeruginosa:

Here almond gum was pre-treated with sodium chloride peptone solution,7.0 pH.100ml of soya bean casein digest medium was inoculated into material being examined and incubated at 35-37^{0}C for 24-48hrs.Then, above was sub cultured on a plate of *cetrimide agar* and inoculated at 35-37^{0}C for 24-48hrs, observed for growth.

Staphylococcus aureus:

Here almond gum was pre-treated as in the test for pseudomonas aeruginosa. Then, above was sub cultured in *baird-parker agar*, incubated at 35-37^{0}C for 24-48hrs, observed for growth.

Acute toxicity studies for almond gum:

The adult male albino mice selected for acute toxicity study. Before the actual LD_{50} determination, a pilot study was made on a small group of mice mainly to select the dose ranges for the subsequent study. The almond gum were taken at various doses levels (100, 200, 400, 800, 1000 mg/kg body weight) dissolved in 1 % carboxymethyl cellulose administered 10 ml/kg body weight orally to pairs of mice per dose level. The control animals received 1% carboxymethyl cellulose in distilled water (10 ml/kg) orally. The animals were observed continuously for two hours and then occasionally for further four hours and finally any mortality. Behavior (gross behavior, general motor activity, writhing, convulsion, response to tail pinching, pupil size, fecal output, water intake, feeding behavior, sedation *etc*.) of the animals and any other toxic symptoms also observed for 72 hours and the animals were kept under observation up to 14 days.

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[7]. The zero-order drug release rate constant was calculated by the following equation:

Dt = Dose (1+ (0.693×t)/ t1/2)

Where,

Dt = total dose of drug

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

t1/2 = half-life of the drug (3 hr).

Dt = 19.8 (1+ (0.693×12)/ 3) = 75mg

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

Fourier Transform Infrared Spectroscopy (FTIR) Study:

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra. ATR analysis is less complicated than using KBr pellets, it is fast and a very small amount of the sample is needed.

Differential Scanning Calorimetry(DSC) Study:

The thermal analysis of the samples was carried out in DSC (200; F3 maia, Netzsch, USA). To study the thermal behaviours of Ambroxol Hcl, polymer alone i.e. (Almond gum) and mixture of drug and polymer were placed in sealed aluminium pans and heated at a rate of 10^0C/min at a temperature range of 30 – 300^0C, under a nitrogen flow rate of 20mL/min. Empty aluminium pan was used as reference.

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 [8].

PREPARATION OF MATRIX TABLETS BY WET GRANULATION METHOD:

Ambroxol hydrochloride-controlled release tablets were prepared by wet granulation technique. Different formulations containing Ambroxol hydrochloride was prepared using PVP K-30 as binder and di-calcium phosphate was taken as filler. As per the formulae (table 1), accurate quantities of Ambroxol hydrochloride, almond gum,PVP K-30 and di calcium phosphate[9] were taken, mixed thoroughly and granulate it with water: isopropyl alcohol(1:1)solution until a wet mass was obtained. Then the coherent mass was passed through sieve #16 and the granules were dried at 40 ±2°C for 2 hours. Dried granules were passed through sieve #20 to separate fines and granules. Those granules are lubricated with magnesium stearate and talc. The lubricated granules were compressed using 8mm round flat punch on a single punch tablet machine (Cadmach, India). Compression was adjusted to obtain tablets with hardness in the range of 5-6 kg/cm^2 [10].

MICROMERITIC EVALUATION OF GRANULES:

Micromeritic properties of the prepared granules of all the formulations were studied by determining the bulkdensity, 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 tabletswas determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of tablets was measured byVerniercallipers. 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 SL150UV-Visible Spectrophotometer (ElicoLtd. Hyderabad) and comparing the content from a calibration curve prepared with standard Ambroxol hydrochloride in the same medium[12].

***In Vitro* DRUG RELEASE STUDIES:**

The prepared matrix tablets were subjected to *in-vitro* dissolution studies using USP type II paddle type dissolution rate test apparatus (Labindia Disso 2000, Mumbai). The dissolution studies were carried out in pH 1.2 for 2 hrs and in pH 7.4 for next 10 hr 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 to maintain the sink condition. 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.

