Asian J. Pharm. Res. Vol 9, Issue 2, 35-41, 2019.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE GASTRO-RETENTIVE FLOATING TABLETS OF AMBROXOL HYDROCHLORIDE

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ABSTRACT
The present study was an attempt to formulate a gastro-retentive floating drug delivery system of Ambroxol Hydrochloride, in order to improve its gastric residence time and bioavailability. Floating lag time, and hardness of the tablets of Ambroxol Hydrochloride, by applying the optimization technique. The data from the release profile were fitted to various mathematical models, and fitting to the Korsmeyer and Peppas equation revealed that the release mechanism from the dosage form followed the non-fickian transport.

Key words: Sustained Release, Ambroxol Hydrochloride, Gastro-retentive, Floating Drug Delivery System.

INTRODUCTION

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process [1-4]. This variability may lead to unpredictable bioavailability and time to achieve plasma level. On the other hand, incorporation of the drug in controlled release gastro-retentive forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment [5-8]. Gastro-retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastro-retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients [9-11].

Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro-retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs[12].

The present study is an attempt to formulate a gastro-retentive floating drug delivery system of Ambroxol Hydrochloride, in order to improve its gastric residence time and bioavailability, Floating lag time, and hardness of the tablets of Ambroxol Hydrochloride, by applying the optimization technique. This also increases the half-life of drug in the stomach sothat the dose frequency also reduces [12,13].

Gastro retentive systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems [14].

MATERIALS AND METHODS

Ambroxol Hydochloride was obtained as gift sample Alembic Pharma Vadodra, other chemicals like HPMC K 15, HPMC K 4, MCC Mapromax, PVP K30 Mapromax procured from Life sciences Pvt. Ltd., Dehradun and Talc, Magnesium Stearate, Sodium bi carbonate and citric acid procure from Renkem chemicals Ltd, Mumbai.

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METHODS

Direct compression was followed to manufacture the gas generating floating tablets of Ambroxol HCl. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. Polymers selected for tablets are: HPMC K 15, HPMC K4, PVP K 30.

Procedure: First the drug, polymer and other excipients selected were passed through 40- mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5 min.

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.

Procedure: Taken 50 mg accurately weigh of Ambroxol dry powder and 50 mg of excipients and mix the blend of drug and excipients and binary/tertiary blends of extract and excipients were prepared and transferred to inert glass vials. The mouths of the vials were covered with rubber closures followed by the aluminum seal caps. Binary/tertiary blends of extract and excipients, Ambroxol HCl neat and excipients were stored at 4˚C (refrigerator) as control and at 40˚C/75% RH for accelerated stability studies for 4 weeks. The visual observations (color, flow, & sticking) were recorded for initial and at the end of the first, second, third and fourth week.

Flow Properties

Flow properties determination of powder or granules is the unique tools to avoid the weight variation of tablet Angle of repose, Carrs index, Hausner ratio are some technique by which we can estimate the flow properties of powder.

The angle of repose is a relatively simple technique for estimating the flow ability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone is measured and using the following equation, the angle of repose can be calculated.

$$\mathbf{Tan\ \theta = h/r}$$

Where h, r is the relatively height and radius of the powder cone. For most pharmaceutical powders, the angle of repose values range from 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest a poorly flowing material.

Bulk Density

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Tapped Density

Tapped density is determined by measuring the volume of a known mass of powder sample before and after the tapping that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Compressibility Index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material.

Hausner Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

Dissolution rate studies

In vitro drug release of the sample 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 dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 10ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37˚C) was replaced every time with the same quantity of the sample.

Stability Study

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 a 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 25^0C/60% RH; stress testing should be done at 40^0C/75 % RH for 6 months. If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e. 30^0C/75 % RH.

RESULTS AND DISCUSSION

Physical evaluation

It refers to the evaluation by sensory characters- taste, appearance, odor, feel of the drug, etc.

Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test

tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH, SGF, Chloroform and acetone). Shacked vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Melting Point: It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Partition Coefficient: It is a measurement of a drug's lipophilicity and an indication of its ability to cross cell membrane is the oil/water partition coefficient in system such as octanol/water and chloroform/water. The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were placed in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to raise to the surface and float was determined as floating lag time.

Table 1. Various Formulations of Sustained Release Gastro-retentive Floating Tablets of Ambroxol Hydrochloride

Excipients	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Ambroxol HCl	75	75	75	75	75	75	75
HPMCK 15	25	50	75	100	125	65	-
HPMC K 4	100	75	50	25	-	60	125
PVP K30	10	10	10	10	10	10	10
Citric acid	25	25	25	25	25	25	25
Sodium bicarbonate	50	50	50	50	50	50	50
Magnesium stearate	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5
Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Table 2. List of Sensory Characters

S. No.	Sensory characters	Result
1.	Taste	Tasteless
2.	Appearance	White to Off-White
3.	Odor	Odorless
4.	Texture	Crystalline

Table 3. Solubility of Ambroxol HCl

S. No.	Solvent	Solubility
1.	Water	Soluble (+)
2.	Ethanol	Soluble (+)
3.	Methanol	Freely soluble (++)
4.	0.1N HCL	Soluble (+)
5.	0.1N NaOH	Insoluble (--)
6.	Chloroform	Poorly soluble (-)
7.	Acetone	Poorly soluble (-)

Table 4. Melting point of the Ambroxol HCl

S. No.	Melting Point of Ambroxol HCl	Average Melting Point of Ambroxol HCl
1.	220-225˚ C	220-225˚ C
2.	219-225˚ C	
3.	220-225˚ C	

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Table 5. Partition Coefficient of the Ambroxol HCl

S. No.	Amount of drug in octanol	Amount of drug in water	Partition coefficient ($P_{o/w}$)	Average partition coefficient
1.	370.08	440.47	0.84	0.84
2.	375.50	447.02	0.84	
3.	365.25	440.06	0.83	

Calibration Curve of Ambroxol HCl at λ_{max} 244 nm
Observation Table:

Table 6. Calibration Curve of Ambroxol 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

Table 7. Evaluation of sustained release Gastro-retentive Floating Tablets of Ambroxol Hydrochloride

Code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)
F_1	3.53±0.05	4.8	328.19± 2.94	0.58 ± 0.10	98.33± 0.92	8
F_2	3.94± 0.10	4.4	332.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	10
F_3	3.96± 0.05	4.5	335.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	>12
F_4	3.95± 0.05	4.7	336.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	>12
F_5	3.93± 0.10	5.2	327.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	>12
F_6	4.03± 0.06	5.3	332.16 ± 2.33	0.27 ± 0.05	97.50± 1.81	>12
F_7	4.05± 0.05	4.8	338.18 ± 3.11	0.29 ± 0.08	98.34 ± 0.37	>12
F_8	3.98± 0.05	4.5	327.04 ± 2.56	0.34 ± 0.12	98.31± 0.91	>12

Table 8. Pre Compression Properties of Sustained Release Gastro-Retentive Floating Tablets of Ambroxol Hydrochloride

Mat-erial	Angle of repose(Degree)	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F_1	28.31	0.582±0.002	0.732±0.007	27.33±0.73	0.721±0.01
F_2	26.35	0.581±0.008	0.730±0.006	28.33±0.72	0.723±0.01
F_3	27.82	0.576±0.002	0.728±0.005	27.30±0.68	0.720±0.01
F_4	27.69	0.570±0.007	0.729±0.003	29.30±0.65	0.726±0.03
F_5	28.30	0.580±0.003	0.735±0.004	30.30±0.61	0.730±0.04
F_6	29.28	0.585±0.003	0.732±0.006	32.80±0.64	0.728±0.06
F_7	28.46	0.582±0.004	0.742±0.003	36.24±0.70	0.720±0.03

Table 9. *In vitro* Buoyancy Study of Ambroxol HCl FGR Floating Time.

