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FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING MATRIX TABLETS OF TOLPERISONE HYDROCHLORIDE

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ABSTRACT

In the present research work gastro retentive floating matrix formulation of Tolperisone Hydrochloride by using various polymers were developed. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimised. Then the formulation was developed by using different concentrations of polymers Sodium Alginate, Locust bean gum and HPMC K4M as polymeric substances. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations HPMC K4M as polymer were retarded the drug release more than12 hours. whereas in low concentrations the polymer was unable to produce the desired action. The formulations prepared with Sodium Alginate were also retarded the drug release up to 12 hours (F2=82.93%). The optimised formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order mechanism of drug release.

KEYWORDS: Tolperisone Hydrochloride, Sodium Alginate, Locust bean gum and HPMC K4M, Floating Tablets.

INTRODUCTION

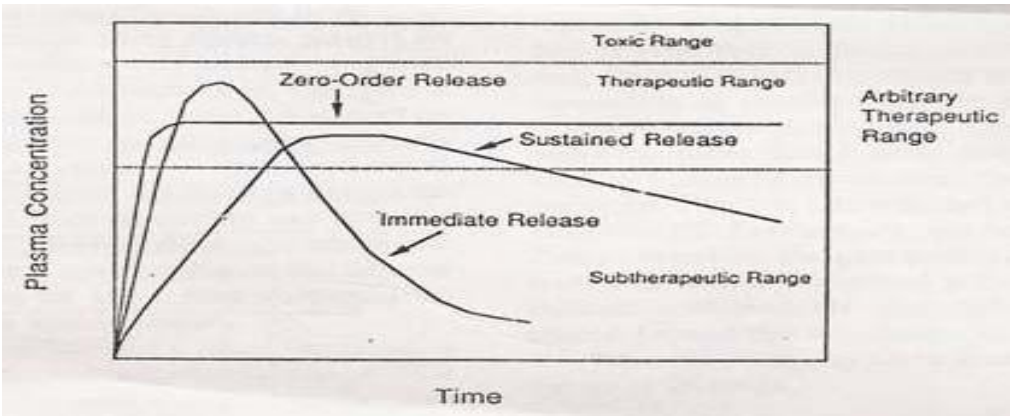
Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient

compliance and flexibility in formulation and cost effective manufacturing process.[1] Many of the drug delivery systems, available in the market are oral drug delivery type systems Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.

Controlled Drug Delivery Systems

More precisely, controlled delivery can be defined as:-

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4. Provide physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.[5]



Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

It is suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so

that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs.

Controlled release or Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs. which are

1. Administered two or more time a day.
2. Only absorbed in the upper GI regions.
3. Targeted at sites in the upper GI tract.
4. Bioavailable through active transport mechanisms.
5. Irritating to the mucosa.
6. Misbalancing, irritating, or unsafe in the lower GI region.
7. More effective when plasma levels are more constant.
8. That is locally active in the stomach.
9. That has an absorption window in the stomach or in the upper small intestine.
10. That is unstable in the intestinal or colonic environment or degrades in colon.
11. Have low solubility at high pH values.

Transit time of Different Dosage Forms across the Segments of GI Tract.

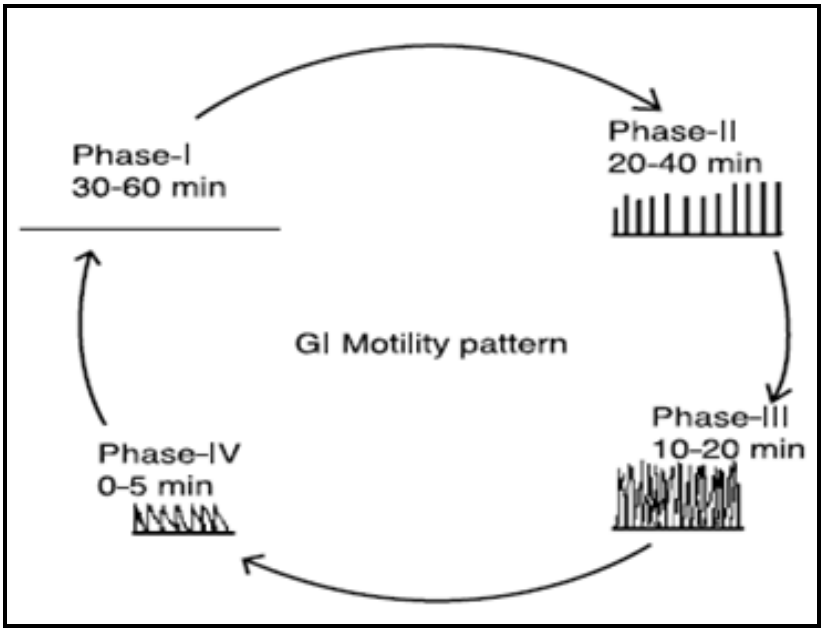
Dosage form	Transit time (h)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Oral solution	0.3±0.07	4.1±0.5	4.4

