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Effect of combination polymers of natural and semi synthetic origin on the drug release of Flavoxate. HCl

Raghavendra Kumar Gunda[a*], Prasada Rao Manchineni[b] , Rajini Sudireddy[c]

a. Department of Pharmaceutics, M.A.M College of Pharmacy, Kesanupalli (V), Narasaraopet, Guntur, Andhra Pradesh, India - 522601.
b. Department of Pharmaceutical Analysis, M.A.M College of Pharmacy, Kesanupalli (V), Narasaraopet, Guntur, Andhra Pradesh, India - 522601.
c. Department of Pharmacy Practice, M.A.M College of Pharmacy, Kesanupalli (V), Narasaraopet, Guntur, Andhra Pradesh, India - 522601.

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*** Corresponding Author:**
Raghavendra Kumar Gunda
Email:
raghav.gunda@gmail.com

Abstract:

The objective of current work is to study the effects of combination of macromolecules (polymers) of natural (*Lannea coromandelica* gum) and semi synthetic (HPMCK100M) origin on the drug release of Flavoxate.HCl from the Gastro retentive floating formulation.Flavoxate.HCl, an antispasmodic agent,Mainly used for treating urinary incontinence andurgency of urination.Floating tablets of Flavoxate.HClwere prepared using variable composition of HPMCK100M, *Lannea coromandelica* gum (LCG) with effervescent mixturesby direct compression technique.9 formulations weremade and evaluated for quality control parameters. the obtained results showthat all formulations pass the compendial limits. Data obtained from the dissolution study fitted well to kinetic modeling andkinetic parameters were determined.$GRFX_5$composed of 40mgof HPMCK100M &40mg of LCG, is the best formulation showing similarity f_2=84.66, f_1=4.29with the marketed product (**URISPAS**). Formulation $GRFX_5$follow first order, whereas release mechanism found to be nonfickian type (n= 0.77).

Keywords: Flavoxate.HCl; gastro retentive; HPMCK100M; *Lannea coromandelica* gum; Non-Fickian Diffusion.

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1. Introduction

Gastric emptying is a dynamic process and gastro retentivity of dosage forms results in improved clinical response [1].

Effectiveness of oral delivery practice was influenced by certain factors such as gastric emptying process, GI transit time, Drug release pattern from theformulation and Absorption site of drug.Gastric transit time in humans influences absorption of drugs, thatcan result in inappropriate drug release from formulation leading to diminished clinical response. Gastric transit time is a dynamic process and ability to sustain the release of drug at predictive rate, which retain in the acidic environment for a longer period of time than prompt release formulations.

The controlled gastric retention of solid dosage forms was obtained by numerous mechanisms such as flotation, bioadhesion, High density (sedimentation), modified shape systems, expansion, or by simultaneous administration of pharmacological agents that delay gastric emptying [2-6].

Floating Drug Delivery Systems (FDDS) have a bulk density that is less than gastric fluids and thus remain buoyant in gastric environment for prolonged period of time, without affecting the gastric emptying rate. Dosage form stayed in stomach due to flotation mechanism,

which results in controlled rate of drug release. After the release of drug, the residual system is run out from the gastro environment; this will increase GRT and a better control of fluctuations in plasma drug concentrations [7-10]. Flavoxate.HCl, an antispasmodic. It is a competitive Muscarinic blocker.Mainly used in the effective management of overactive bladder Urinary urgency and incontinence. It acts by relaxing the bladder muscles and helps decrease the feeling of nocturnal polyuria or Nocturia [11-12].

An attempt is made in current study to develop gastro retentive drug delivery system (preferably by Flotation) with the help of polymers (Natural- *Lannea coromandelica* gum (LCG), Semisynthetic-HPMCK100M) along with effervescent mixtures.[13]From the literature, few work reported for LCG, though it is natural and have more benefits from economy point of view as well as risk incidence is also low. Hence LCG was selected as polymer for the formulation development of Flavoxate.HCl Gastro retentive delivery [6,9].

Preparation of tabletsby Direct Compression technique is most frequently utilised method in many of Pharmaceutical companies as well as in academiafor research purpose [13-14].

To study the effect of both polymers on the drug release profile of Flavoxate.HCl to reduce the dosing frequency by maintaining the steady state level of drug concentration at serum or plasma level was achieved by manipulating the optimized ratio of above mentioned composition (HPMCK100M, LCG) [6,13].They also improve penetrability of drug via mucosa thereby improving the clinical efficacy of Flavoxate.HCl.

