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Design and Evaluation of Gastroretentive Floating Matrix Tablets of Ambroxol Hydrochloride

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Abstract
Gastro retentive drug delivery is a special approach which remains in the gastric region for a prolonged period to increase gastric residence time and also have the advantage of site-specific drug delivery especially in the upper gastrointestinal tract (GIT) for local or systemic effects. Ambroxol hydrochloride is a systemically active mucolytic agent with a half-life of 3-4 hours. It acts by breakdown of acid muco polysaccharide fibres which make the sputum thinner and less viscous as long as treatment is maintained and therefore more easily sputum was removed by coughing. The main aim of the present work is to develop the oral controlled release floating matrix tablets of Ambroxol hydrochloride by direct compression method, using various hydrophilic polymers such as HPMCK100M, Carbopol971P, Polyethylene oxide. FT-IR studies revealed that there was no incompatibility between the drug and polymers used. All the formulations remained buoyant without any disintegration. The formulations F4, F9, F15 have shown the extended drug release close to that of marketed formulation for a period of 12 hours. To ascertain the mechanism of drug release in-vitro data was fitted into various release kinetic models like zero order, first order, Higuchi and Peppas. The values indicated the non-fickian diffusion with slow erosion of polymer matrix followed by drug diffusion and resulted in linear drug release profile over a prolonged period of time.

Keywords
Ambroxol hydrochloride, floating tablets, buoyancy, mucolytic

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INTRODUCTION
Oral route is the most preferred route for administration of drugs. Drugs with short half-life require frequent administration, which increases chances of missing dose, delay in therapeutic activity. The fluctuating drug levels due to frequent dosing may lead to precipitation of drugs and other adverse effects especially in drugs with small therapeutic index.[1] These limitations of conventional immediate release systems were reduced by these novel controlled release systems. The primary benefit of a controlled release dosage form is the uniform therapeutic effect due to uniform drug concentration in plasma.[2]

Drugs that are easily absorbed from gastrointestinal tract (GIT) with short half-lives are eliminated quickly

from the systemic circulation. To overcome this limitation and to increase the bioavailability of such drugs gastro retentive drug delivery systems were developed.[3] After oral administration, such a drug delivery would be retained in the stomach for a prolonged time and controls the release of drug, and increases the drug concentration at its absorption sites in the gastrointestinal tract (GIT). Prolonged gastric retention improves bioavailability, increases the duration of drug release, improves the solubility of poorly soluble drugs in a high pH environment and also provides local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.[4]

Different types of Gastro retentive drug delivery approaches being designed and developed includes: high density (sinking) systems that are retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, muco-adhesive systems that causes bio-adhesion to stomach mucosa, unfoldable, extendible or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach. Among them floating system was intended to float in and over the gastric contents resulting in prolonged gastric retention time (GRT). It is a low-density approach which has a bulk density lower than gastric fluids and hence remains buoyant in the stomach, releasing the drug slowly without affecting the gastric emptying rate for a prolonged period of time.[5]

Ambroxol hydrochloride is a systemically active mucolytic agent with a half-life of 3-4 hours. It is mainly used to treat tracheal bronchitis, chronic inflammatory pulmonary conditions, bronchospasm asthma. It acts by breakdown of acid muco polysaccharide fibres which make the sputum thinner and less viscous as long as treatment is maintained and therefore more easily sputum was removed by coughing. It is rapidly absorbed (70-80%) after oral administration and reaches peak plasma concentration in approximately 2 hours. It mainly undergoes hepatic metabolism.[6] The main aim of the present work is to develop the oral controlled release floating matrix tablets of Ambroxol hydrochloride by direct compression method, using various polymers such as HPMCK100M, Carbopol971P, Poly ethyl oxide. These floating matrix tablets are used to prolong the gastric retention there by increasing the drug absorption and maintaining the therapeutic efficacy for a prolonged period of time.

MATERIALS AND METHODS

Materials: Ambroxol hydrochloride was a gift sample from Life Line Formulations Vijayawada, HPMC K100M was purchased from Aqualon USA, Poly ethylene oxide (POLYOX WSR 303) was purchased from Colorcon Asia Pvt. Ltd., Mumbai, Carbopol 971P was purchased from Lubrizol pharmaceutical sciences, Ahmadabad, Micro crystalline cellulose, Calcium carbonate, Magnesium stearate and Talc were purchased from S.D. Fine Chem. Ltd., Mumbai. Other materials used were of analytical grade.