DRUG RELEASE KINETICS:

The rate and mechanism of release of Ambroxol hydrochloride from the prepared matrix tablets were analyzed byfitting 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,

$K_o$is the zero-order release rate constant [13].

First order equation:

$\ln Q_t = \ln Q_o x K_o t$

Where,

$Q_t$is the initial amount of drug dissolved at time t,

$Q_o$is the initial amount of drug in the solution,

K_1 is the first order release rate constant.

In this way a graphic of the decimal log of the released amount of drug vs. time will be linear [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].

Koresmeyer-Peppas equation:

$M_t/M_\infty = Kt^n$

Where,

M and M∞ are the absolute cumulative amount 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].

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 [17].

Swelling index (S.I.) = {(Mt –Mo)/ Mo} x 100

Where,

Mt = weight of tablet at time't'

Mo = weight of tablet at time t = 0.

SIMILARITY FACTOR:

The similarity factor (f2) 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 50and 100, the two profiles are nearly identical [18,19]. The value is determined by the following equation

$$f2 = 50 + log\left\{[1 + (1/n)\sum_{t=1}^{n}(Rt - Tt)^2\ ]^{-0.5} \times 100\right\}$$

Where, n is the number of dissolution time points,

Rt and Tt are the reference and test dissolution values at time t.

RESULTS AND DISCUSSIONS

PURIFICATION OF ALMOND GUM:

%yield= Final weight of gum (after purification)/Initial weight of gum (before purification) *100

Hence, for Almond Gum Percentage yield = 358.28/500*100= 71.64%

MICROBIAL LIMIT TESTS FOR ALMOND GUM:

The total microbial load of the selected polysaccharide hydrogel (Almond gum) is given in (Table 2). The total microbial load is an important parameter which decides the suitability of a substance for use as excipient in pharmaceutical dosage forms. According to many Pharmacopoeias, for synthetic and semi-synthetic substances, the total aerobic count should not be more than 100 colony forming units (cfu) per gram, and the total fungal count (including yeasts and molds) should not exceed 50cfu/g. In case of excipients from natural origin, the total aerobic count should not be more than 300cfu/g and total fungal count should not exceed 100cfu/g. In the present study, the hydrogel (Almond gum) exhibited bacterial and fungal counts less than the specified limits and the pathogenic organisms were absent in the polysaccharide after purification.

General behavior and acute toxicity study of almond gum

The almond gumup to 1000 mg/kg did not cause any mortality in mice. None of the doses tested produced any gross apparent effect on general motor activity, muscular weakness, fecal output, feeding behavior etc. during the period of observation.

FTIR studies:

Figure 1-3 shows the IR spectra of pure drug Ambroxol hydrochloride, formulations F3 and F6. The IR spectrum of ambroxol hydrochloride shows peak at 3397 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 results, 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.

