10.37021/ijper.v4i1.6

RESEARCH ARTICLE

Development and Characterization of Sustained Release Gastro-retentive Floating Tablets of Ambroxol Hydrochloride

Shobhana Thakur[1], Dolly Jain[2,3], Shiv K. Prajapati[4]*

ABSTRACT

Introduction: The objective of this study was to formulate floating tablets of Ambroxyl hydrochloride (AMB HCl) using the dry granulation technique to increase its bioavailability and the gastric residence time (GRT) of the dosage form.

Material and Method: The gastro-retentive floating tablets of AMB HCl were prepared by direct compression method using different concentrations of polymers such as HPMC K4, HPMC K15 and PVP K30, gas releasing agents (sodium bicarbonate and citric acid) and diluents (Microcrystalline cellulose). Citric acid was also used as an antioxidant. The final mixing was done by adding talc and magnesium stearate to the granules.

Result and Discussion: The prepared formulation of AMB HCl was evaluated by some evaluation parameters such as hardness, friability, weight variation, buoyancy lag time, drug contents, total floating time, in vitro dissolution study, and drug release study etc. The result from the FTIR data study of formulation discloses no interaction between the drug and excipients. In the FT-IR study, it was revealed that there is no interaction between the drug and excipients. The formulation containing the combination of HPMC K 15M polymer and Sodium bicarbonate shows a good drug release pattern with less floating lag time and good floating duration. In vitro drug release study of the prepared formulation (gastro retentive floating tablets of AMB HCl) showed that the formulation F5 was the best formulation found to be 99.87% drug release. The release mechanism and its kinetics were evaluated by plotting various mathematical models of release data such as the Higuchi model, Korsmeyer model, First-order and Zero-order drug release. The optimized formulation showed no significant change at various evaluation parameters such as hardness, friability, weight variation, and %drug release for accelerated stability conditions at 40 ± 2°C temperature and 75 ± 5% (RH) relative humidity for 3 months. The floating tablets of AMB HCl showed their potential over a prolonged period as a gastro retentive drug delivery system (GRDDS).

Keywords: Ambroxol Hydrochloride, Carbopol 971P, Floating Tablets, Gastro retentive drug delivery, HPMC K15, HPMCK100M polymers.

How to cite this article: Thakur S, Jain D, Prajapati SK. Development and Characterization of Sustained Release Gastro-retentive Floating Tablets of Ambroxol Hydrochloride. Int. J. Pharm. Edu. Res. 2022;4(1):43-49.

Source of support: Nil

Conflict of interest: None

[1]Department of Pharmacy, Shree Ram Group of Institutions, Jabalpur, Madhya Pradesh, India

[2]Department of Pharmacy, Oriental University, Indore, 453555, Madhya Pradesh, India

[3]Adina College of Pharmacy, Sagar, 470002, Madhya Pradesh, India

[4]Institute of Pharmacy, Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, 201310, Uttar Pradesh, India

Corresponding Author: Shiv K. Prajapati, Assistant Professor (Pharmaceutics), Institute of Pharmacy, Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, 201310, Uttar Pradesh, India, E-mail: shivprajapati1992@gmail.com

INTRODUCTION

The controlled release (CR) and gastro-retentive (GR) dosage form has been broadly used to improve therapy with several important drugs. Although the development processes were accepted, several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract (GIT) and the highly variable nature of the gastric emptying process. This variability may show unforeseeable bioavailability and time to achieve plasma levels. On the other hand, the incorporation of the drug in controlled release gastro retentive floating dosage forms, which can remain in the gastric region for several hours to enhance the solubility of the drugs, which are less soluble in a high pH environment, improves the bioavailability of drugs and reduce drug waste. The GRDDS also facilitates local drug delivery to the stomach and proximal small intestine.[1] Gastroretentive dosage forms offer an alternative strategy for achieving an extended-release profile, in which the formulation will remain in the stomach for prolonged periods, releasing the drug in situ, which will then dissolve in the liquid contents and slowly pass into the small intestine.[2]