Methods:

Drug Excipient Compatibility studies:[7]

Fourier Transform Infrared Spectroscopy (FT-IR) study: Infrared spectrum of the sample was taken by using Bruker FT-IR by scanning samples of optimized formulations placed in potassium bromide discs. The FT-IR spectrums of Ambroxol hydrochloride, mixture of Ambroxol Hydrochloride HPMCK 100M, Carbopol 971P, and PEO (1:1:1).

DSC studies:[8]

The thermal analysis of the samples was carried out in DSC (thermal analysis centre). The samples of pure drug, Physical mixture of drug and binders in the ratio 1:1 were placed in sealed aluminium pans and heated at a rate of 10˚C/min at a temperature range of 30- 300˚C, under a nitrogen flow rate of 10mL/min. The DSC thermograms of Ambroxol hydrochloride, mixture of Ambroxol hydrochloride, HPMCK 100M, Carbopol 971P and PEO.

Formulation of Ambroxol hydrochloride-controlled release floating matrix tablets:[9]

Ambroxol HCL floating tablets were prepared by effervescent technique. Effervescent systems were prepared by using Calcium carbonate as gas generating agent. Hydrophilic polymers such as HPMC K-100M, PEO (POLYOX WSR 303) and Carbopol 971P were used as release rate controlling agents. Accurately weighed polymer was mixed with drug and other ingredients were added in geometric dilutions and mixed thoroughly. The power blend was then compressed into tablets by using 10 mm round flat punch on a single punch tablet machine (Cadmach, Ahmedabad). All the formulations were prepared by direct compression as per formulae given in **Table I.**

Table I: Composition of Ambroxol hydrochloride floating tablets

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Ambroxol HCL	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
HPMC[1] K 100M	20	40	60	80	125	_	_	_	_	_	_	_	_	_	_
Carbopol 971P	_	_	_	_	_	20	40	60	80	125	_	_	_	_	_
POLYOX [2]WSR 303	_	_	-	_	_	_	_	_	_	_	25	50	75	100	150
Micro crystalline cellulose	75	45	25	5	2.5	65	45	25	5	2.5	102.5	77.5	52.5	27.5	20
Calcium carbonate	20	30	30	30	37.5	30	30	30	30	37.5	37.5	37.5	37.5	37.5	45
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	200	200	200	200	250	200	200	200	200	250	250	250	250	250	250

1-Hydroxy propyl methyl cellulose, 2- polyethylene oxide.

EVALUATION OF AMBROXOL HYDROCHLORIDE FLOATING TABLETS:

Pre-formulation Studies:[10] The powder blend was evaluated for pre-compression properties like Bulk density, tapped density, Angle of repose, Carr's index, Hausner's ratio.

Post compression evaluation:[11] The compressed tablets were evaluated for post compression parameters like thickness, hardness, weight variation, friability, disintegration test.

***In-Vitro* Dissolution Studies:**[12] The tablets prepared were subjected to *in-vitro* dissolution studies using USP Type II paddle type dissolution apparatus at 37 ± 2 °C and 50 rpm speed. The dissolution rate was studied using 900 mL of 0.1N HCL for 12 hrs. Samples were withdrawn at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 hrs and each sample withdrawn was replaced with an equal amount of fresh medium, to maintain sink conditions throughout the experiment. Concentration of drug in each sample was determined by UV Spectrophotometric method at 248.00 nm after suitable dilution of the samples.

Drug Release Kinetics: To study the mechanism of drug release from the floating tablets, the dissolution data was fitted into the following equations:

Zero orderequation:[13]

$Q_t=Q_o+K_ot$

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.

First orderequation:[14]

$\ln Q_t=\ln Q_o x K_1 t$

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.

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

Higuchi's equation:[15]

$Q = kHt ½$

Where,

Q is the amount of drug released at time t per unit area,

k_H is the Higuchi diffusion rate constant.

Korsmeyer- Peppasequation:[16]

$M_t/M_\infty=K t^n$

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.

***In-Vitro*BuoyancyStudies:**[17]

The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100mL beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Swelling Studies:[18]

The extent of swelling was measured in terms of percent weight gain by the tablets. One tablet from each formulation was placed in a petri dish containing 0.1N HCl buffer solution (pH 1.2). At the end of 1 hr 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.

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:[19]

The similarity factor (f_2) is 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, whenthe value is between 50 and 100, the two profiles are nearly identical. The value is determined by the following equation

f2 = 50+log {[1+ (1/n) t = 1×n (Rt-Tt)] ×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

Drug Excipient Compatibility studies:

FTIR Spectral Analysis: FTIR spectra of pure Ambroxol hydrochloride and the best formulations F4, F9 and F15 were shown in Figures I, II, III and IV. All these characteristic bands (Table II) were all retained in formulations indicating that there is no interaction between drug and polymers.

