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FORMULATION AND EVALUATION OF SUSTAINED RELEASE AMBROXOL HCL TABLETS BY USING NATURAL POLYMERS

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Abstract:

The main objective is to formulate and evaluate the ambroxol Hcl sustained release matrix tablets for treating bronchial asthma and chronic bronchitis. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of newdrug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in and cost-effective manufacturing process. Ambroxol hydrochloride tablets wereprepared by direct compression method by using natural polymers like Xanthane gum, Gum karaya and Guargum. The prepared matrix tablets were tested for evaluation parameters such as drug content, hardness, friability, weight variation, in-virto drug release and release kinetics. The formulation F showed better sustained release of about 99.81% and follows Higuchi order with high regression value of 0.993 with complete drug release in 12 hrs made it to select as an optimized formulation compared with other formulations. Thus it was selected for invivo investigation.

Keywords: Ambroxol hydrochloride, Sustain release, Xanthane gum, Gum karaya and Guargum.

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INTRODUCTION:

Ambroxol hydrochloride is an expectoration improver and a mucolytic agent used in the treatment of bronchial asthma and chronic bronchitis. Ambroxol hydrochloride has also been reported to have a cough suppressing effect and anti-inflammatory action. Ambroxol hydrochloride has been used to increase surfactant secretion in the lungs.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. The overall process of oral delivery is frequently impaired by several physiological and pharmaceutical challenges that are associated with the inherent physicochemical nature of the drugs and/or the variability in GI conditions such as pH, presence of food transit times as well as enzymatic activity in the alimentary canal. Manipulation of these problems and challenges is considered an important strategy for improving oral drug delivery.

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. The onset of its pharmacologic action is often delayed and the duration of its therapeutic effect is sustained. Hydrophilic matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications because of their good compatibility among the hydrophilic polymers.

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodymics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Rationale of sustained and controlled drug delivery:

The basic rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a dosing property of a rate controlled dosage form and less or not at all a property of the drug molecules inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs[6,7].

MATERIALS AND METHODS:

Materials

Ambroxol Hydrochloride drug as gift sample from Dr. Reddy's Laboratories, Hyderabad, India. And all other excipients were procured from SD Fine Chem, Mumbai, India.

Preparation of Ambroxol Hydrochloride matrix tablets

Ambroxol hydrochloride tablets were prepared by direct compression method. Accurately weighed quantities of polymer of Xanthan gum, Karayagumand Guargum and MCC were taken in a mortar and mixed geometrically, to this required quantity of Ambroxol was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no. 40 and mixed with the drug blend which is also passed through sieve no-40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 200mg was compressed into tablets with 10 mm round concave punches at a hardness of 5 kg/cm^2.

SOLUBILITY STUDY OF AMBROXOL

Excess amount of Ambroxol was placed in 0.1 N HCl, Acetate buffer pH 4.5, Phosphate buffer pH and Phosphate buffer pH 7.4 respectively in order to determine its solubility. The samples were shaken for 24 h at 37 °C in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). The supernatant was filtered and the filtrate was diluted with the respective medium and assayed by UV/ Visible Spectrophotometer at248 nm.