Gastric emptying

The process of gastric emptying occurs in two states:

- Fasting as well as
- Fed states.

In fasting state: An interdigestive series of electrical events occurs in a cyclic manner both through stomach and small intestine every 2 to 3 hours. This activity is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 consecutive phases as



Gastrointestinal motility pattern

In fed state: The motor activity in the fed state is induced 5-10 min after ingestion of a meal and persists as long as food remains in the stomach. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state These contractions are not as severe as those in the third phase of the fasted motility pattern.. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

Gastric Floating Drug Delivery systems (GFDDS): The various buoyant preparation s includes tablets, pills, granules, powders, capsules, hollow, Microspheres (micro balloons) and laminated films. Based on the mechanism of buoyancy, two distinctly different technologies i.e., noneffervescent and effervescent systems have been utilized in the development of GFDDS.

Non-Effervescent GFDDS: The approach involved in the formulation of floating dosage forms is intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier as shown in figure 7a. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. Commonly used excipients, here are gel-forming or

highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.

Effervescent GFDDS: The floating drug delivery systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 carbon dioxide is released, causing the beads to float in the stomach[34] The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gellyfied hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy as shown in figure 7b. The carbon dioxide generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for the Sustained Release effect. This concept has also been exploited for floating capsule systems.

Advantages of GFDDS: Floating drug delivery offers several applications for drugs having poor Bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage forms at the site of absorption and thus enhances the Bioavailability. These are summarized as follows.

1. Sustained Drug Delivery
2. Site Specific Drug Delivery
3. Absorption or Bioavailability Enhancement
4. Fewer Doses
5. Improved plasma levels
6. Better Bioavailability
7. Less Irritation
8. Fewer side effects
9. Low risk inactive ingredients
10. Manufacturing ease

METHODOLOGY

Optimisation sodium bicarbonate concentration

Ingredients	DO1	DO2	DO3
Tolperisone Hydrochloride	50	50	50
Sodium Alginate	25	25	25
Sodium Bi-carbonate	7.5	15	22.5
Magnesium Stearate	4	4	4
Talc	3	3	3
MCC	Q.S	Q.S	Q.S
Total weight	250	250	250

All the quantities were in mg

FORMULATION OF TABLETS

Formulation composition for Floating tablets

INGREDIENTS	FORMULATION BATCH CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tolperisone Hydrochloride	50	50	50	50	50	50	50	50	50
Sodium Alginate	25	50	75	-	-	-	-	-	-
Locust bean gum	-	-	-	25	50	75			
HPMC K4M	-	-	-	-	-	-	25	50	75
Sodium Bi-carbonate	15	15	15	15	15	15	15	15	15
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	250	250	250	250	250	250	250	250	250

All the quantities were in mg

RESULTS AND DISCUSSION

Analytical Method

a. Determination of absorption maxima

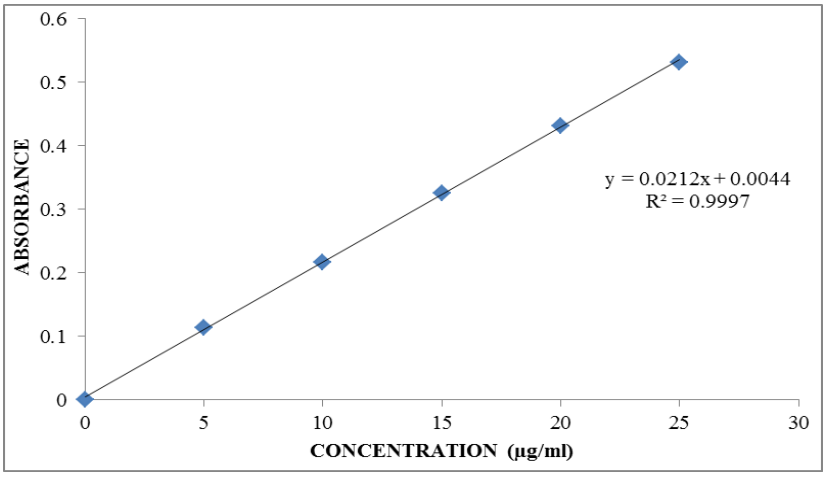
The standard curve is based on the spectrophotometry. The maximum absorption was observed at 254 nm.