Table II: FTIR Spectral data interpretation of Ambroxol hydrochloride:

S. No	Functional group	Frequency Range (cm ^{1})	Frequency observed for Ambroxol HCl (cm^{-1})	F4	F9	F15
1	Aliphatic Bromo compound	657.79-659	657.79	658.73 cm^{-1}	658.65 cm^{-1}	658.65 cm^{-1}
2	Secondary amine	1632-1634	1632.23	1632.18 cm^{-1}	1632.06 cm^{-1}	1633.85 cm^{-1}
3	Secondary Alcohol	1230-1236	1230.27	1230.38 cm^{-1}	1230.36 cm^{-1}	1235.83 cm^{-1}

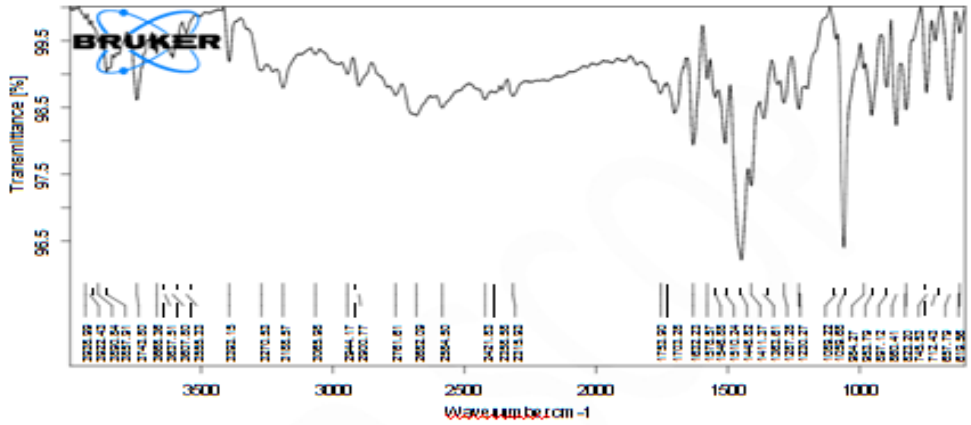


Figure I: FT-IR Spectrum of Ambroxol Hydrochloride

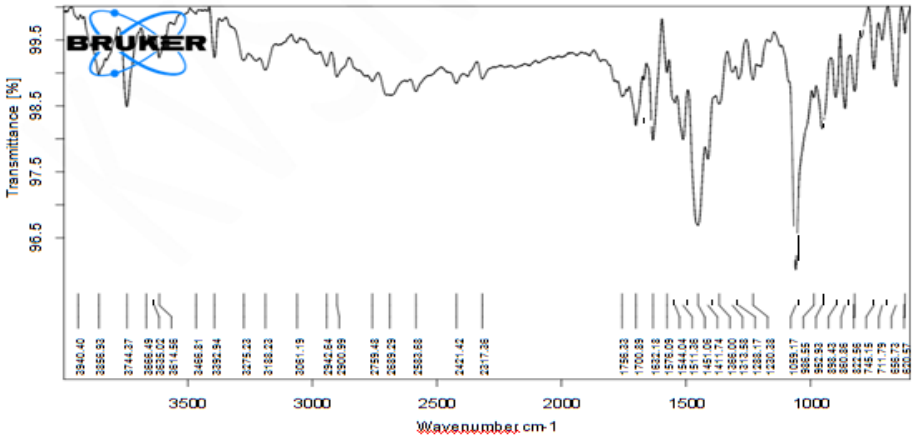


Figure II: FT-IR Spectrum of Formulation F4

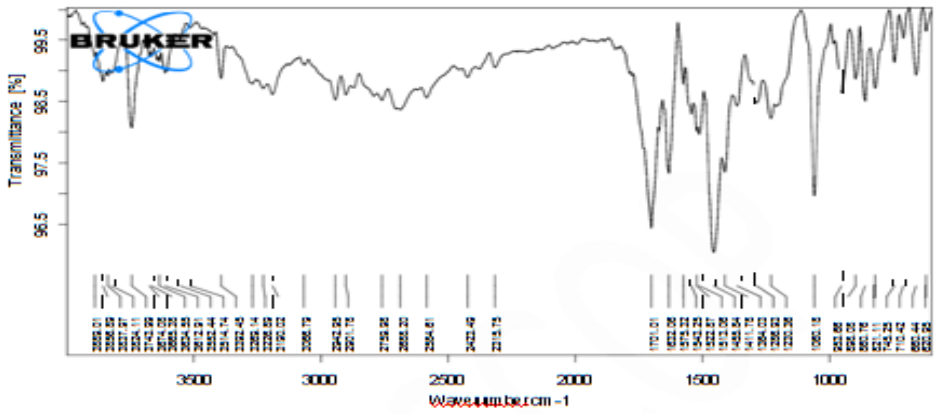


Figure III: FT-IR Spectrum of Formulation F9

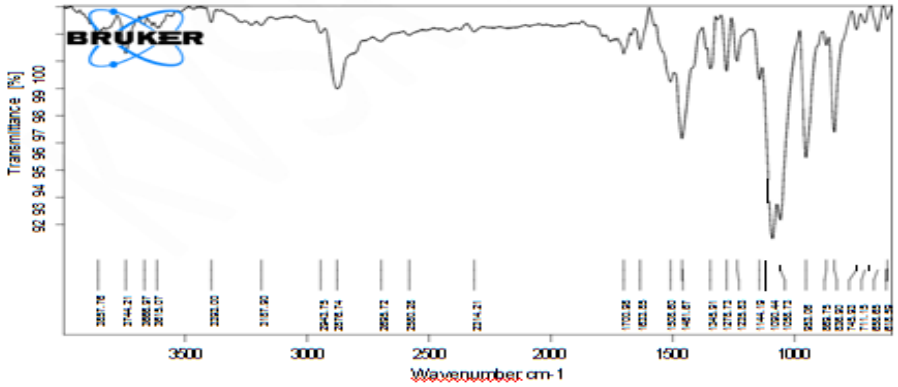


Figure IV: FT-IR Spectrumof Formulation F15

DSC studies: DSC thermo grams of pure drug Ambroxol hydrochloride and formulations F4, F9 & F15 were shown in figures V, VI, VII and VIII. Thermo grams of pure Ambroxol hydrochloride, formulations F4, F9 & F15 showed an endothermic peak having the sharp melting point at 243.99°C, 233.86°C, 239.52°C and 238.01 °C. This was in full agreement with the literature melting point of drug. 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 the other excipients.