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

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Table 10. Release Kinetics of Optimized Formulation F-5

S.no	Zero order		First order			Higuchi equation		Korsemayer -papas	
	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 11. ICH Guideline for Stability Study

Study	Storage condition	Time period
Long term*	25°c±2°c/60% RH±5% RH or 30°c±2°c/65% RH±5% RH	12 months
Intermediate**	30°c±2°c/65% RH±5% RH	6 month
Accelerated	40°c±2°c/75% RH±5% RH	6 month

Figure No. 1 The Linear Regression Analysis for Standard Curve

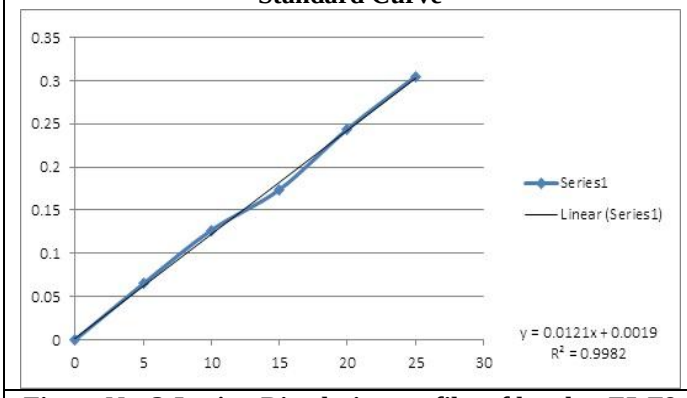

Figure No. 2 *In vitro* Dissolution profiles of batches F1-F4

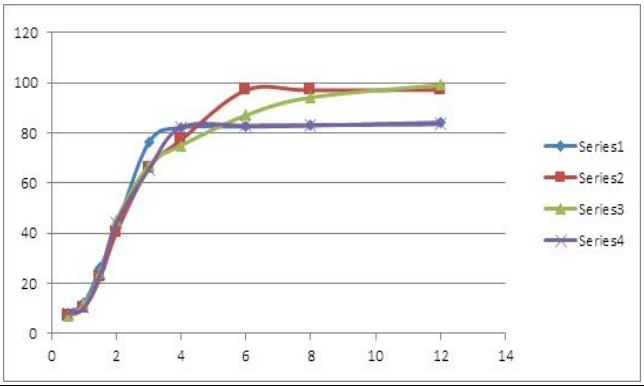

Figure No. 3 *In vitro* Dissolution profiles of batches F5-F8

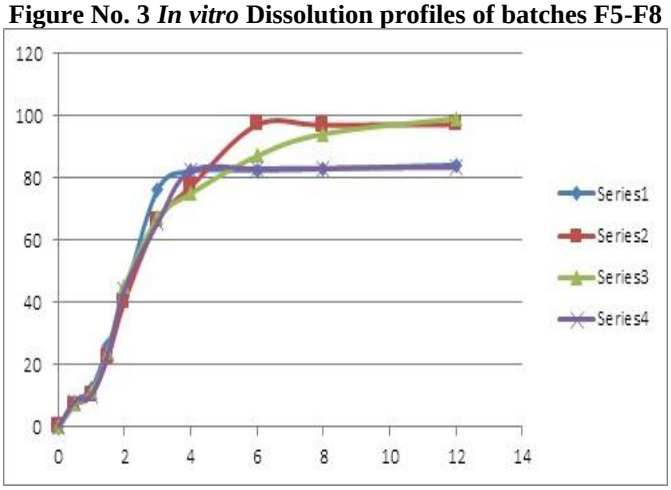

Figure No. 4 Zero order Release Graph

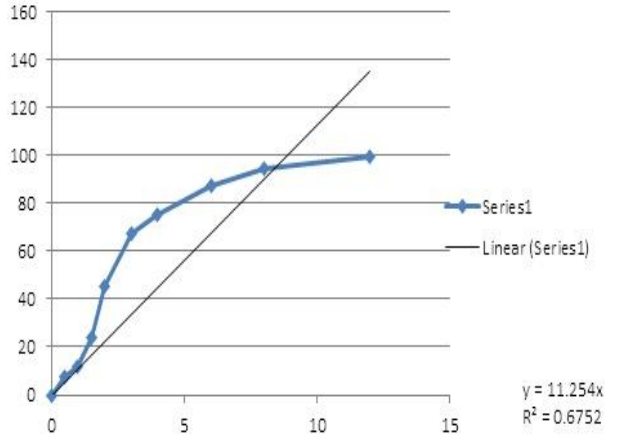