2. Materials *&* Methods

2.1 Materials

A gift sample of Flavoxate.HCl was procured from Konis Pharmaceuticals, Baddi, India. HPMCK100M was obtained from LobaChemie Pvt. Ltd, Mumbai, India. *Lannea coromandelica* Gum was gifted from Sarada Pharmaceuticals, Guntur. All other excipients such as Sodium bicarbonate, Di basic calcium phosphate, Magnesium stearatewere obtained from S.D. Fine Chem. Ltd, Mumbai, India.

2.2 Development of gastro retentive Floating tablets for Flavoxate.HCl

Direct compression technique was utilised for the preparation of floating tablets, each containing 200 mg Flavoxate.HCl. Formulae for the preparation of tablets were presented in Table 1. Accurately weighed ingredients (except Flavoxate.HCl) were screened for obtaining uniform size to ensure proper mixing. The drug was then mixed with the polymer mixture for 10 minutes for uniform mixing of powder blend. Blend was lubricated with magnesium stearate.

Powder blend was subjected to compression with the help of rotary tablet compression machine (Tablet Minipress). Compressed tablets were processed for Quality Control measures as per Pharmacopoeia. Final formulations were transferred to airtight and light resistance packaging bottles.

2.3 Characterization of Flavoxate.HCl Floating Tablets [10, 15-16]

2.3.1 Hardness

The breaking/ crushing strength for the tablet dosageforms were obtained by the diametric break of tablets with the help of Pfizer tablet hardness tester.

2.3.2 Friability

This test is performed by using Friability test apparatus (Roche). Selected number of tablets (20) were weighed accurately weight was noted (W_0), tablets were subjected to rotations (25 rpm for 4 minutes) again weight was noted (W). % weight loss was determined using following formula.

$$\textbf{Weight loss (\%)} = [W_0 - W / W_0] \times 100$$

2.3.3 Assay

Assay was performed by triturating stated number of tablets in Indian pharmacopoeia (20) converted to powder, powder equivalent to 100mg of drug was added in 100 ml of 0.1 N HCl, followed by sonication. The solution was filtered through a 0.45 µ membrane filter, suitable aliquots were prepared, and the absorbance of the resultant solution was measured by spectrophotometry at 291 nm using 0.1 N HCl as blank.

2.3.4 Thickness

Thickness formulations were determined by using vernier calipers, by placing tablet between two armsof it.

2.3.5 In vitro buoyancy studies

This test is performed by placing the tablets in a beaker containing 100 mL of 0.1 N HCl (SGF). The time required for the upward movement of tablet to float on the 0.1 N HCl (SGF) was noted to be floating lag time.

2.3.6 In-Vitro drug release Study

The *In-vitro* dissolution rate study for formulation trails were performed using USP XXIII type-II dissolution test apparatus containing 900 ml of 0.1 N HCl operated under conditions like temperature 37 ± 0.5°C and rotated at a speed of 50 rpm. At predetermined time intervals, 5 ml of the samples were withdrawn as per the pharmacopoeia procedure. The resultant samples were analyzed for estimation of drug release by measuring the absorbance at 291 nm using UV-Visible spectrophotometer after suitable aliquots. The samplings were performed in triplicate manner (n = 3) [11].
The dissolution profile of all the formulations was subjected to kinetic modeling such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to know the drug release mechanisms [17,18].

2.3.7 Swelling Index Study

To evaluate swelling index, tablet was placed in USP dissolution apparatus II with 900 ml 0.1N HCl after measuring the weight of tablet (W_1). Then weight of tablet (W_2) was determined by virtue of time i.e. at different time intervals viz. multiples of 2 h (0-2-12) after using blotting paper to remove surplus fluid. Swelling Index was calculated using following formula.

