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

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ABSTRACT

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. Ambroxol HCl is a secretolytic agent used in the treatment of respiratory diseases associated with viscid or excessive mucus. It is the active ingredient of Mucosolvan, Mucobrox, Lasolvan, Mucoangin, Surbronc and Lysopain. The substance is a mucoactive drug with several properties including secretolytic and secretomotoric actions that restore the physiological clearance mechanisms of the respiratory tract, which play an important role in the body's natural defence mechanisms.

KEY WORDS- *Controlled release (CR) dosage forms, Physiological difficulties, Gastric emptying process, Ambroxol HCl, Mucoactive drug.*

1. INTRODUCTION

GASTRORETENTIVE DRUG DELIVERY SYSTEM

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. This variability may lead to unpredictable bioavailability a n d time to achieve plasma level. On the other hand, incorporation of the drug in a controlled release gastroretentive 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.

Ambroxol HCl is a secretolytic agent used in the treatment of respiratory diseases associated with viscid or excessive mucus. It is the active ingredient of Mucosolvan, Mucobrox, Lasolvan, Mucoangin, Surbronc and Lysopain. The substance is a mucoactive drug with several properties including secretolytic and secretomotoric actions that restore the physiological clearance mechanisms of the respiratory tract, which play an important role in the body's natural defence mechanisms. It stimulates synthesis and release of surfactant by type II pneumocytes. Surfactant acts as an anti-glue factor by reducing the adhesion of mucus to thebronchial wall, in improving its transport and in providing protection against infection and irritating agents.

2. MATERIAL AND INGREDIENTS

Ambroxol Hydochloride was obtained from Alembic Pharma Vadodra. As a Gift Sample, HPMC K 15, HPMC K 4, MCC and PVP K30 was obtained from Mapromax, Life sciences Pvt. Ltd., Dehradun, Talc, Magnesium state, Sodium bi carbonate, Citric acid was obtained from Renkem chemicals Ltd, Mumbai.

3. PREFORMULATION STUDIES

Preliminary stability studies involve chemical, physiochemical and, when necessary, microbiological tests.
Stability studies are sometimes thought of as concerning only chemical stability but the stability of physiochemical characteristics are also important. These are some examples of preformulation studies are- Organoleptic properties, particle shape , size, Melting point, solubility, partition coefficient etc.

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4. METHOD OF PREPARATION

Dry granulation method

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablet or slug are milled to yield the granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilosonator.

Table 1: Various formulation 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	150	-
HPMC K 4	125	100	75	50	25	-	150
PVP K30	15	15	15	15	15	15	15
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

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	

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	

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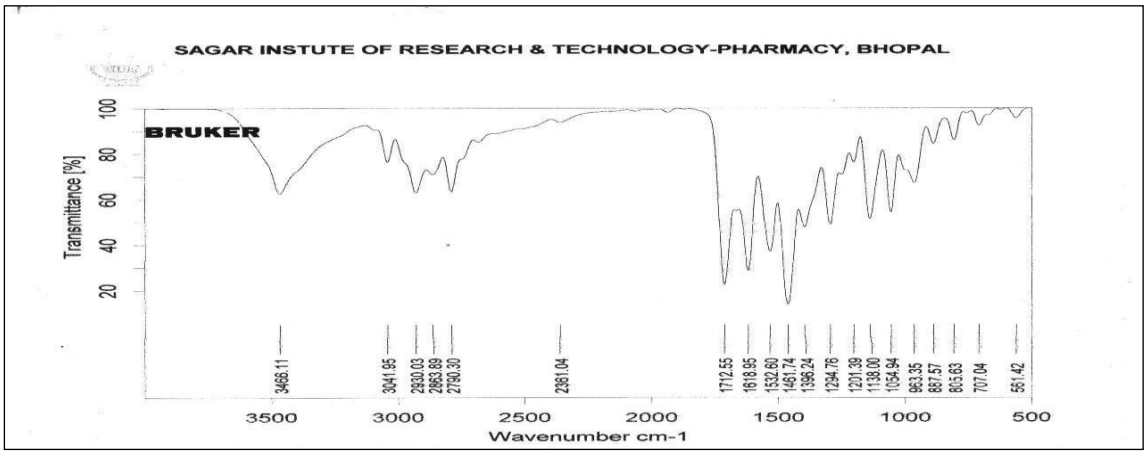

Fig. 1: FT-IR Spectrum of Pure Drug (Ambroxol HCl)