Unlike a conventional release form, which gradually release the drug during transit along the GIT, such a delivery system would overcome the problems of drug that are absorbed preferentially from specific sites within the gastrointestinal tract (for example, many drugs are absorbed poorly from the distal gut, where an extended release dosage form may spend the majority of its time), and producing non-uniform plasma time

profile delivery systems that do not rely on polymers' presence. To achieve gastro retention, mucoadhesive and low-density polymers have been evaluated, with little success so far, for their ability to extend gastric residence time by bonding to the mucus lining of the stomach and floating on the top of the gastric contents, respectively. Cellulose based polymers such as ethylcellulose (EC) of different viscosity grades find wide application in the preparation of floating tablets for water-soluble drug for control release.[3-6]

Ambroxol Hydrochloride (Amb- trans-4-(2-amino-3,5-dibromobenzyl) amino cyclo- hexanol) is an active metabolite of bromhexine and is used to cure many kinds of acute and chronic breathing diseases with the general symptoms of phlegm and inflammation. Its short biological half-life of 4hrs requires frequent daily dosing of the drug (two to three times) and its therapeutic use in chronic respiratory diseases necessitates its formulation into the controlled release dosage form. Hence the purpose of the present work was to prepare a controlled release dosage form (floating tablets) of AMB HCl using different grades of hydroxypropyl methylcellulose (HPMC) as a retarding material.[7,8]

MATERIALS AND METHODS

Materials

AMB HCl was a gift sample from Alembic Pharma Vadodra, India. HPMC K 15 (hydroxypropyl methylcellulose), HPMC K 4, MCC (Microcrystalline Cellulose), and Carbopol 971P were purchased from Mapromax Life Sciences Pvt. Ltd., Dehradun. Talc, Magnesium stearate, Sodium bicarbonate, and Citric acid were purchased from Rankem Chemicals Ltd, Mumbai, India.

Methods

UV Spectroscopy

The λ_{max} of AMB HCl is determined by running the spectrum of drug solution in a UV spectrophotometer (double-beam). For the standard calibration curve, exactly weighed 100 mg of drug was dissolved in 100 mL of 0.1 N HCl buffer solution in 100 mL of volumetric flask. The resulted solution was 1000 µg/mL and from this solution, 1-mL solution was pipette out into a 100 ml volumetric flask and diluted up to 100 ml to make the final stock concentration of 10 µg/mL and volume makes up with 0.1 N HCl buffer solution, then different aliquots were prepared by taking 0.5, 1, 1.5, 2, and 2.5 mL in 10 mL volumetric flask separately, and volume makeup up to 10 mL by 0.1 N HCl to make the concentration range from 5–25 µg/mL. The spectrum of different concentrations was observed by the UV spectrophotometer (Labindia-3000+) at 244 nm. The spectrum peak point graph of absorbance of AMB HCL versus wavelength was shown in Figure 1.

Fourier Transform Infrared (FTIR) Spectroscopy

The infrared spectrum is an important record that gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption bands from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 to 2.5 µ is known as Near infra-red (NIR) and 15 to 200 nm is known as Far infra-red (FIR). The identification of the drug (AMB HCl) is carried out by FTIR spectroscopy to marker compounds.

Direct Compression Method

The floating tablets of AMB HCl were prepared by direct compression method using different concentrations of polymers in different batches (F1-F9). The different concentrations of polymers were mixed with the drug and passed through the 40 meshes sieve, in which magnesium stearate was used as a lubricant, talc used as a glidant, sodium bicarbonate and citric acid used as gas generating agent. All the ingredients were mixed uniformly in a polybag and evaluated for several tests.[9,10] The composition of AMB HCl floating tablets was shown in Table 1.

Evaluation of AMB HCl Tablets

General Appearance

The five tablets of each batch were selected to evaluate their organoleptic properties such as colour, taste, and odor. The appearance was judged visually.