b. calibration curve

Graphs of Tolperisone Hydrochloride was taken in 0.1N HCL (pH 1.2).

Observations for graph of Tolperisone Hydrochloride in 0.1N HCL

Conc [µg/mL]	Abs
0	0
5	0.114
10	0.217
15	0.326
20	0.432
25	0.531



Standard graph of Tolperisone Hydrochloride in 0.1N HCL

Standard graph of Tolperisone Hydrochloride was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Tolperisone Hydrochloride showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend

Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	26.04	0.354	0.503	29.62	1.421
F2	27.34	0.351	0.491	28.71	1.403
F3	27.69	0.346	0.485	28.65	1.401
F4	27.69	0.350	0.485	27.83	1.387
F5	27.66	0.338	0.494	28.57	1.463
F6	28.34	0.335	0.470	28.72	1.404
F7	27.69	0.353	0.502	29.68	1.422
F8	26.34	0.336	0.502	28.09	1.494
F9	26.01	0.399	0.559	28.62	1.401

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.335 to 0.399 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.485 to 0.559 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.387 to 1.494 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration

Three formulations were prepared with varying concentrations of sodium bicarbonate by direct compression method and three more formulations were prepared by wet granulation method to compare the floating buoyancy in between direct and wet granulation methods. The formulation containing sodium bicarbonate in 15mg concentration showed less floating lag time in wet granulation method and the tablet was in floating condition for more than 12 hours.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

***In vitro* quality control parameters.**

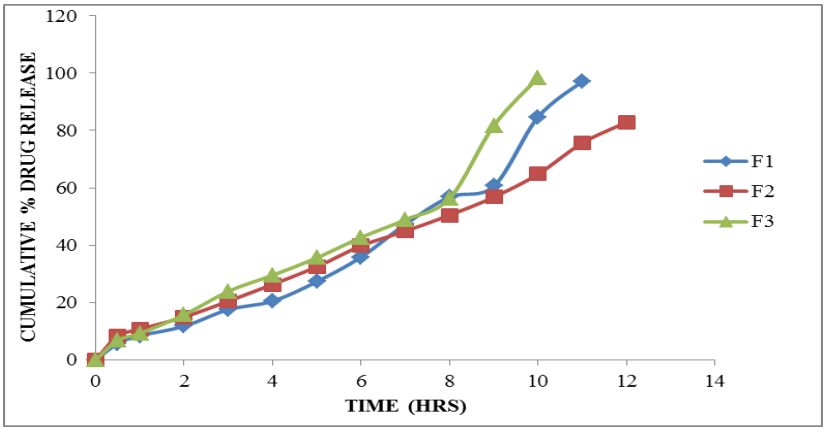
Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time(Hrs)
F1	249.2	4.2	0.25	3.1	97.31	26	6
F2	250.1	4.6	0.64	3.0	99.26	30	11
F3	248.2	4.1	0.35	3.4	96.26	50	7
F4	249.9	4.7	0.41	3.7	99.15	52	12
F5	248.7	4.3	0.54	3.2	96.48	46	6
F6	247.8	4.0	0.41	3.1	98.95	39	12
F7	250.1	4.8	0.33	3.6	97.89	62	12
F8	250.0	4.3	0.60	3.4	99.75	47	12
F9	249.1	4.2	0.71	3.5	100.1	24	12

All the parameters for tablets such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