$$\textbf{Swelling Index (\%)} = [(W_2 - W_1) / (W_1)] \times 100$$

3. Results and Discussion

Gastro retentive floating tablets of Flavoxate.HCl were developed using combination of drug release modifiers (HPMCK100M, LCG) along with effervescent mixtures as the formula presented in Table 1.
All trials have Flavoxate.HCl (200 mg) as a gastro retentive formulation, obtained as tablet by direct compression technique.Developed formulations evaluated for pharmaceutical product performance tests. Data was presented in Table 2.All formulations have sufficient mechanical strength.All formulations found to be less friable, as within the limits. All batches pass the drug content uniformity test. All formulation batches passed the Weight variation test. From the swelling study it is found that, all formulation trails were shown swelling phenomenon exposed tosimulated gastric fluid but stayed without breaking during the study period. Formulation $GRFX_1$ was found to have highest swelling property and the same was presented in Figure 1.
Dissolution rate test was carried as per standard procedures, the dissolution specifications such as 900mL of simulated gastric fluid, Dissolution test apparatus consists of paddle, rotated at a speed of 50 rpm, temperature maintained as 37±0.5ºC throughout the test period. Dissolution profile was well fit to kinetic modeling, results were presented in Table 3 and the same was presented as plots from Figures 2-5. From the results, observed that there was a clear relation existed between quantities of polymers in combination to the drug release rate (both were inversely proportional to each other).[19]Predicted sustained release of drug was obtained by appropriate composition of HPMCK100M, *Lannea coromandelica* gum.
$GRFX_5$ is considered as best formulation among all batches. $GRFX_5$composed of both HPMCK100M andLCG in equal quantity i.e. 40 mg each, producedpromising dissolution characteristics, which helps in meeting the purpose of research by means of gastro retentivity & optimum delivery of drug from dosageform.
Dissolution parameters for $GRFX_1$-$GRFX_9$ were summarized as Table 4.$GRFX_5$wasconsidered to beideal, It shows similarityfactor (f_2)84.66, difference factor (f_1) 4.29,t_{cal}<0.05 when compared with marketed product (**URISPAS**). Comparative dissolution plots for best formulation (**$GRFX_5$**) and marketed product shown in Figure 6.

4. Conclusion

On the basis of the current research study, the use of macro molecules (Natural and Semisynthetic polymers) in combination had its own advantages of maintaining integrity and buoyancy of tablets. The effervescent based FDDS is a promising formulation to obtain gastro retentivity by using gel forming polymers such as HPMCK100M, LCG employing sodium bicarbonate as gas generating agent. Among the various FDDS formulations studied, the formulation (GRFX5) showed the best result in terms of the required %CDR, Floating lag time and total floating time was considered as the ideal formulation**.** Best formulation GRFX5 follows First order release, Non-Fickian Diffusion, it may improve patient compliance by reducing the dosing frequency, which will ultimately improve the clinical response.

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Conflict of interest

None.

Authors' ORCIDs

Dr. Raghavendra Kumar Gunda ; 0000-0002-4271-8614 (https://orcid.org/0000-0002-4271-8614)
Dr. Prasada Rao Manchineni; 0000-0003-2975-4538 (https://orcid.org/0000-0003-2975-4538)
Rajini Sudireddy; 0000-0001-7734-7588 (https://orcid.org/0000-0001-7734-7588)

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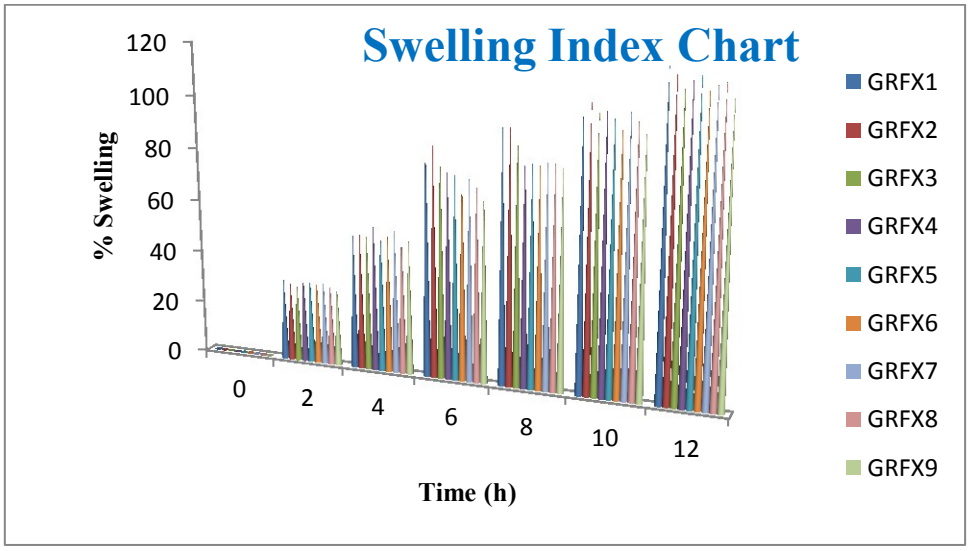