Thickness and Diameter

The thickness and diameter of AMB HCl tablets were

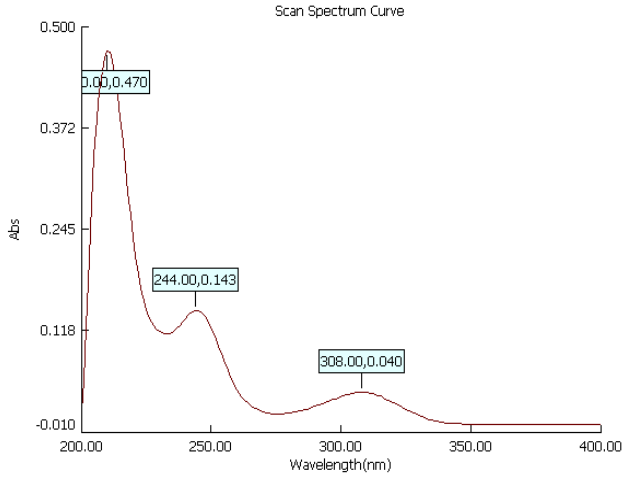


Figure 1: Determination (λ_{max}) of AMB HCl by UV spectroscopy

determined by a vernier caliper. Five tablets from each batch were used, and an average value was calculated.[11]

Hardness

The hardness of AMB HCl tablets was studied by a Monsanto hardness tester (Cadmach). Fixed the table in hardness tester and applied the pressure on the tablet. The pressure value noted on which the tablet was broken.

Friability

The friability of different batches of drugs was studied by a Roche friability tester in the Electro lab. 10 tablets of each batch were weighed separately, placed in friability, and rotated at 25 rpm for 4 minutes. After rotation, the same tablets were reweighed, and the % weight loss was calculated.[10]

Uniformity of Weight

The twenty tablets of each batch were selected for the test. The tablet was weighed individually from the batch of 20 tablets and calculated the average weight and standard deviation of each batch.[12]

Drug Content

Twenty tablets were taken and the amount of drug in each tablet was determined. The 20 tablets of AMB HCl of each batch were crushed and converted in powder form equivalent to 100 mg and transferred in the standard flask and added 50 mL of 0.1 N HCl solution, dissolved it and finally make up the volume up to 100 mL. the prepared solution was filtered through the 0.45 membrane filter and analyzed under UV spectrophotometer at wavelength 244 nm using 0.1N HCl as blank.[13]

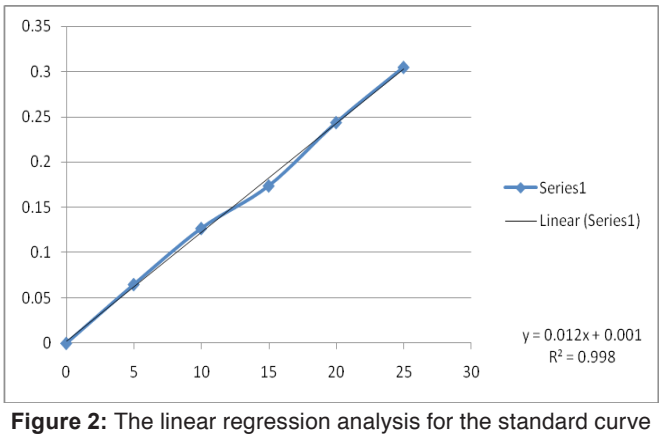


Figure 2: The linear regression analysis for the standard curve

In Vitro Buoyancy Studies

The buoyancy was determined by floating lag time. The tablet of each batch was placed in a beaker containing simulated gastric fluid (SGF) at pH 1.2 as per USP protocol. The time interval at which the tablet raised to the surface and floated was determined as floating lag time.[12,14,15]

In Vitro Dissolution Rate Studies

In vitro drug release of the tablet of AMB was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 mL 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37 ± 0.5°C and rpm of 75. One Ambroxol tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 10 hours. Samples measuring 10ml were withdrawn after every 1-hour up to 10 hours using a 10 mL pipette. The fresh dissolution medium was replaced every time with the same quantity of the sample.[16,17]

Kinetic Modeling of Drug Release

To determine the kinetic modeling of drug release, the dissolution profiles of all formulations were fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.[18-21]

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and to establish a re-test period for the drug substance or shelf life for the drug product and recommended storage conditions. The ICH Guidelines Q 1 A (R2) have established that long term stability testing should be done at 25°C/60% RH; stress testing should be done at 40°C/75% RH for 6 months. If a significant change occurs under these stress conditions, then the formulation

Table 1: Optimization and development of sustained-release gastro-retentive floating tablets of AMB HCl (F1-F9)