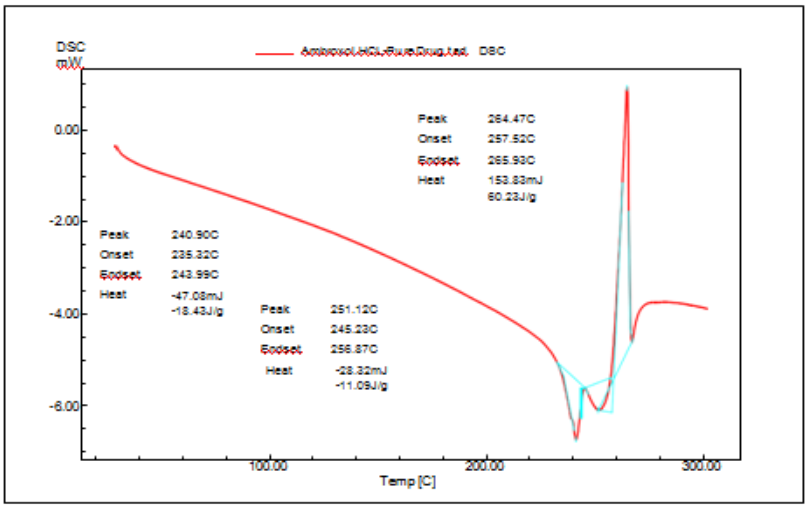


Figure V: DSC Thermograph of Ambroxol Hydrochloride

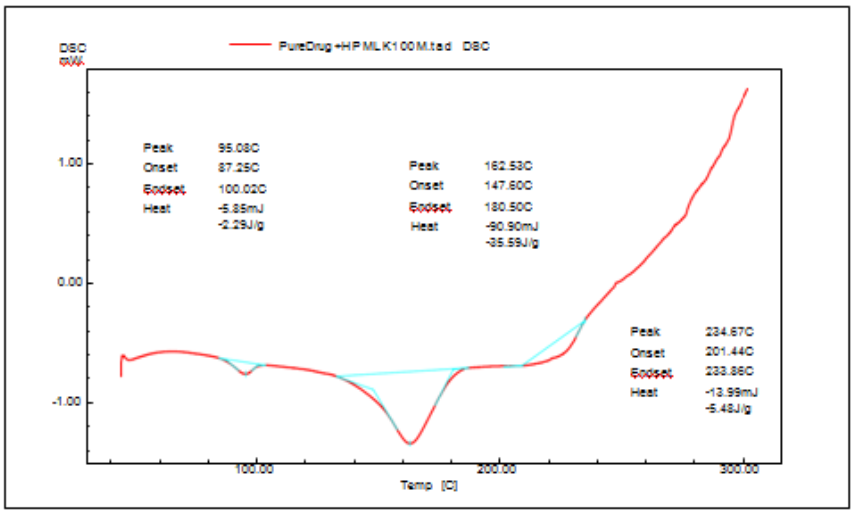


Figure VI: DSC Thermograph of Formulation F4

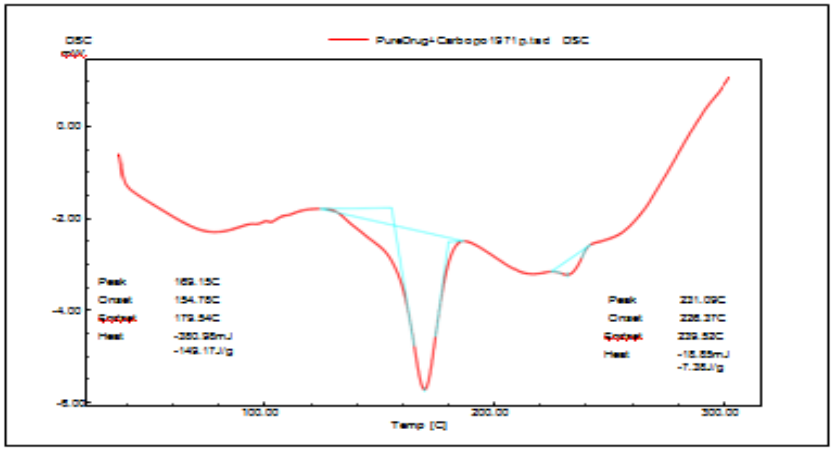


Figure VII: DSC Thermograph of Formulation F9

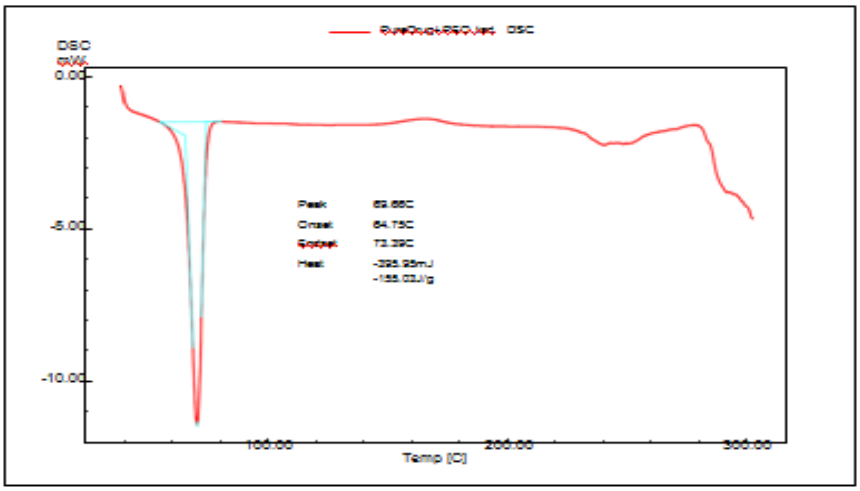


Figure VIII: DSC Thermograph of Formulation F15

Pre-formulation Studies:

Bulk density and Tapped density (Alfred martin) for all the formulations were within