Figure 1. Swelling Profile/ Swelling Index Chart

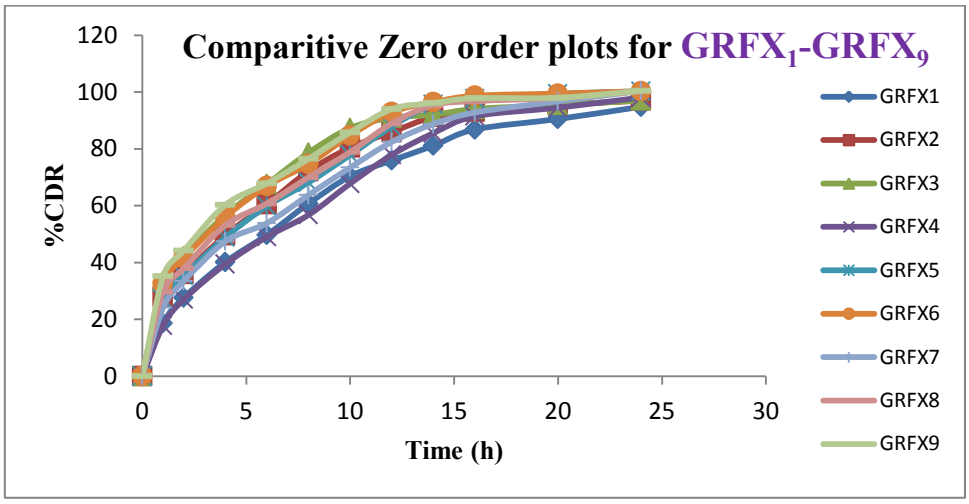

Figure 2. Comparative zero order plots

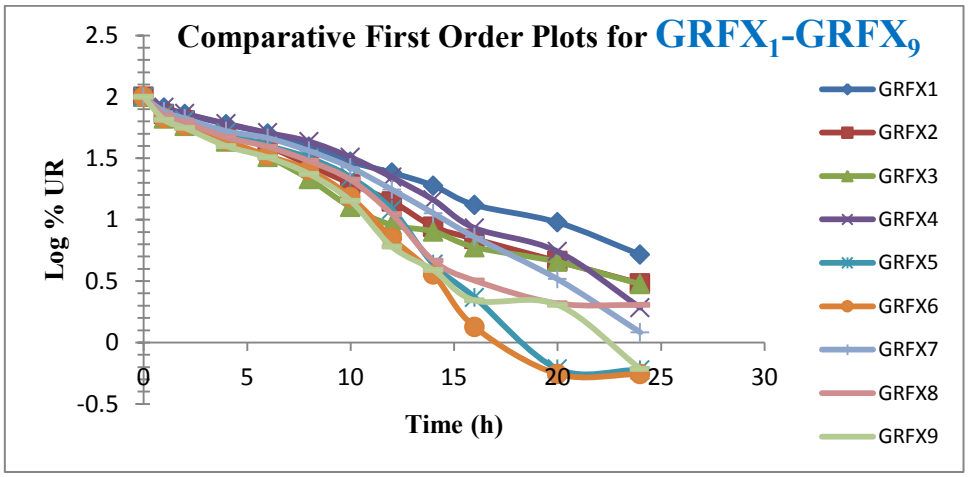

Figure 3. Comparative first order plots

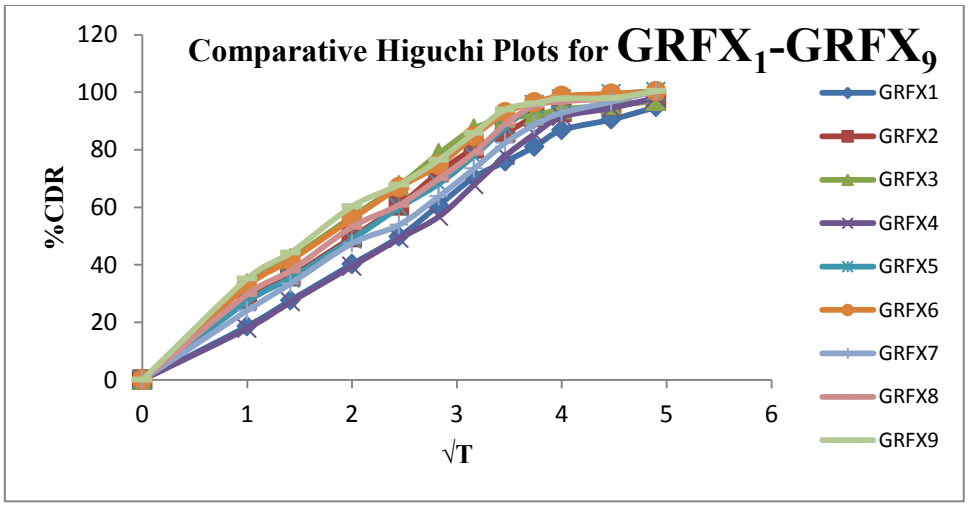

Figure 4. Comparative higuchi plots

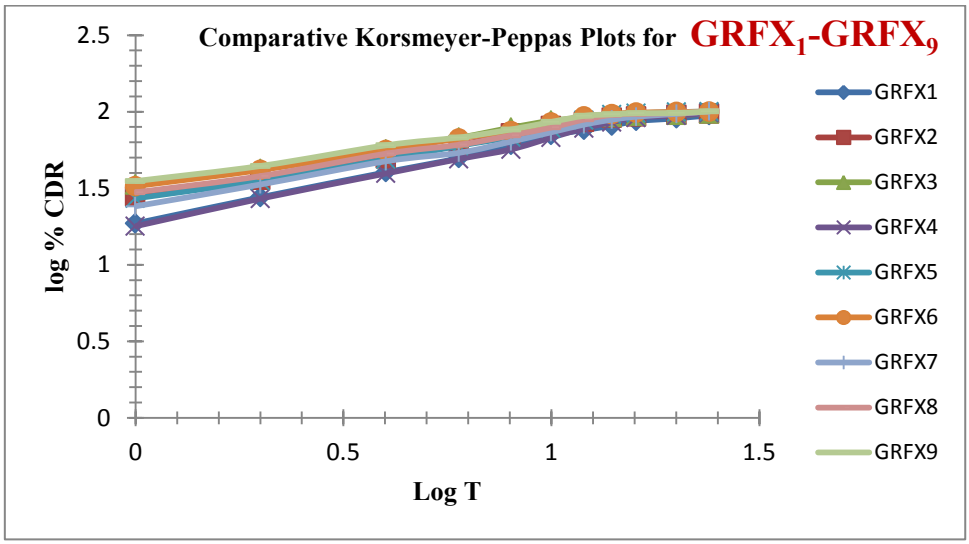

Figure 5. Comparative korse-meyer peppas plots

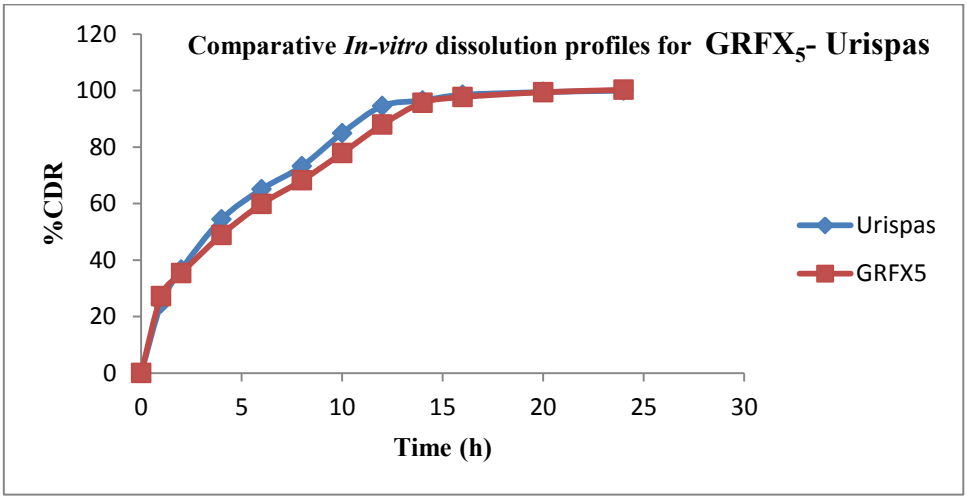

Figure 6. Comparative Dissolution Profile for $GRFX_5$-Urispas

Table 1: Formulae for Flavoxate Gastro Retentive Floating Tablets

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	$GRFX_1$	$GRFX_2$	$GRFX_3$	$GRFX_4$	$GRFX_5$	$GRFX_6$	$GRFX_7$	$GRFX_8$	$GRFX_9$
Flavoxate. HCl	200	200	200	200	200	200	200	200	200
Di Calcium Phosphate	45	55	65	55	65	75	65	75	85
HPMCK100M	50	50	50	40	40	40	30	30	30
LCG	50	40	30	50	40	30	50	40	30
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total Weight	400	400	400	400	400	400	400	400	400

Table 2: Post Compression Parameters (n= 3)