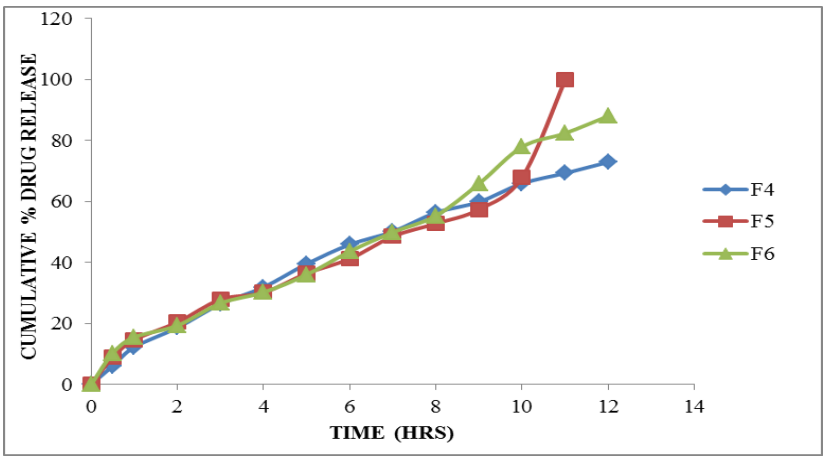
***In Vitro* Drug Release Studies**

Dissolution data of Floating Tablets

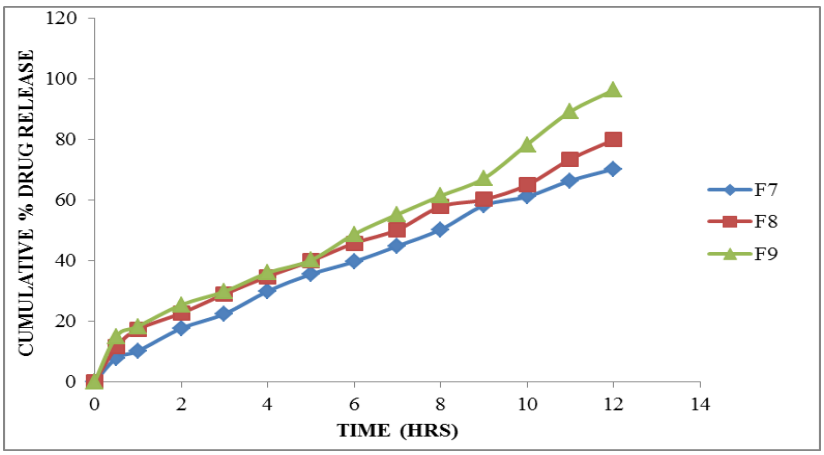
Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	5.71	8.32	6.86	6.12	8.91	10.26	7.83	11.49	14.99
1	8.45	10.72	9.25	12.25	14.62	15.48	10.15	17.31	18.27
2	11.75	14.96	15.72	18.64	20.39	19.32	17.59	22.61	25.36
3	17.56	20.47	23.93	26.38	27.85	26.59	22.38	28.90	29.78
4	20.48	26.31	29.52	31.89	30.14	30.21	29.86	34.72	35.94
5	27.31	32.48	35.60	39.52	36.41	35.99	35.48	39.87	40.12
6	35.85	39.77	42.72	45.87	41.20	43.61	39.61	45.74	48.70
7	47.31	44.92	48.93	50.12	48.53	49.89	44.78	50.15	55.23
8	56.82	50.48	56.37	56.32	52.75	55.28	50.22	57.81	61.38
9	60.64	56.79	81.72	59.84	57.36	65.82	58.19	60.13	67.12
10	84.72	64.81	98.41	65.89	67.90	77.88	61.11	64.96	78.33
11	97.10	75.67		69.25	99.87	82.36	66.37	73.47	89.19
12		82.93		72.88		87.99	70.21	79.87	96.28



Dissolution data of Tolperisone Hydrochloride Floating tablets containing Sodium Alginate



Dissolution data of Tolperisone Hydrochloride Floating tablets containing Locust bean gum