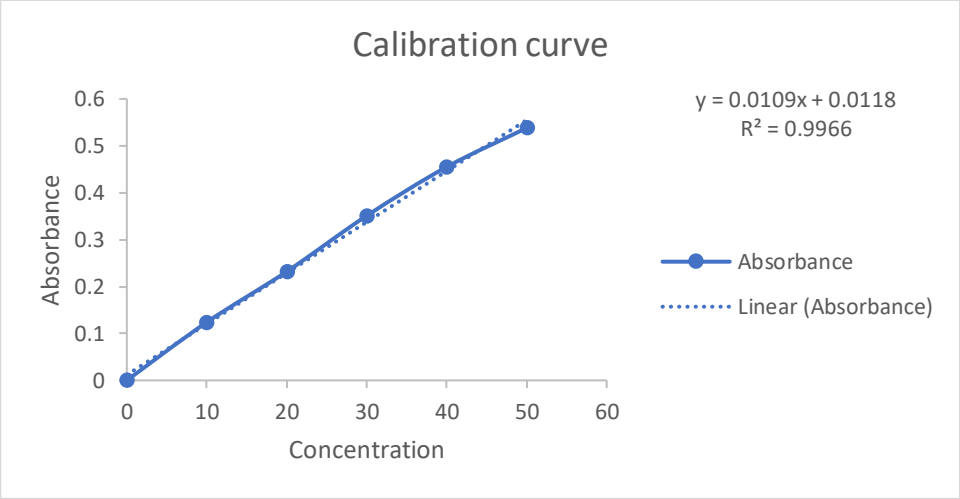

Fig1: Standard graph of Ambroxol hydrochloride in pH 6.8 buffer

Concentration (µg/ml)	**Absorbance**
0	0
10	0.124
20	0.232
30	0.351
40	0.455
50	0.538

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromideof equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000cm^{-1}.

FT-IR Spectrum of Ambroxol hydrochloride

The compatibility between the drug and the selected Drug and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-excipients mixture, which confirmed the absence of any chemical interaction between the drug, polymers and other chemicals.

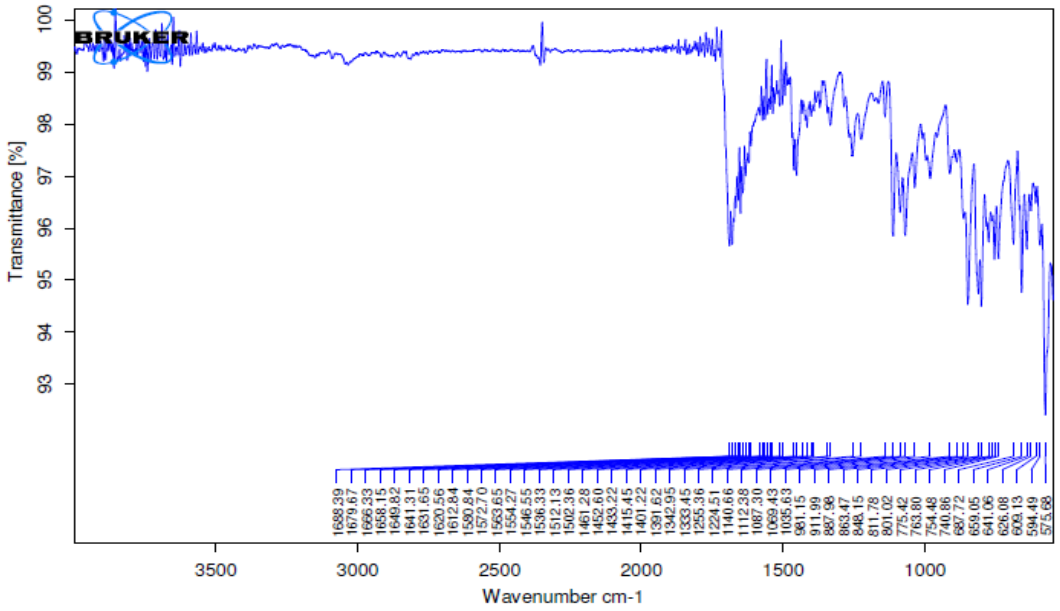

Fig-2 : FTIR Studies of Pure Drug

Table -1: Characteristic Peaks and frequency of Ambroxol Hcl

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3500-3000	3254.09
2	OH Bending	3000-2500	2666.87
3	C-H stretching	2000-1500	1740.66
4	C=O stretching	1500-1000	1275.42