the range of 0.513±0.05 to 0.592±0.03 gm/ml and 0.597±0.03 to 0.684±0.06gm/ml. Compressibility index and Hausner's ratio were in the range of 12.51±1.32 to16.75±1.02 % and 1.14±0.11 to 1.21±0.37 %. The angle of repose of the formulations was found to be in the range of $25^0.42\pm0.51'$ to $28^0.37 \pm 1.24'$. The results obtained confirm that all the formulations

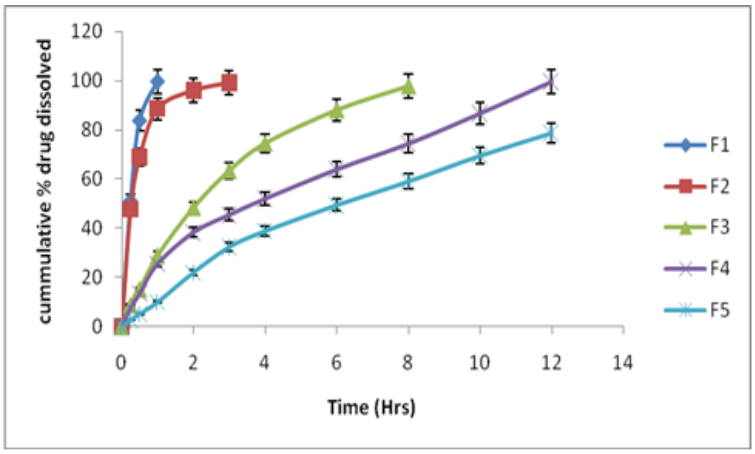
exhibited good flow properties and good packing characteristics.