Excipients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Ambroxol HCl	75	75	75	75	75	75	75	75	75
HPMCK 15	25	50	75	-	-	-	-	-	-
Carbopol 971P	-	-	-	25	50	75	-	-	-
HPMCK100M							25	50	75
Citric acid	25	25	25	25	25	25	25	25	25
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

should be tested at an intermediate condition, i.e., 30°C/75% RH.[22]

RESULTS AND DISCUSSION

Determination of λ_{max} of Ambroxol HCl

The λ_{max} of AMB HCl was determined by running the spectrum of drug solution in a double beam ultraviolet spectrophotometer. The spectrum of this solution was run 200–400 nm range in U.V. spectrophotometer (Labindia-3000+). The maximum absorption λ_{max} of Ambroxol HCl was found at 244.0 nm (Figures 1 and 2; Table 2).

Identification Test by FTIR

Identification of AMB HCl was done by FTIR Spectroscopy. AMB HCl was obtained as a white or almost white crystalline powder. It was further identified by IR spectrum and was compared with standard IR spectra of AMB HCl as per specification. The IR spectrum of the sample drug showed the same characteristics peak values as compared to standard IR spectra of the drug. The IR spectrum of the sample drug shows the peak values which are the drug's characteristics and the graph shown in Figure 3.

General Appearance

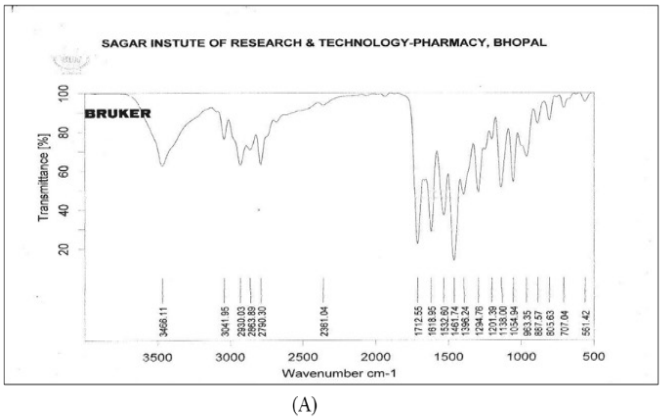
Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, and shape, were evaluated. The appearance was judged visually. The tablets of all batches (F_1-F_9) were prepared and evaluated on various parameters. The results of evaluation parameters are recorded in Table 3 and show that batch F5 was found to be suitable for the formulation. The thickness, hardness, weight variation, % Friability, and percentage drug content of batch F5 were found to be 3.93 ± 0.10, 5.2 ± 1.2, 327.13 ± 2.83, 0.31 ± 0.07 and 97.21 ± 1.07 respectively.

Optimization of Powder Blend

In the optimization, different compositions of drug and excipients were prepared by triturating the drug with

Table 2: Calibration curve of AMB HCl

S. No.	Conc. (µg/ml)	Absorbance (λ max at 244 nm)			
		I	II	III	Average
1	5	0.065	0.066	0.065	0.065
2	10	0.127	0.128	0.127	0.127
3	15	0.174	0.174	0.175	0.174
4	20	0.244	0.245	0.246	0.245
5	25	0.305	0.305	0.306	0.305



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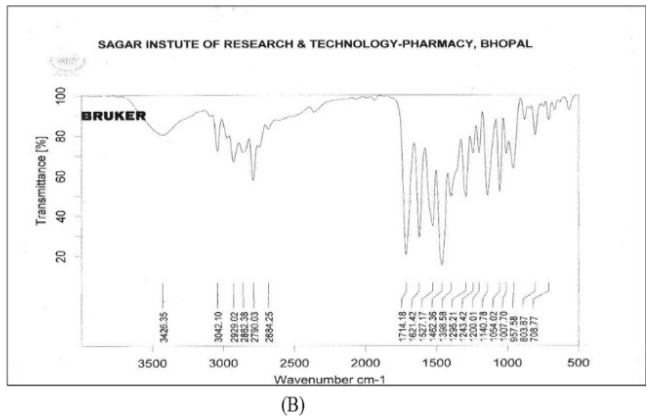