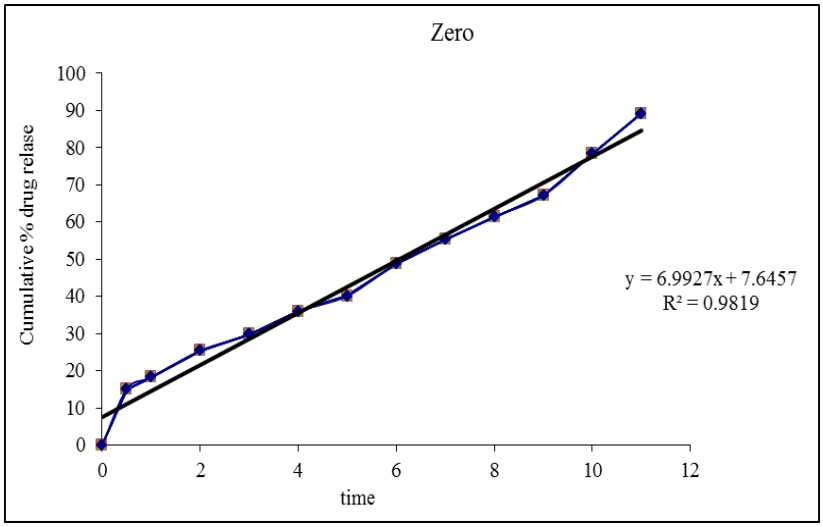


Dissolution data of Tolperisone Hydrochloride Floating tablets containing HPMC K4M

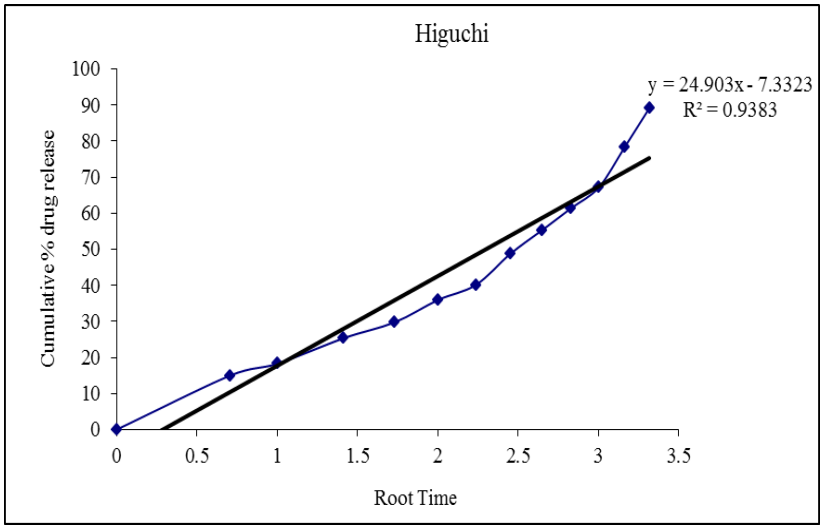
Hence from the above dissolution data it was concluded that F9 formulation was considered as optimised formulation because good drug release (96.28%) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation

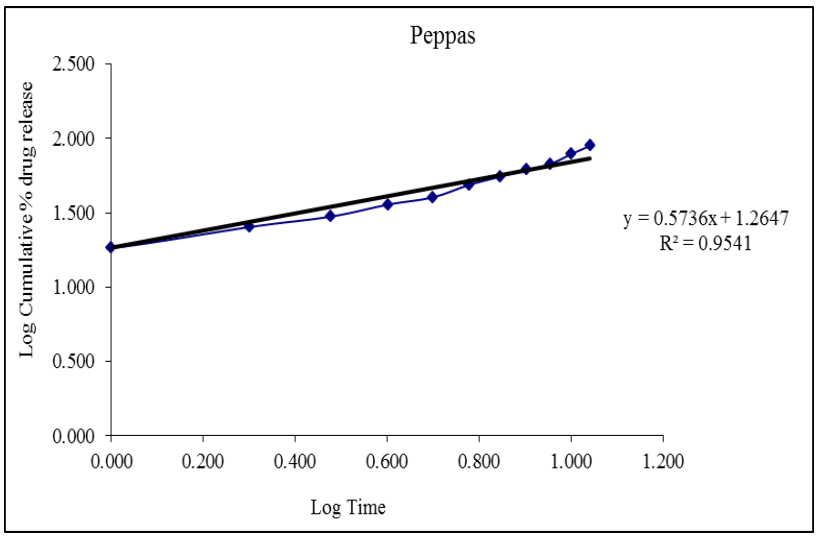
CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
14.99	**0.5**	0.707	1.176	-0.301	1.929	29.980	0.0667	-0.824	85.01	4.642	4.397	0.245
18.27	**1**	1.000	1.262	0.000	1.912	18.270	0.0547	-0.738	81.73	4.642	4.340	0.302
25.36	**2**	1.414	1.404	0.301	1.873	12.680	0.0394	-0.596	74.64	4.642	4.210	0.431
29.78	**3**	1.732	1.474	0.477	1.846	9.927	0.0336	-0.526	70.22	4.642	4.126	0.516
35.94	**4**	2.000	1.556	0.602	1.807	8.985	0.0278	-0.444	64.06	4.642	4.001	0.640
40.12	**5**	2.236	1.603	0.699	1.777	8.024	0.0249	-0.397	59.88	4.642	3.912	0.729
48.7	**6**	2.449	1.688	0.778	1.710	8.117	0.0205	-0.312	51.3	4.642	3.716	0.926
55.23	**7**	2.646	1.742	0.845	1.651	7.890	0.0181	-0.258	44.77	4.642	3.551	1.091
61.38	**8**	2.828	1.788	0.903	1.587	7.673	0.0163	-0.212	38.62	4.642	3.380	1.261
67.12	**9**	3.000	1.827	0.954	1.517	7.458	0.0149	-0.173	32.88	4.642	3.204	1.438
78.33	**10**	3.162	1.894	1.000	1.336	7.833	0.0128	-0.106	21.67	4.642	2.788	1.854
89.19	**11**	3.317	1.950	1.041	1.034	8.108	0.0112	-0.050	10.81	4.642	2.211	2.430
96.28	**12**	3.464	1.984	1.079	0.571	8.023	0.0104	-0.016	3.72	4.642	1.549	3.092