Batch Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Average Weight (mg)	Drug Content (%)	Floating Lag Time (sec)	Total Floating Time (h)
$GRFX_1$	5.39±0.2	4.32±0.04	0.20±0.13	401.6±2.06	97.37±0.31	47.3±1.2	>20
$GRFX_2$	5.20±0.17	4.27±0.02	0.34±0.1	403.61±4.07	97.715±0.36	49.7±1.3	>20
$GRFX_3$	5.24±0.2	4.25±0.01	0.24±0.12	400.6±3.06	97.26±0.38	51.75±1.5	>20
$GRFX_4$	5.46±0.2	4.24±0.04	0.18±0.13	402.55±2.2	98.96±0.33	48.43±1.4	>20
$GRFX_5$	5.26±0.17	4.17±0.03	0.33±0.1	404.54±4.2	99.3±0.39	49.95±1.5	>20
$GRFX_6$	5.32±0.18	4.19±0.01	0.22±0.13	401.57±3.2	99.95±0.41	52.84±1.6	>20
$GRFX_7$	5.71±0.22	4.28±0.04	0.18±0.12	401.6±2.06	99.91±0.43	50.9±1.5	>20
$GRFX_8$	5.48±0.22	4.25±0.02	0.33±0.1	403.65±4.1	99.26±0.49	53.51±1.6	>20
$GRFX_9$	5.54±0.26	4.23±0.01	0.22±0.1	400.62±3.1	99.96±0.51	55.5±1.7	>20

Table 3: Regression analysis for formulation trials

Formulation Code	Kinetic Parameters											
	Zero order			First order			Higuchi			Korsmeyer-peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