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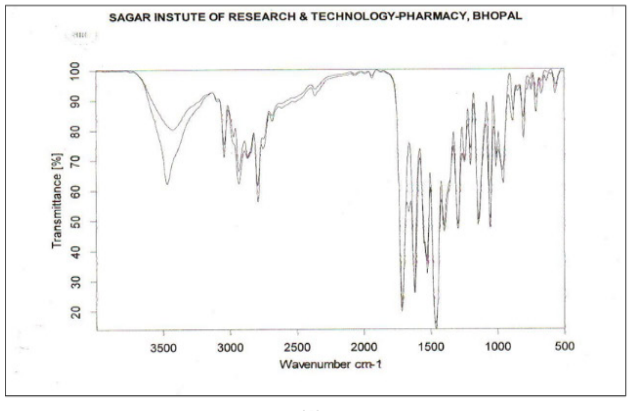

(C)

Figure 3: (A) FT-IR Spectrum of Pure Drug (AMB HCl) (B) FT-IR Spectrum of Pure Drug and Excipients (C) Interpretation of FT-IR Spectrums of Pure Drug and Excipients

Table 3: Evaluation of sustained release gastro-retentive floating tablets of AMB HCl

Formulation code	*Thickness (mm)*	*Hardness (kg/cm^2)*	*Weight variation (mg)*	*Friability (%)*	*Drug content (%)*	*Total floating duration (hrs)*
F1	3.53 ± 0.05	4.8 ± 0.06	328.19 ± 2.94	0.58 ± 0.10	98.33 ± 0.92	8
F2	3.94 ± 0.10	4.4 ± 0.15	332.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	10
F3	3.96 ± 0.05	4.5 ± 0.25	335.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	>12
F4	3.95 ± 0.05	4.7 ± 0.04	336.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	>12
F5	3.93 ± 0.10	5.2 ± 1.20	327.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	>12
F6	4.03 ± 0.06	5.3 ± 1.22	332.16 ± 2.33	0.27 ± 0.05	97.50 ± 1.81	>12
F7	4.05 ± 0.05	4.7 ± 1.31	328.16 ± 3.01	0.29 ± 0.8	98.34 ± 0.37	>12
F8	4.80 ± 0.06	4.6 ± 1.31	330.17 ± 3.12	0.28 ± 0.78	93.34 ± 0.37	>12
F9	4.85 ± 0.03	4.4 ± 0.4	331.18 ± 3.01	0.27 ± 0.5	96.34 ± 0.37	>12

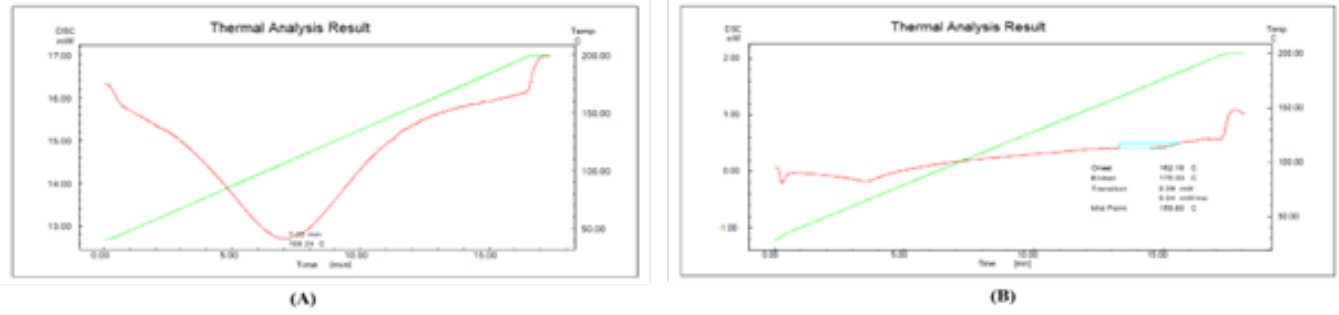

Figure 4: (A) DSC graph of standard AMB HCl (B) DSC graph of standard AMB HCl+excepients

Table 4: *In Vitro* buoyancy study of AMB HCl floating time

Formulation Code	*Buoyancy lag times (sec)*	*Total Floating Time (hrs)*
F_1	25	>8
F_2	35	>10
F_3	56	>12
F_4	75	>12
F_5	60	>12
F_6	80	>12
F_7	110	>10
F_8	115	>12
F_9	120	>10