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Figure 5. First order Release Graph

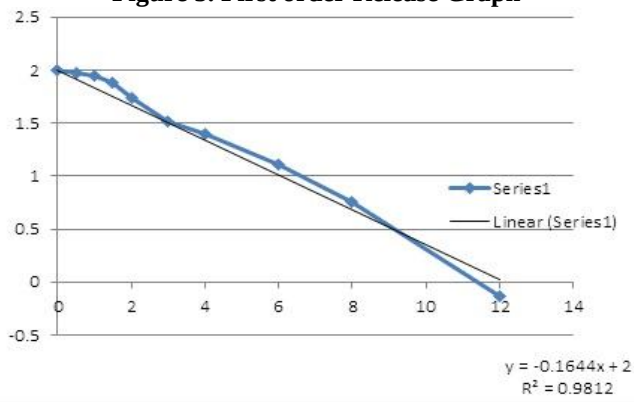


Figure 6. Higuchi Release Graph

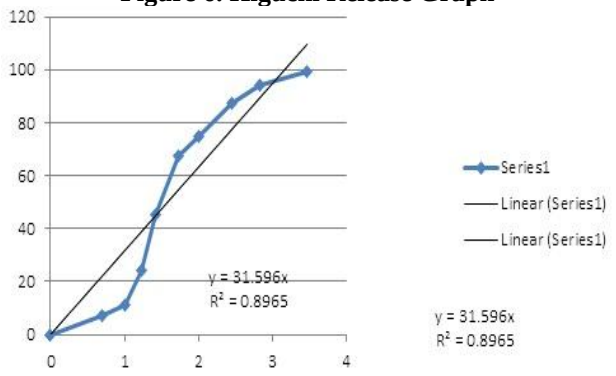
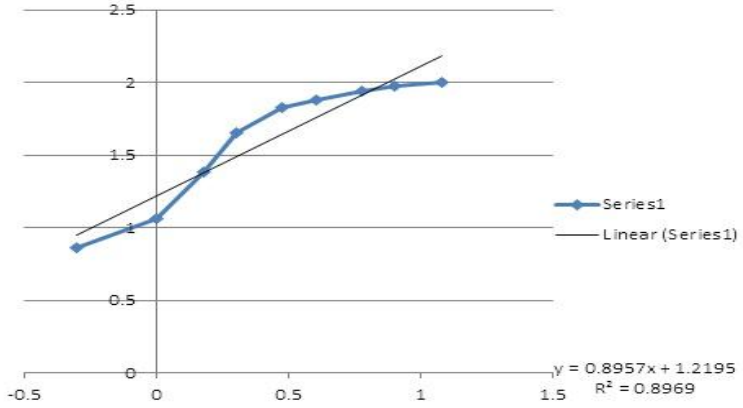


Figure 7. Korsmayer Papas Release Graph



DISCUSSION

Gastro retentive systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of less than1 as a result of which they can float on the gastric contents.

CONCLUSION

On the basis of Pre-formulation study of Ambroxol Hydrochloride it was concluded that the drug Ambroxol Hydrochloride was suitable for the preparation of sustained release dosage form. The various dosage form of Ambroxol Hydrochloride are available in market such as tablets, syrups and injectable but its sustained release dosage form increase its gastric residence time and decrease its dosing frequency.

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