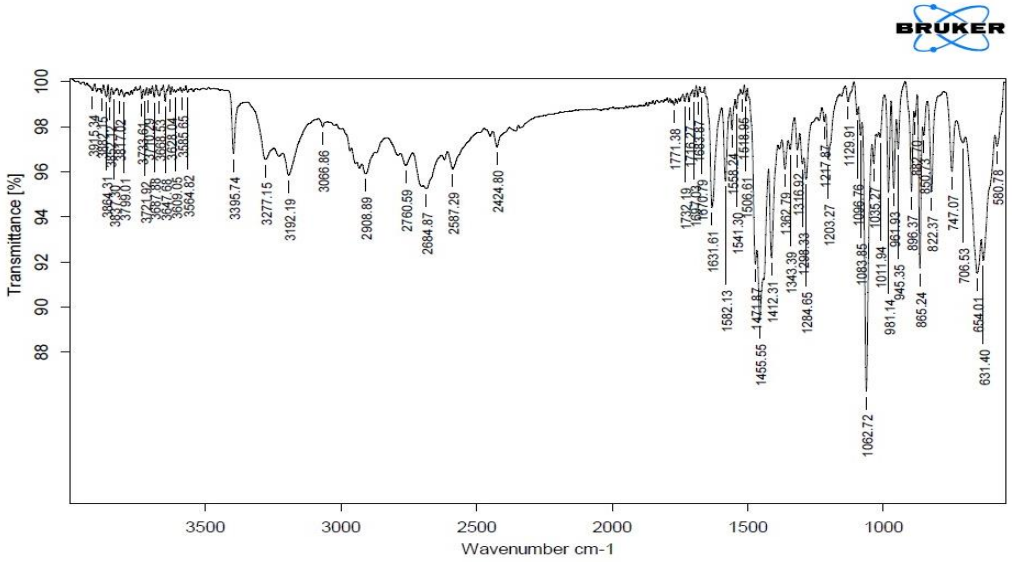

Fig 1: FTIR Spectrum of Ambroxol hydrochloride

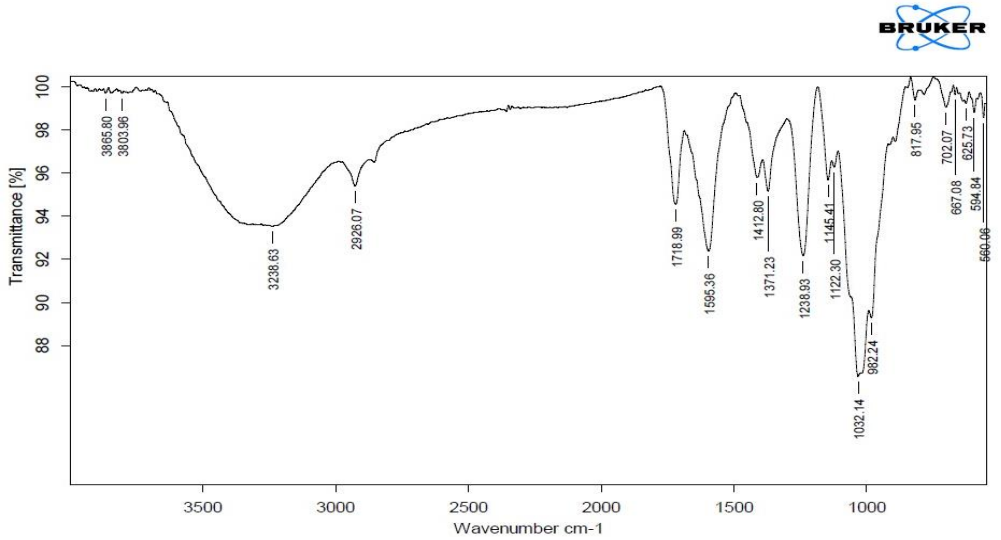

Fig 2: FTIR Spectrum of Almond gum

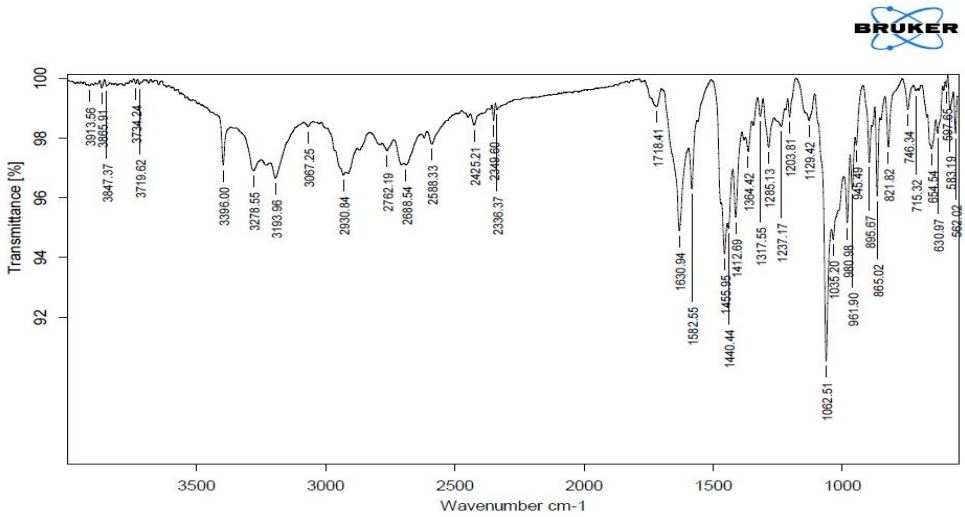

Fig 3: FTIR Spectrum of Formulation F4

DSC Studies:

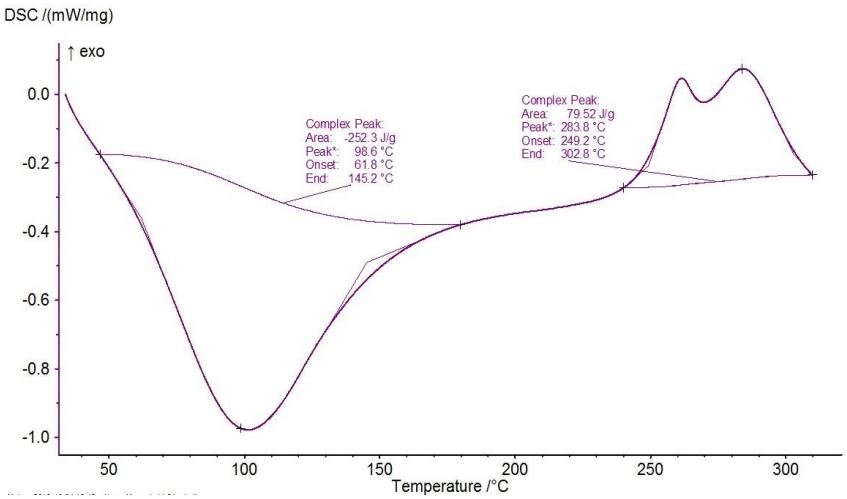

Fig 4: DSC thermogram of pure Almond Gum

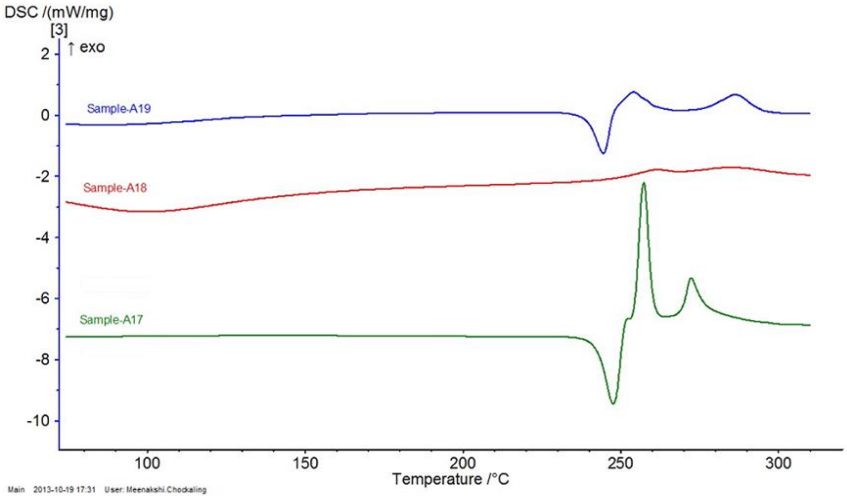

Fig 5: Overlay of DSC thermograms

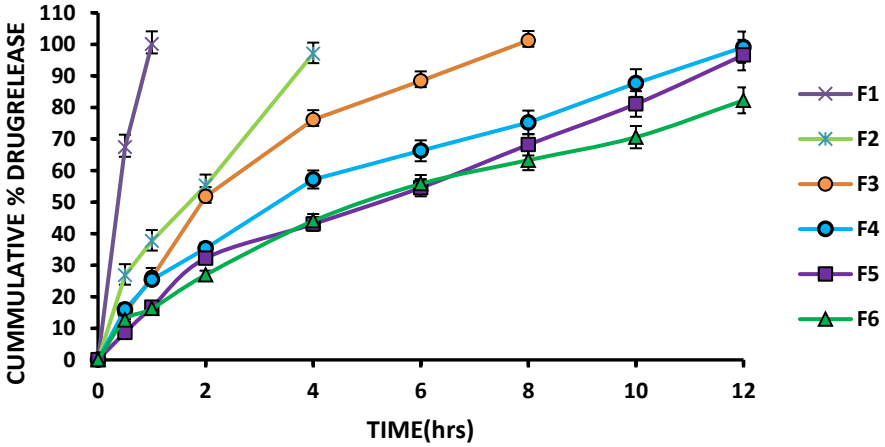

Fig 6: Cumulative percent drug release profiles of formulations F1-F6