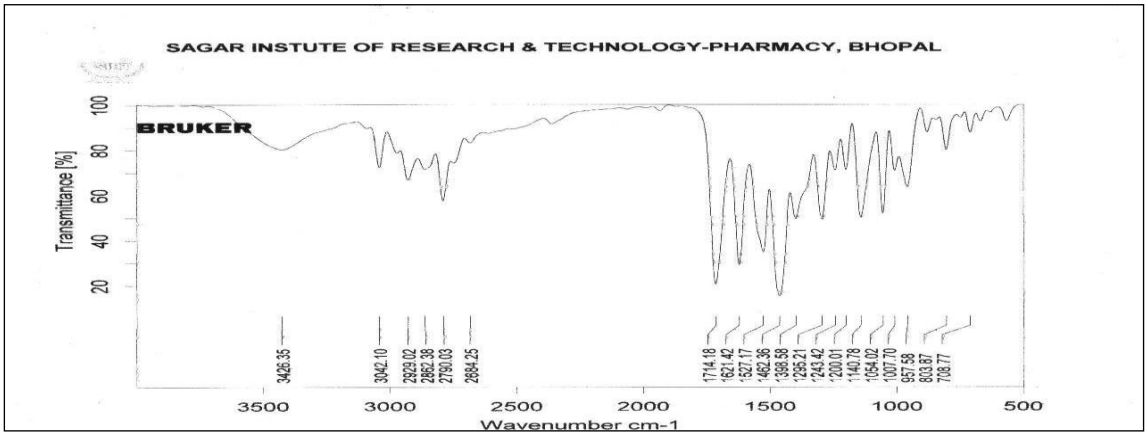

Fig. 2: FT-IR Spectrum of Pure Drug and Excipients

Table 6: Bulk density of Ambroxol HCl

S. No.	Bulk mass	Bulk volume	Bulk density	Avg. bulk density
1.	10 gm	15 ml	0.666 g/ml	0.625 g/ml
2.	10 gm	16 ml	0.625 g/ml	
3.	10 gm	16 ml	0.625 g/ml	

Table 7: Angle of repose of Ambroxol HCl

S. No.	Height of pile	Radius of pile	Angle of repose	Avg. angle of repose
1.	2.3 cm	5 cm	25 º	**25 º**
2.	2.4 cm	5.1 cm	25 º10’	
3.	2.5 cm	5.4 cm	25 º	

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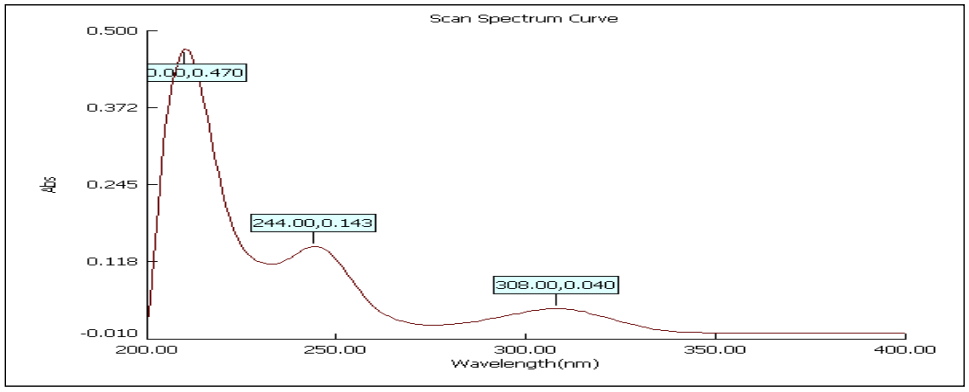

Fig. 3: Standard calibration curve of Ambroxol HCl

Table 8: Calibration curve of Ambroxol HCl

S. No.	Conc. (µg/ml)	Absorbance (λ max at 244nm)			
		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 9: Evaluation of Sustained Release Gastro-Retentive Floating Tablets of Ambroxol Hydrochloride

Formul.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 10: 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 11: In-vitro drug release of floating tablets

Time	% of Drug Release							
(hr)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26
1	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87
1.5	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28
2	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21
3	76.34	66.11	67.21	65.71	50.56	67.02	71.13	68.24
4	82.23	77.33	75.11	82.34	55.00	88.13	91.23	89.12
6	82.55	97.13	87.13	83.00	56.00	99.13	92.00	99.25
8	83.00	97.10	94.23	83.21	57.25	99.99	93.00	99.56
12	84.21	97.23	99.26	83.50	57.85	99.87	94.56	99.76