Post compression evaluation:

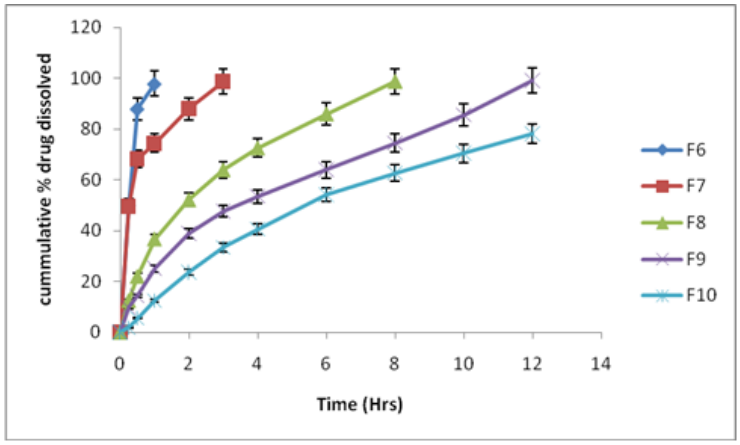
The tablets of 200mg, 250mg, which were prepared by direct compression method, were subjected for evaluation of the post compression parameters such as hardness, friability, weight variation, thickness and drug content uniformity. The results complied with the pharmacopoeia limits. The mean values for the hardness, weight variation and thickness were found to be in the range of 5.16 ± 0.1 to 5.46 ± 0.2 Kg/cm^2, 199.11 ± 1.4 to 256 ± 2.2 mg and 2.58 ± 0.04 to 2.66 ± 0.05 mm respectively. All the formulations exhibited friability less than 0.7%during the friability determination. The drug content of the formulations was found to be uniform as the amount of the active ingredients in each of the 10 units tested were within the range of 97.54 ± 0.05, to 99.72 ± 0.05% indicating uniform mixing of the drug, and other excipients.

***In-Vitro* Dissolution Studies:**

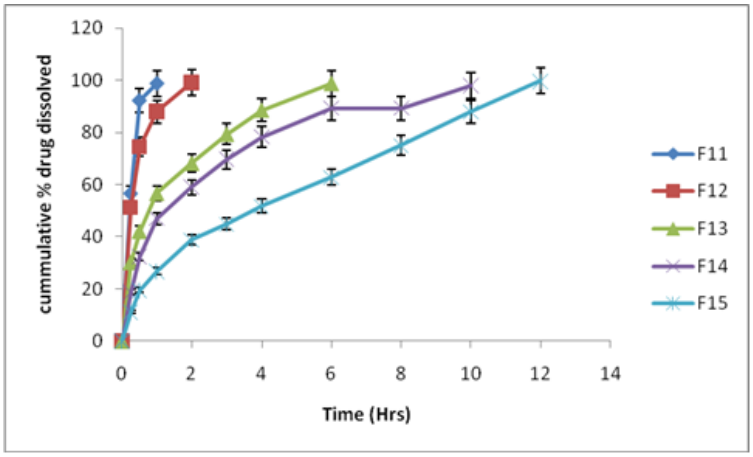
The in-vitro drug release profile of Ambroxol Hydrochloride from the floating tablets was studied in the medium 1.2 pH acidic buffer for a period of 12hrs. Based on the results it was found that the formulations F1, F2, F6, F7, F11, F12 showed complete Ambroxol release in 1hr to 3hr which may be due to less polymer concentration in the formulation. Whereas the formulations F3, F4, F8, F9, F13, F14, F15 showed prolonged drug release rates when compared to other formulations that can be attributed due to increase in polymer concentration. But the formulations F5, F10 showed less drug release compared to remaining formulations it is due to further increase in polymer concentration. The formulations F4, F9, F15 showed 99.69 ± 2.24, 99.07 ± 3.68 and 99.69 ± 2.01% drug release at the end of 12hrs. from the results it can be proved that the controlled release of Ambroxol Hydrochloride from the tablets can be attributed due to presence of release retardant materials like HPMCK100M, Carbopol 971P and PEO. These polymers swelled upon contact with dissolution medium and formed gel layer on surface of tablets. The gel layer had retarded further uptake of fluid and subsequent drug release.