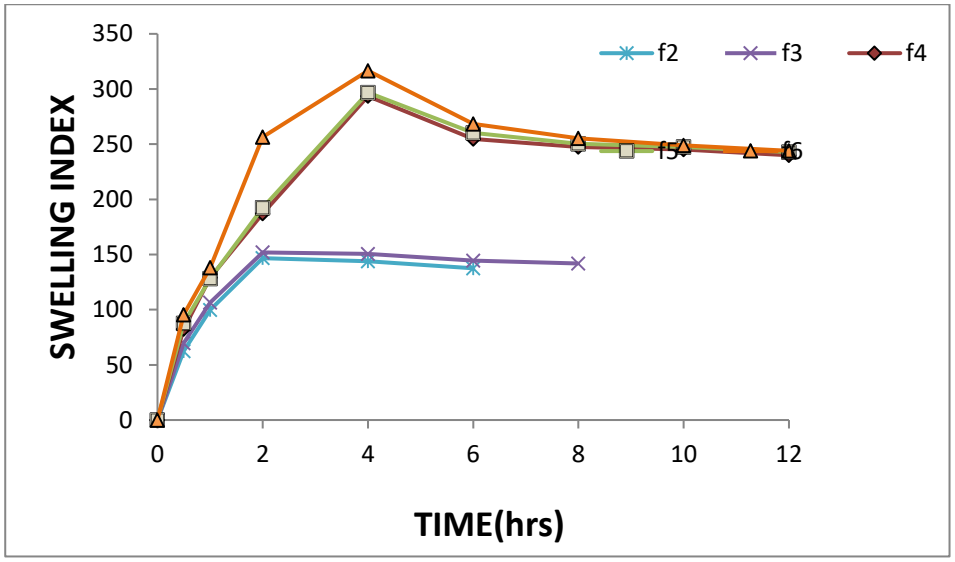

Fig 7: Swelling behaviour of Almond gum matrix tablet Formulations

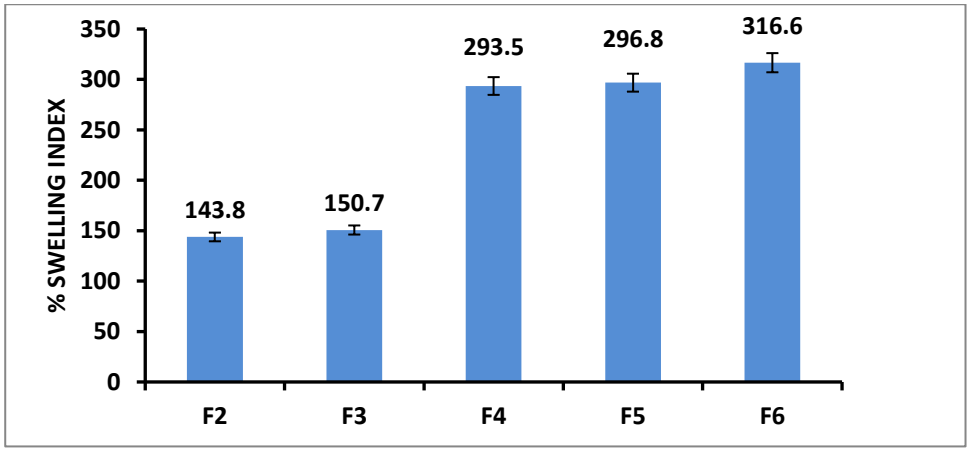

Fig 8: Swelling behaviour of Almond gum matrix tablet Formulations at 4hr time point