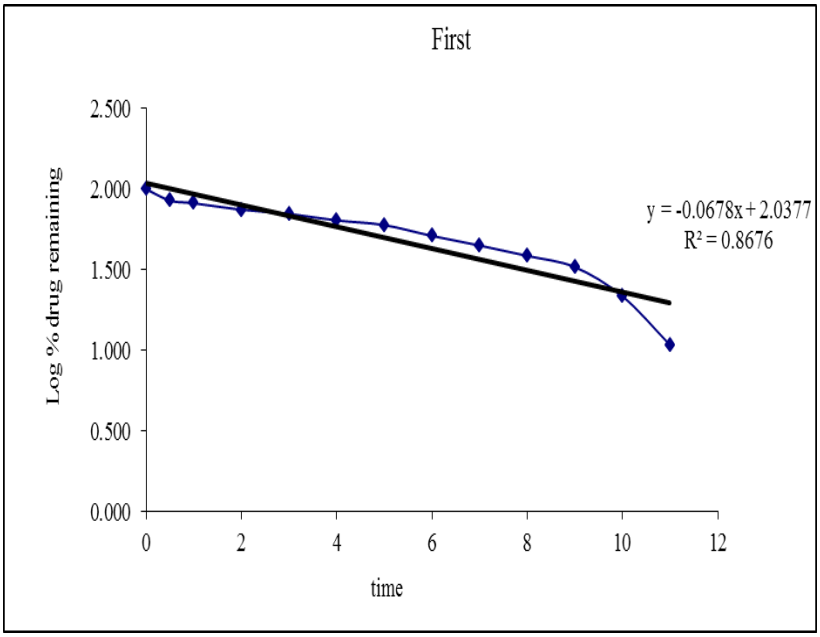
Zero order release kinetics



Higuchi release kinetics



Kors mayer peppas release kinetics

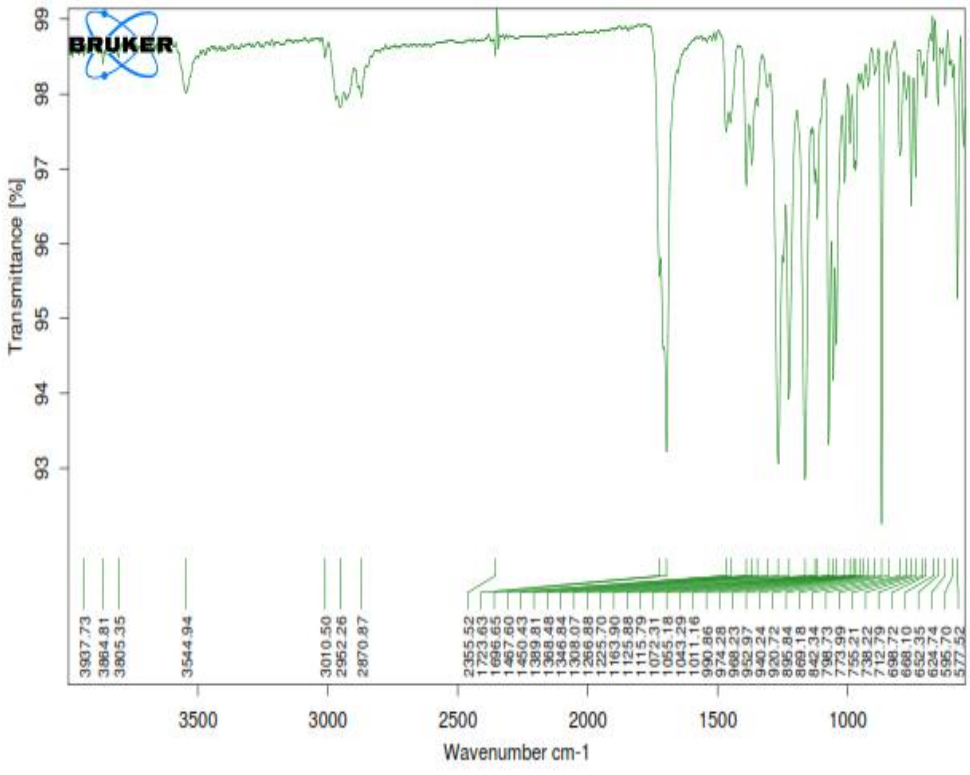


First order release kinetics

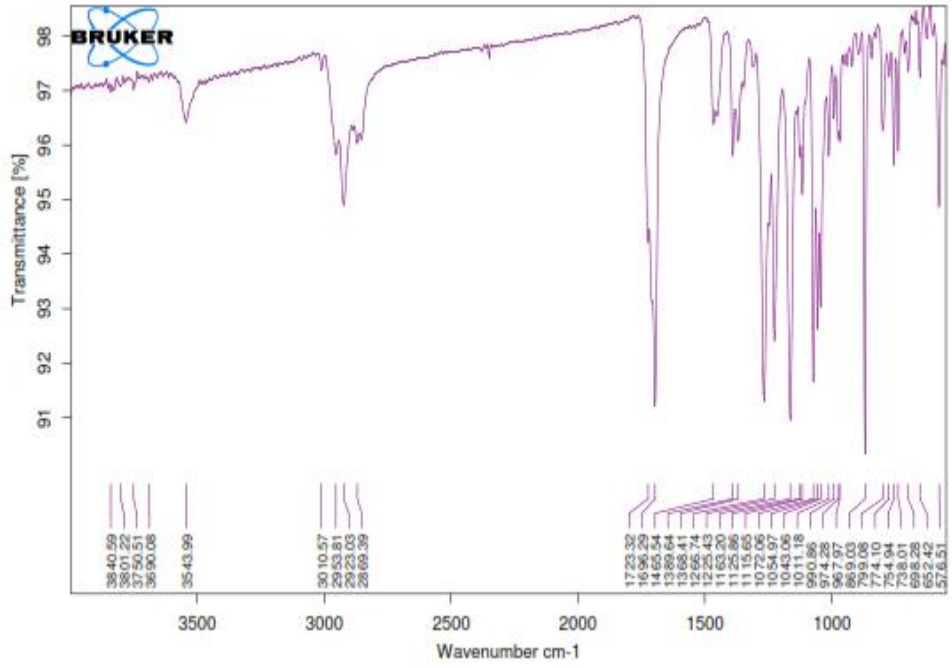
Optimised formulation F9 was kept for release kinetic studies. From the above graphs it was evident that the formulation F9 was followed Zero order release mechanism.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy



FTIR Spectrum of pure drug



FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Tolperisone Hydrochloride are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

The effervescent-based floating drug delivery system was the promising system. The use of hydrophobic retardant and hydrophilic polymer in combination had its own advantages of maintaining integrity and buoyancy of tablets. And also in initial burst effect was minimized. It could be concluded that for proper floating duration and *in vitro* release, the hydrophobic retardant and hydrophilic polymer must be used in proper ratio. Formulation F9 showed release similar to marketed tablet and was considered optimized formulation. F9 followed zero order release kinetics. The aim of preparation of gastroretentive tablets of Tolperisone Hydrochloride was achieved.