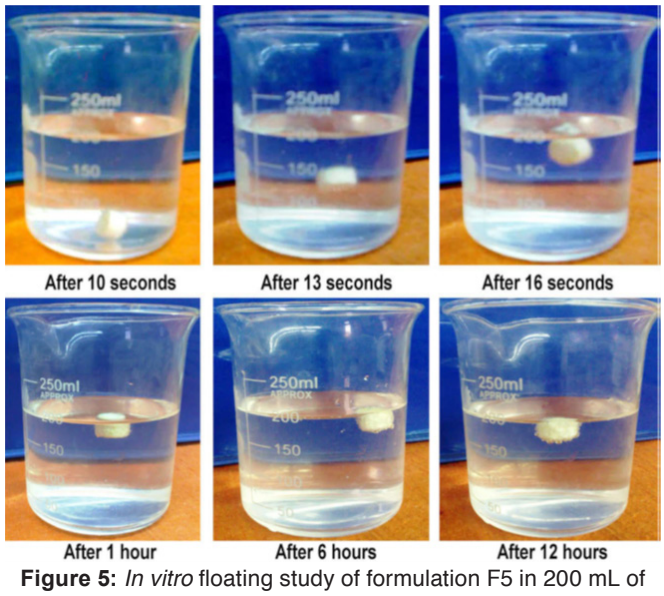

Figure 5: *In vitro* floating study of formulation F5 in 200 mL of 0.1 N HCl at a different time interval

excipients. The precompression parameters of all the batches were evaluated and the results are shown in Table 3. Batch F5 was selected as an optimized batch whose angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner ratio was found to be 28.30, 0.580 ± 0.003, 0.735 ± 0.004, 30.30 ± 0.61 and 0.730 ± 0.04 respectively.

Compatibility Studies of Drug and Excipients

In the compatibility testing program, blends of drug and excipients are prepared by triturating the drug with Individual excipients (Figure 4).

In vitro Buoyancy Studies

The result of *in vitro* buoyancy studies indicates that the optimized formulation F_5 on immersion in 0.1N HCl solution at pH 1.2 at 37 ± 0.50°C tablets floats immediately and remains buoyant for up to 12 hrs without disintegration as results shown in Table 4 and Figure 5.

In Vitro Drug Release Studies

Seven formulations with variable polymer concentrations were prepared by direct compression method and evaluated for physical properties, buoyancy lag time, and *in vitro* drug release. The floating property of the tablet is governed by both the swelling (hydration) of the polymer when it contacts the gastric fluid. The *in vitro* drug release data of the optimized formulation was subjected to a goodness of fit test by linear regression analysis according

Table 5: *In vitro* drug release profile of floating tablets

Time	Drug Release (%)								
(Hrs)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08.32	09.30	10.87
1	12.32	10.23	11.45	10.45	10.45	11.23	12.23	13.23	17.23
1.5	26.23	22.42	24.23	23.76	31.23	38.23	32.13	35.32	48.25
2	42.45	40.32	45.23	44.23	48.23	46.32	47.14	49.21	57.43
3	76.34	66.11	67.21	65.71	50.56	67.02	71.13	59.09	63.34
4	82.23	77.33	75.11	82.34	55.00	88.13	91.23	82.85	84.21
6	82.55	97.13	87.13	83.00	56.00	99.13	92.00	90.34	91.31
8	83.00	97.10	94.23	83.21	57.25	99.99	93.00	95.45	96.56
12	84.21	97.23	99.26	83.50	57.85	99.87	94.56	96.43	97.34

Table 6: Release kinetics of optimized formulation F-5

	Zero order		First order			Higuchi eq.		Korsemayer -papas	
SN	Time (hrs.)	Cum%DRs	Time (Hrs.)	LOG Cum%CDt	Cum%CDt	ROOT T	cum% DRs	log time	log cum% DRs
1	0	0	0	0	0	0	0	0	0
2	0.5	7.24	0.5	1.967	92.76	0.707	7.24	-0.301	0.859
3	1	11.45	1	1.947	88.55	1	11.45	0	1.058
4	1.5	24.23	1.5	1.879	75.77	1.224	24.23	0.176	1.384
5	2	45.23	2	1.738	54.77	1.414	45.23	0.301	1.655
6	3	67.21	3	1.515	32.79	1.73	67.21	0.477	1.827
7	4	75.11	4	1.396	24.89	2	75.11	0.602	1.875
8	6	87.13	6	1.109	12.87	2.449	87.13	0.778	1.940
9	8	94.23	8	0.761	5.77	2.828	94.23	0.903	1.974
10	12	99.26	12	0.130	0.74	3.464	99.26	1.079	1.996