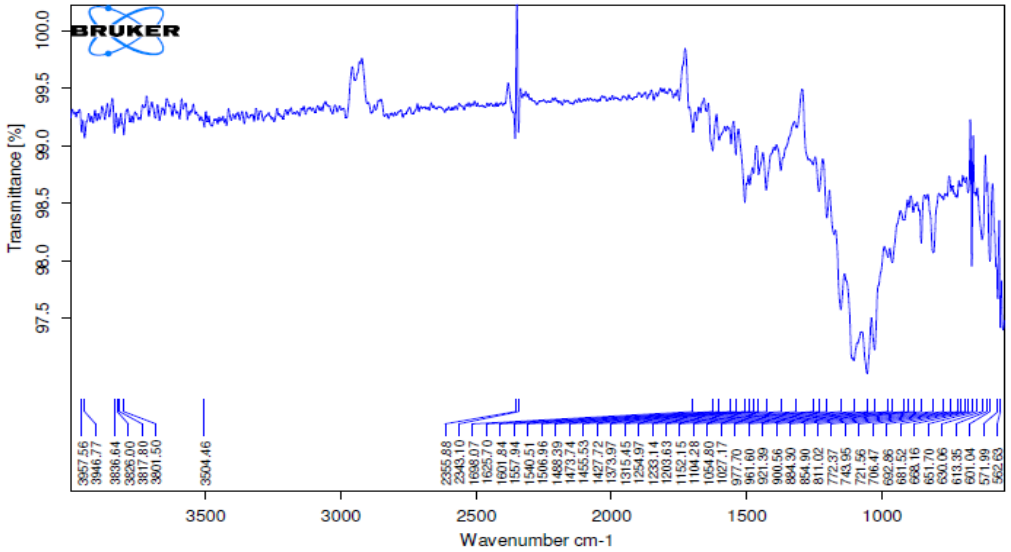

Fig -3: FTIR Studies of physical mixture of drug and excipients

Table-:2 Characteristic Peaks of physical mixture of drug and excipients

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3500-3000	3304.46
2	OH Bending	1000-1500	1106.47
3	C-H stretching	2500-2000	2257.94
4	C=O stretching	2000-1500	1804.28

Table 3: Composition of matrix tablets of Ambroxol

Ingradients (wt in mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ambroxol HCL	75	75	75	75	75	75	75	75	75
Xanthan gum	20	30	40	-	-	-	-	-	-
Guar gum	-	-	-	20	30	40	-	-	-
Gum karaya	-	-	-	-	-	-	20	30	40
MCC	95	85	75	95	85	75	95	85	75
Talc	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5

Evaluation of matrix tablets of Ambroxol

Weight Variation test

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight.

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliperse. The average thickness and standard deviation were reported.

Hardness test

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness, and the standard deviation was reported.

Friability test

Twenty (20) tablets were selected from each rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets

***In vitro* Drug Release Studies**

The *in vitro* drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus under the following conditions:

Dissolution test parameters

Medium : 900ml of 01.N HCl
Rotation speed : 50 rpm
Temperature : 37±0.5ºC
Sampling Volume : 5ml
Sampling Time : 0.5, 1, 2, 4, 6, 8, 10, 12hours

At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 220 nm.

RESULTS AND DISCUSSION:

Ambroxol hydrochloride matrix tablets were prepared with Natural polymers xanthangum, Guargum, Gumkaraya with different formulations by direct compression method.

Table 4: Physical parameters of single unit Sustained release matrix tablet of Ambroxol HCl

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm	Friability (%)	Assay (%)
F1	196±3.84	6.8±0.4	3.68±0.05	0.29	99.65
F2	198±3.84	6.9±0.4	3.68±0.05	0.27	99.25
F3	199±3.84	6.9±0.4	3.68±0.05	0.25	99.19
F4	198±3.84	6.8±0.4	3.68±0.05	0.26	99.09
F5	196±3.84	6.7±0.4	3.68±0.05	0.29	99.62
F6	198±3.84	6.8±0.4	3.68±0.05	0.27	98.69
F7	200±3.84	6.9±0.4	3.68±0.05	0.29	99.01
F8	199±3.84	6.8±0.4	3.68±0.05	0.28	99.22
F9	198±3.84	7.0±0.4	3.68±0.05	0.25	99.11