REFERENCES

1. Leon lachman, herbert a. Liberman, the theory and practice of industrial pharmacy, 293-302.
2. Robinson jr, lee v.h.l, controlled drug delivery: fundamentals and applications, 2nd edn. Marcel dekker, new york, 1978; 24-36.
3. Brahmankar d.m, jaiswal s.b, biopharmaceutics and pharmacokinetics a treatise, 1st ed. Vallabh prakashan; new delhi, 1995; 64-70.
4. Chein y.w, novel drug delivery systems, 2nd ed.: marcel dekker; new york, 1992; 4-56.
5. Ansel, pharmaceutical dosage form and drug delivery system, lipincott, 7th edition, 553.
6. Gennaro r.a. Remington, the science and practice of pharmacy., 20th ed. New york: lippincott williams, 2000; 1045.
7. Banker g.s, rhodes c.t, modern pharmaceutics. 3rd ed. Marcel dekker, new york, 1996; 678-721.
8. Vyas s.p, khar r.k, controlled drug delivery: concepts and advances, 1st ed. Vallabh prakashan, new delhi, 2002; 345-376.
9. Shweta arora, floating drug delivery: a review, aaps pharmscitech., 2005; 47(11): 268-272.
10. Libo yang, a new intragastric delivery system for the treatment of h.pylori associated with gastric ulcers, elsevier j. Of controlled release., apr, 1999; 34(5): 215-222.
11. Ross and wilson, anatomy physiology and health education. 9th ed. Churchil livingston, 295-311.
12. Wilson k.r.w, waugh a. Anatomy and physiology in health and illness, 9th ed. Churchill livingstone: london, 1996; 342-345.
13. Garima chawla- a means to address regional variability in intestinal drug absorption: pharmtech., 2003; 234-238.
14. Chawla g, gupta p, koradia v, bansal a, gastroretention: a means to address regional variability in intestinal drug absorption, pharm. Tech., 2003; 50-68.
15. Desai s, bolton s. A floating controlled release system: in-vitro and in-vivo evaluation, j. Pharm. Res., 1993; 10; 1321-1325.
16. Garg s, sharma s. Gastroretentive drug delivery systems, pharmatech, 2003; 160-164.
17. Dr.jose, khalid shah, gastroretentive drug delivery system, business brief, pharmtech., 2003; 165-173.
18. Deshpande a.a, shah n.h, rhodes c.t, development of a novel controlled release system for gastric retention, j. Pharm. Res., 1997; 14(6): 815-819.

19. Garima chawla- a means to address regional variability in intestinal drug absorption: pharmtech., 2003; 234-238.
20. David s.s. The effect of density on the gastric emptying on single and multiple unit dosage forms. J. Pharm Res., 1986; 3: 208-213.
21. H.g. Sivakumar, floating drug delivery system for prolonged gastric residence time: a review, ind. J. Pharm. Edu., Oct-Dec, 2004; 311-316.
22. B.n.singh, h.kim, floating drug delivery system an approach to control drug delivery via gastric retention, j. Controlled release., 2000; 63(7): 235-259.
23. B.y.choi, h.j.park, preparation of alginate beads for floating drug delivery system: effect of co2 gas forming agent. J. Contolled release., 2000; 25(6): 488-491.
24. Ingani h.m, timmermans j, moes a.j, concept and in-vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit, int. J. Pharm., 1987; 35: 157-164.
25. Bhavana v, khopade a.j, jain w.d, shelly and jain n.k, targeted oral drug delivery, indian drugs., 1996; 33: 365-373.
26. Roop k. Khar, controlled drug delivery, gastroretentive system 4th edn., 202-203.
27. Hradman j.g, limbrid, goodman gilman's, the pharmacological basis of therapeutics, 10th edn, newyork, 2001; 1765.
28. Dr.shenoy, hand book pharmaceutical chemicals, multitech publication, 2000; 204.
29. Kibbe, american pharmacetical assosiation and pharmaceutical society of great britain. Hand book of pharmaceutical excipients, 3rd end. 1986.
30. Mendhan j, denney r.c, barnes d.j, thomas m. Vogel's textbook of quantitative chemical analysis, 6th ed. Pearson education ltd: new delhi, 2000: 367-384.
31. Himasankar k, design and biopharmaceutical evaluation of gastric floating drug delivery system of metformin hcl, ind. J. Pharm.edu., Jan-Mar, 2006; 40(1): 369-382.