Table 12: Release Kinetics of Optimized Formulation F-5

	Zero order		First order			Higuchi equation		Korsemayer - papas	
S.n.	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

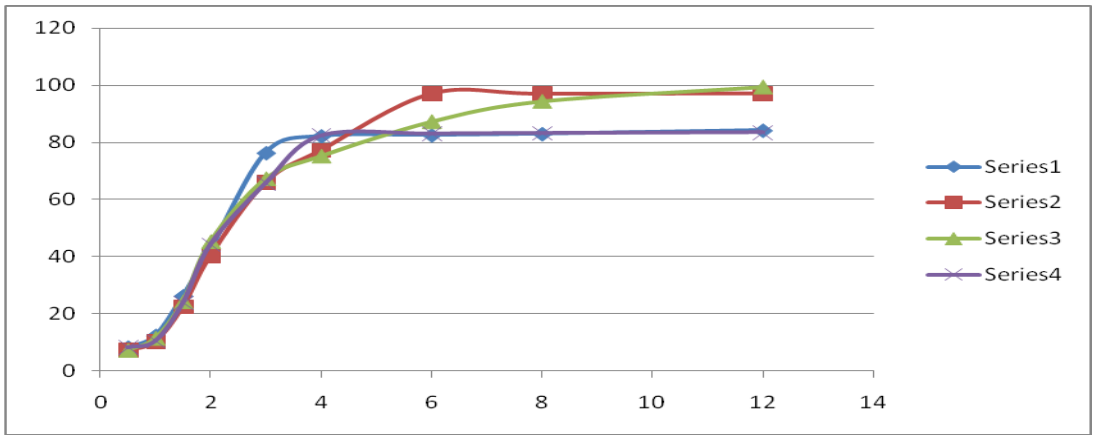

Fig. 4: In vitro Dissolution profiles of batches F1-F4

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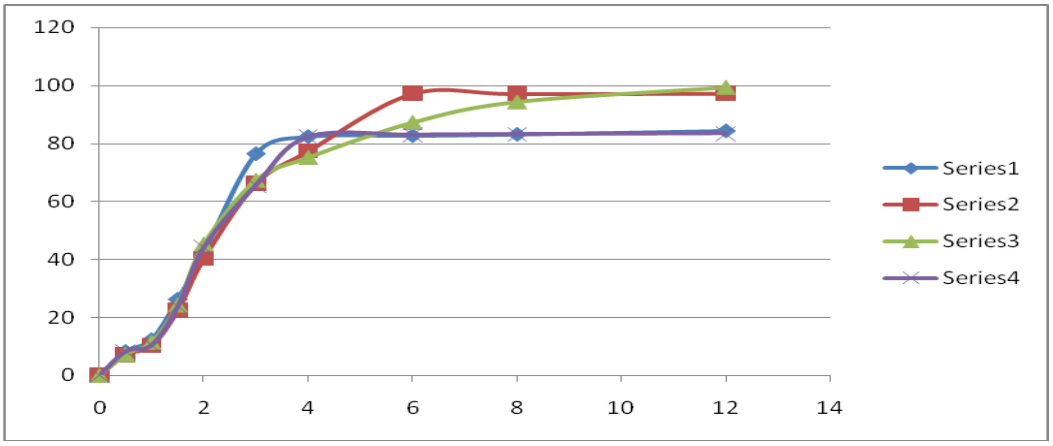

Fig. 5: In vitro Dissolution profile of batches F5-F8

Table 13: Evaluation parameters of stability batch of Amroxol Hydrochloride

Evaluation parameters	Before stability	After 1 month storage	After 2 months Storage	After 3 months storage
Hardness (kg/cm^2)	5.2±0	5.2±0	5.2±0	5.2±0
Friability (%)	0.31	0.33	0.34	0.34
Drug content (%)	98.3±0.49	97.84±0.3	97.45±0.37	97±0.03
Weight variation (mg)	327.13±2.8	327.37±0.39	328.09±0.75	328.03±0.45

5. SUMMARY AND CONCLUSION

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.

The present study was an attempt to formulate a gastroretentive 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.

On the basis of preformulation 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 injectables but its sustained release dosage form increase its gastric residanse time and decrease its dosing frequency.

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