Table 7: Stability analysis of AMB HCl tablet (F5)

Evaluation parameters	Before stability	After 1 month storage	After 2 months Storage	After 3 months storage
Hardness (kg/cm^2)	5.2 ± 0.1	5.2 ± 0.2	5.2 ± 0.25	5.2 ± 0.3
Friability (%)	0.31 ± 0.07	0.33 ± 0.09	0.34 ± 0.09	0.34 ± 0.1
Drug content (%)	97.21 ± 1.07	96.84 ± 1.03	95.45 ± 1.07	94 ± 1.03
Weight variation (mg)	327.13 ± 2.8	327.37 ± 0.39	328.09 ± 0.75	328.03 ± 0.45

to zero-order, first-order kinetic equation, Higuchi's and Korsmayer models to determine the mechanism of drug release. The %drug release of batches from F1-F3 was increased, then from F3-F5 were decreasing and from F5–F6 were increased F7- F9 gradually increased as shown in Tables 5 and 6; Figure 6. The %drug release of F5 was found to be 57.85, which was very low as compared to other batches.

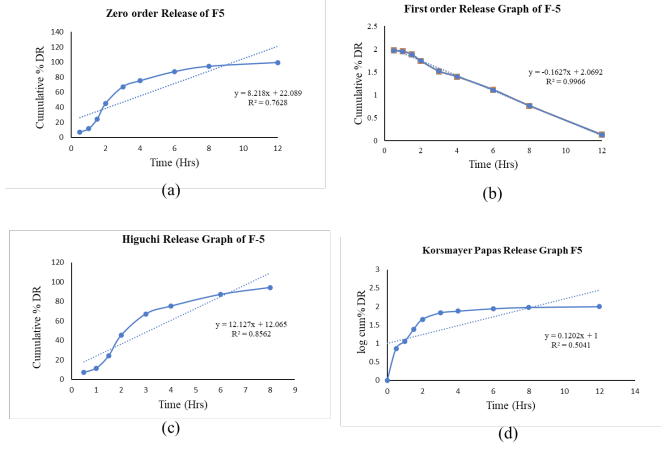

Figure 6: Drug Release Kinetics of floating tablet

Stability Studies

Stability studies were performed with optimized batch formulations (F5) that were stored for periods of one, two, and three months at 40 ± 2°C temperature and 75 ± 5% relative humidity (RH). The formulation was determined by UV spectrophotometer using the calibration curve method. The % assay of tablets was found to slightly decrease at higher temperatures. A minor difference was found between evaluated parameters before and after aging/storage and all were within acceptable limits. After storage of sustained-release gastro-retentive floating tablets of AMB HCl (F5) were analyzed for various physical parameters, results are shown in Table 7. Therefore formulations remain stable for sufficient time.

CONCLUSION

AMB HCl, which is currently available in the market as conventional tablets, can be successfully formulated as sustained release floating tablets, which have the advantage of retaining the dosage form in the effective site of absorption for a long time and releasing the drug in a sustained manner, resulting in the desired steady-state concentration level and increased bioavailability of the drug. It is possible to conclude from the experimental data that a successful gastro retentive floating drug delivery system for AMB HCl has been designed using the direct compression method. The current study examines the application of rate retarding and gas-producing agents such as HPMC K15M, HPMCK100M, and sodium bicarbonate in the design and development of Gastro Retentive Floating tablet formulations of AMB HCl. It was clear from the results that as the amount of polymer in the tablet formulation increases, the drug release rate decreases, and as the concentration of gas generating agent ($NaHCO_3$) increases, the drug release rate increases. These polymers can be used in combination because they do not interact with the drug and may be more helpful in achieving the desired floating delivery of the drug for longer periods.

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