In-vitro drug release

i.) Release profiles of formulations containing Xanthan gum

Table 5: Cumulative percentage drug release of formulations with Xanthan gum

Time (Hrs)	Cumulative % of drug release		
	F1	F2	F3
0	0	0	0
0.5	21.27±1.77	±3.14	±3.73
1	27.47±4.57	24.22±1.6	28.71±5.47
2	40.33±3.59	34.08±2.57	36.95±3.14
3	52.25±2.65	41.44±1.49	44.96±2.26
4	65.81±5.46	49.3±3.35	51.55±3.7
6	81.16±2.97	57.67±2.57	62.39±4.82
8	87.12±1.77	68.77±1.71	70.26±1.42
10		76.5±2.09	79.36±2.72
12		83.86±3.57	85.1±2.68

ii.) Release profiles of formulations containing Guargum

Table 6: Cumulative percentage drug release of formulations with Guargum

Time (Hrs)	Cumulative % of drug release		
	F4	F5	F6
0	0	0	0
0.5	20.13±2.84	21.34±1.34	21.61±3.27
1	31.91±1.39	29.22±4.61	27.35±1.59
2	42.18±2.72	39.7±3.15	37.45±2.92
3	53.72±1.48	48.31±2.06	48.65±2.77
4	66.19±2.4	59.67±1.82	58.79±1.67
6	80.15±4.66	68.77±0.92	69.89±4.08
8	88..53±2.12	77.51±3.29	79.49±2.53
10	97.53±2.12	85.6±2.57	88.47±4.28
12		93.09±1.27	96.82±3.19

Table 7: Cumulative percentage drug release of formulations with Karayagum

Time (Hrs)	Cumulative % of drug release		
	F7	F8	F9
0	0	0	0
0.5	17.52±2.59	22.97±1.92	23.72±3.72
1	24.85±2.08	31.09±3.1	32.83±4.28
2	36.2±1.41	39.69±2.65	41.81±3.64
3	45.68±1.92	47.05±2.95	49.3±2.73
4	51.54±2.54	58.78±3.83	59.27±1.53
6	56.78±3.94	65.77±1.92	66.88±4.17
8	65.39±1.48	71.77±1.18	75.24±2.97
10	73.37±3.84	77.87±3.23	86.09±3.98
12	79.99±2.77	87.22±4.37	94.81±2.87

From the above figure it is evident that the polymer Gum karaya has sustaining effect on the release of drug from the Sustained release matrix tablet. The percent of drug release from formulations F1 to F9 were failed to release the drug within the desired time (12 hrs). The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymers. Formulation **F6** was considered as best formulation among all the formulations sustained the drug release was found to be 96.8% for desired period of time (12 hrs).

In-vitro release kinetics

Table 8: Regression coefficient (R2) values of Sustained release matrix tablets for different kinetic models

Formulations	**Zero order**	**First order**	**Higuchi**	**Korsemeyer peppas**	
				R^2	**N**
F1	0.963	0.476	0.990	0.476	0.336
F2	0.987	0.486	0.965	0.467	0.365
F3	0.948	0.498	0.996	0.449	0.298
F4	0.952	0.466	0.993	0.478	0.366
F5	0.987	0.481	0.978	0.432	0.379
F6	0.989	0.477	0.989	0.455	0.365
F7	0.988	0.488	0.977	0.488	0.338
F8	0.976	0.454	0.991	0.444	0.354
F9	0.984	0.494	0.973	0.471	0.416

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 90 days. Parameters quantified at various time intervals were shown.

Table-9: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	95.47	94.56	93.98	91.89	Not less than 85 %
F-4	30^0C/75% RH % Release	95.47	94.52	93.78	91.28	Not less than 85 %
F-4	40^0C/75% RH % Release	95.47	94.24	92.64	91.88	Not less than 85 %

SUMMARY AND CONCLUSION:

The present study was undertaken with an aim to formulate and evaluate ambroxol hydrochloride sustained release tablets using different polymers as release retarding agents. Preformulation study was carried out and all the parameters were found within the specification. Hence different batches of ambroxol hydrochloride were prepared using selected excipients. Powders were evaluated for Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets.

Various formulations of sustained release tablets of Ambroxol hydrochloride were prepared by using different polymers viz, xanthan gum, guar gum, and gum karaya in different proportions and combinations by direct compression technique. The tablets were evaluated for physical parameters, *in vitro* release study and stability studies. All formulations were found to be within the specifications of official pharmacopoeias and/or standard references.

In-vitro release indicated that the formulation F4 had better dissolution profile along with sustained action as compare to other formulations.

Stability study was conducted on tablets of Batch F4 stored at room temperature, 40^0C, and 2-8^0C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters during the study period (3 months), thus it could be concluded that formulation was stable.

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