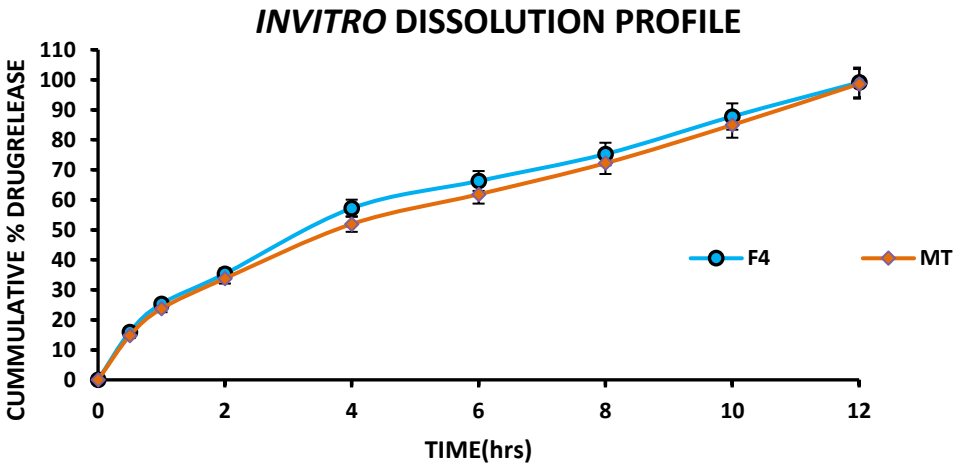

Fig 9: Comparison of Dissolution Profile of F4 with Marketed Product

Table 1: Composition of Controlled Release Formulations of AmbroxolHcl Matrix Tablets

S.NO.	Ingredients (mg/tab)	FORMULATIONS					
		F1	F2	F3	F4	F5	F6
1	AmbroxolHcl	75	75	75	75	75	75
2	Almond Gum	40	60	75	150	188	225
3	Di-calcium phosphate	55	35	20	40	52	15
4	PVP K-30	20	20	20	25	25	25
5	Talc	5	5	5	5	5	5
6	Mg Stearate	5	5	5	5	5	5
Total Weight		200	200	200	300	350	350

Table 2: Total Viable Count (TVC)

S.NO	MATERIAL	TOTAL BACTERIALCOUNT (cfu/g)	TOTAL FUNGAL COUNT (cfu/g)
1	ALMOND GUM	93	70

Table 3: Micromeritic properties of the prepared granules (n=3)

Formulation	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio	Angle of Repose (^{0})
F1	0.403±0.08	0.481±0.05	16.12±0.14	1.19±0.01	27.33±0.27
F2	0.417±0.03	0.510±0.01	18.33±0.11	1.20±0.12	22.90±0.76
F3	0.431±0.04	0.521±0.01	17.24±0.13	1.208±0.05	22.92±0.42
F4	0.463±0.06	0.556±0.06	16.67±0.09	1.21±0.07	24.79±0.95
F5	0.446±0.03	0.532±0.05	16.07±0.13	1.19±0.03	27.42±0.63
F6	0.481±0.06	0.595±0.09	19.23±0.19	1.23±0.02	27.56±0.44

Table 4: Post Compressional Parameters of AmbroxolHcl Matrix Tablets (n=3)

Formulations	Hardness (Kg/cm^2)	Friability (% wt loss)	Weight variation (mean ±SD)	Thickness (mm)	Drug Content (%)
F1	5.5 ± 0.95	0.62 ± 0.04	198.02 ± 2.4	3.46 ± 0.04	96.15 ± 0.02
F2	5.6 ± 0.63	0.66 ± 0.02	196.01 ± 1.2	3.35 ± 0.06	98.23 ± 0.06
F3	5.4 ± 0.51	0.64 ± 0.01	198.04 ± 2.1	3.45 ± 0.03	97.14 ± 0.04
F4	5.5 ± 0.45	0.59 ± 0.03	298.02 ± 1.8	3.58 ± 0.05	98.54 ± 0.05
F5	5.7 ± 0.46	0.59 ± 0.04	347.06 ± 2.6	3.83 ± 0.03	97.26 ± 0.02
F6	5.4 ± 0.51	0.62 ± 0.02	346.02 ± 1.6	3.96 ± 0.02	98.20 ± 0.06

Table 5: *In-vitro* Drug Release Kinetic Data of Ambroxol HCl Matrix Tablets Prepared Using Almond gum