Graph I: Comparative *in-vitro* drug release profiles of floating formulations (F1, F2, F3, F4, F5)



Graph II: Comparative *in-vitro* drug release profiles of floating formulations (F6, F7, F8, F9, F10)



Graph III: Comparative *in-vitro* drug release profiles of floating formulations (F11, F12, F13, F14, F15)

Drug Release Kinetics:
To ascertain the mechanism of drug release, the *in-vitro* drug release data was fitted into various release kinetics models such as zero order, first order, Higuchi and Peppas models. For formulations F1-F15 when cumulative % drug release values were plotted against time, straight lines were obtained indicating that the drug release from the floating tablets followed first order kinetics. The regression coefficients (R^2) obtained for first order kinetics were found to be higher when compared to zero order kinetics indicating that drug release, from all the formulations followed first order kinetics. To evaluate the drug release mechanism from the tablets, Higuchi plot was plotted, and it was found to be linear indicating that the drug release mechanism from the floating tablets was diffusion controlled. To confirm the diffusion mechanism, the data was fitted into Korsmeyer-peppas plot which resulted in "n" value>0.5 from which the optimized formulations F4, F9, F15 indicated that the mechanism of drug release followed anomalous transport with slow erosion of polymeric matrix followed by diffusion of drug resulting in linear drug release over a prolonged period of time. The kinetic data of optimized formulations were given in table III.

Table III: *In-vitro Drug* release kinetic data of optimized formulations F4, F9, F15

Formulations	Zero order		First order		Higuchi		Peppas	
	K (mol. $L^{-1}h^{-1}$)	R^2	K (h^{-1})	R^2	K $mg/hr^{1/2}$	R^2	'n' Value	R^2
F4	7.647	0.947	0.179	0.979	28.79	0.994	0.630	0.985
F9	7.49	0.940	0.209	0.924	28.33	0.995	0.592	0.993
F15	7.46	0.953	0.181	0.962	28.01	0.994	0.532	0.993

***In-Vitro* Buoyancy Studies:** All the tablets prepared by effervescent approach were subjected to *in-vitro* buoyancy studies and were shown in Figure IX . Calcium carbonate induced carbon dioxide generation in presence of dissolution medium (0.1N hydrochloride).It was observed that the gas generated was trapped and protected within the gel, formed by hydration of polymer (HPMC, PEO and CARBOPOL971P), thus decreasing density of the tablet below 1and tablet becomes buoyant. The tablets welled radially and axially during *in-vitro* buoyancy studies. All the batches of tablets were found to exhibit short floating lag times due to presence of calcium bicarbonate.