Formulations	Zero order		First order		Higuchi		Peppas	
	K ($mg.hr^{-1}$)	r^2	K (hr^{-1})	r^2	K $mg/hr^{1/2}$	r^2	'n' Value	r^2
F1	96.32	0.961	0.972	0.996	99.2	0.998	--	--
F2	22.45	0.921	0.375	0.968	85.12	0.982	0.520	0.998
F3	14.63	0.933	0.157	0.998	42.68	0.975	0.701	0.997
F4	8.06	0.979	0.151	0.994	32.79	0.996	0.707	0.991
F5	7.45	0.951	0.165	0.987	31.22	0.979	0.735	0.974
F6	6.38	0.957	0.128	0.985	24.07	0.992	0.622	0.988

DSC studies:

Figure 4 and5 shows the thermograms of pure drug Ambroxol hydrochloride and formulations F4 showed an endothermic peak having the sharp melting point at 247.8°C and 244.4°C respectively. The above observation indicated that there was no change in the thermal properties of the drug in its normal pure form and in the formulation with other excipients. Because there was no significant difference in the melting point observed with the formulations and the same melting range of the drug in its pure form, it clearly indicates that, there was no interaction of the drug with other excipients used in the present study.

EVALUATION OF GRANULES:

The micromeritic properties such as bulk density, tapped density, Hausner's ratio and angle of repose for the granules of the formulations were evaluated and the results were within the limits (Table 3). Bulk density and tapped density for the formulations were within the range of 0.403±0.08 to 0.484±0.05gm/mL and 0.481±0.05 to 0.595±0.09gm/mL. Compressibility index and Hausner's ratio were in the range of 15.30±0.11% to 19.23±0.19% and 1.15±0.07 to 1.23±0.04. The angle of repose of the formulations was found to be in the range of 22.36^0±0.36 to 28^0±0.63. 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 200 mg to 350mg, 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 pharmacopoeia limits of the tablets (Table 4). 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% to 99.60±0.03% 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 to 5.7±0.63 kg/cm2and all the formulations exhibited friability less than 0.8% during the friability determination.

***IN-VITRO* DRUG RELEASE STUDIES:**

The formulations F1 and F2 which contained 20% and 30% of almond gum used as release modifier, released almost 95% of the drug in the first 4 hrs and hence could not provide controlled release of the drug, which indicated that a sufficient polymer concentration in the hydrophilic matrix systems is required to form a uniform gel barrier around the tablet upon hydration. This barrier is expected to prevent the drug from immediate release into the dissolution medium, thus it was necessary to incorporate a high concentration of binder into the formulations to control the release of the drug for an extended period of time (12 hr). Then formulation F3containing 1:1 ratio of drug: polymer showed cumulative drug release of 101.22±0.41% in 6hrs which showed some retardation but not enough to form a matrix and the drug release was not controlled due to insufficient binder concentration in the matrix system so the ratio of the binder is increased further to attain retardation up to 12 hr.

Almond gum matrix tablets containing, 1:2, 1:2.5 and 1:3 ratios of drug: polymer formulations are F4, F5, and F6 respectively. With the contact of dissolution medium, they take up water and swell, forming gel layer around the matrix. Then the dissolved drug diffuses-out of the swollen almond gum matrix at a rate determined by the amount of almond gum in the tablet formulation. The mean amounts of Ambroxol hydrochloride released at different time intervals from formulations F4, F5, and F6 are shown in fig 6.

The cumulative percent drug release for F4, F5, and F6 was 98.84±1.39, 96.58±1.42, and 82.24±0.94 at the end of 12hrs.Formulations (F4-F6) showed the burst release of Ambroxol hydrochloride in the initial hours, which is due to faster dissolution of the highly water soluble drug from the superficial layers of matrix .The diffusion of drug from the core is by entry of dissolution media through the pores formed in the matrix tablet. The release of Ambroxolhydrochloride from the matrix tablets was found to be slow and extended up to a period of 12 hrs. It was observed that as the proportion of binder (almond gum) increased in the formulations, the release rate of Ambroxol hydrochloride decreased. This may be due to increase in concentration tortuosity or gel strength of the polymer by hydration and chain relaxation. It form viscous gelatinous layer resulted in lengthening of the drug diffusion and drug release. The hydrated gel layer thickness determines the diffusional path length of drug.

Formulation (F4) having an optimum amount of almond gum gives a good and desirable controlled effect. The failures of formulations F5 and F6 may be due to the very high concentration of the polymers whichmay have

restricted the release of the AmbroxolHcl. High polymer concentration may slower the drug release profile due to long period of time is required to reach the polymer chain disentanglement concentration at the tablet surface, which in turn equates to greater resistance of the matrix to surface erosion.

According to theoretical controlled release profile, an oral controlled release formulation of Ambroxol hydrochloride should provide a release of 24.89% in 1 hr, 33.81% in 2 hr, 46.65% in 4hr, 74.56% in 8hr and 100% in 12 hrs. A comparison of the drug release profiles of controlled release matrix tablets prepared, with that of the theoretical release profile revealed that the release profiles for Formulation-F4 was very close to the theoretical controlled release profile needed for Ambroxol hydrochloride. Hence, Formulation F4 was considered as an optimized formulation in providing controlled drug release of Ambroxol hydrochloride.

DRUG RELEASE KINETICS:

The kinetic models used in the assessment of the dissolution data in this study were Zero order, first order and Higuchi model while; Korsmeyer-Peppas model was used to determine the mechanism of drug release.

The percentage drug release of Ambroxol hydrochloride was fitted to the different kinetic models (Table 5), formulation F4 followed first order kinetics with r^2 value obtained is 0.994 shows good linearity and Higuchi model kinetics with r^2value of 0.996 whereas formulations F5and F6 followed first order kinetics. The mean diffusion exponent values (n) by Korsmeyer-Peppas model ranged from 0.622 to 0.735 indicating that Ambroxol hydrochloride released from almond gum matrices followed anomalous or non-fickian diffusion. This means drug release is a complex mechanism involving swelling of the matrix tablets and subsequent erosion. Gel type matrix tablets swell upon ingestion, and a gel layer forms on the tablet surface. Almond gum is hydrophilic natural polysaccharides will form pores after the erosion takes place on the surface from which drug can diffuse. This gel layer retards further ingress of fluid and subsequent drug release. It has been shown that in the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug release rate [20].

SWELLING BEHAVIOUR STUDIES OF PREPARED MATRIX TABLETS:

The formulations of the prepared almond gum matrix tablets were subjected to swelling studies, and the tablets were found to swell when in contact with the dissolution medium up to 4 hours and later on the swelling decreased.Itwas observed from (Fig 7&8) that most of the tablets swelled up to four hours and erosion began to take place. However, formulations F4, F5 and F6 showed good swelling behaviour even upto 12hr with showing the good water absorption. It was observed that while increasing the concentration of almond gum in matrix tablets the swelling factor of the tablets also increases with their respective concentrations and the reason was attributed to the hydrophilic nature of the polymer. This also proved the assertion that almond gum achieves good swelling in phosphate buffer pH 7.4 due to the ions present [21].

SIMILARITY FACTOR:

The drug release profiles of the prepared matrix tablets were compared with the drug release profile of the marketed tablet (ACOCONTIN, Mfd by Modi Mundi Pharma) and it was found that the formulation F4 of the prepared matrix tablets of Ambroxol hydrochloride showed slow and extended release of the drug up to 12 hrs and the release of drug from the matrix tablets was linear and showed good release which was similar to that of the marketed tablet.F4 showed similar drug release profile as marketed tablet with the release of 23.98% in first hour followed by 98.84% at 12thhour.The similarity factor (f_2) was calculated in order to compare the release profile of F4 with that of the marketed formulation. The formulation F4 has a release profile similar to that of the marketed formulation, with similarity factor **f_2 =75.24**, hence the F4 formulation was comparable to the marketed formulation.

CONCLUSION:

The present study was carried out to design and evaluate gum-based matrix tablets of Ambroxol hydrochloride using natural hydrophilic polymer like Almond gum for controlled drug delivery. Formulation F4with Almond gum (1:2) shown maximum f2 value of 75.24. The release of the drug from the almond gum formulations was governed mainly by diffusion-controlled process. Hence the use of natural hydrophilic polymer like almond gum was successful in the formation of matrix and at the same time extending the

drug release of Ambroxol hydrochloride effectively over a prolonged period of time. Hence from the above investigation it was concluded that, controlled release matrix tablets of Ambroxol hydrochloride were developed successfully with Almond gum by wet granulation technique.

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