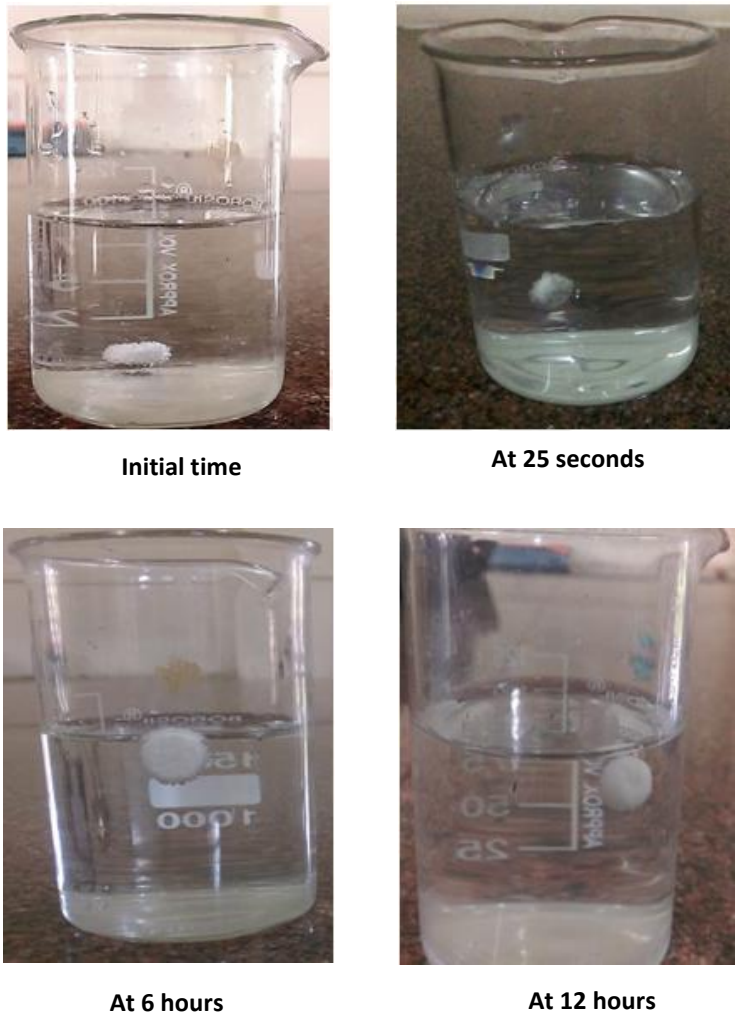
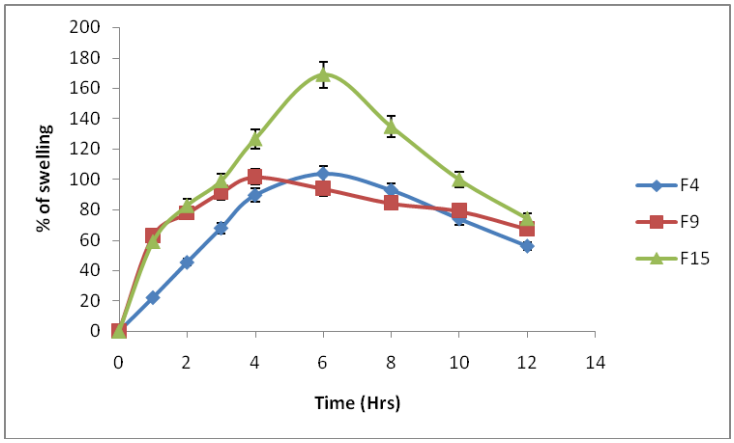


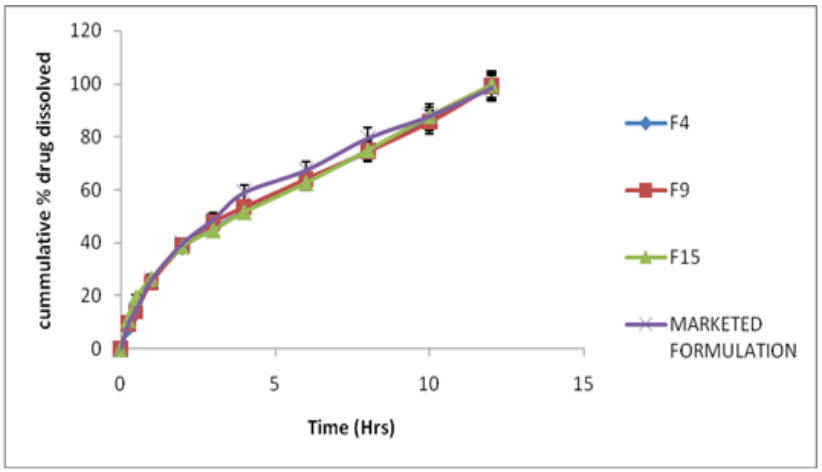
Figure IX: In-vitro buoyancy of optimized formulation

Swelling Studies: The formulations of the prepared floating tablets were subjected to swelling studies. The tablets swelled upon contact with the dissolution medium up to 7 hrs and later on the swelling was decreased. The percent swelling of optimized formulations were shown in the Graph IV.



Graph IV: Swelling behavior of matrix formulations (F4, F9, F15)

Similarity Factor: The similarity factor (f2) was calculated in order to compare the release profiles of F4, F9 and F15 with that of reference formulation. The formulations F4, F9 and F15 had a release profiles similar to that of the marketed formulation, with similarity factor **f2=88.94, 90.66 and 78.54 respectively**, hence these three formulations were comparable to the marketed formulation and the plots were shown in graph V.



Graph V: Comparison of Dissolution profile of F4, F9, F15 formulations with Marketed formulation.

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Conclusion:
In this investigation it was concluded that the Ambroxol Hydrochloride floating controlled release tablets can be formulated successfully with polymers like HPMCK100M, Carbopol 971P, POLYOX WSR 303 by direct compression method for a prolonged release of 12 hours. These floating matrix tablets can prolong the gastric retention which can reduce the side effects, increase the drug absorption and maintain the therapeutic efficacy for a prolonged period of time.

Conflict of interest:
There was no conflict of interest.

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