$GRFX_1$	21.37	3.77	0.938	1.99	0.052	0.998	0.03	20.83	0.994	1.01	0.80	0.94
$GRFX_2$	30.18	3.65	0.895	1.95	0.065	0.995	7.52	20.92	0.981	1.11	0.75	0.91
$GRFX_3$	36.29	3.42	0.854	1.87	0.064	0.984	13.45	20.17	0.965	1.18	0.71	0.88
$GRFX_4$	19.67	4.02	0.949	2.07	0.068	0.986	2.33	21.95	0.993	0.99	0.82	0.95
$GRFX_5$	28.57	3.89	0.910	2.11	0.101	0.978	5.30	21.96	0.984	1.01	0.76	0.92
$GRFX_6$	34.71	3.65	0.876	2.04	0.104	0.982	11.23	21.21	0.973	1.17	0.72	0.89
$GRFX_7$	25.56	3.84	0.929	2.06	0.076	0.988	3.32	21.43	0.992	1.1	0.77	0.92
$GRFX_8$	31.13	3.72	0.896	1.99	0.079	0.977	8.20	21.23	0.980	1.14	0.74	0.90
$GRFX_9$	37.07	3.51	0.861	1.97	0.091	0.990	13.93	20.60	0.967	1.19	0.70	0.88
Urispas	16.01	7.03	0.966	2.02	0.090	0.970	1.28	26.98	0.999	0.998	0.99	0.92

Table 4: Dissolution parameters

Formulation Code	Dissolution Parameters				
	$t_{10\%\ (h)}$	$t_{25\%\ (h)}$	$t_{1/2\ (h)}$	$t_{75\%\ (h)}$	$t_{90\%\ (h)}$
$GRFX_1$	0.88	2.41	5.79	11.58	19.24
$GRFX_2$	0.71	1.93	4.65	9.30	15.44
$GRFX_3$	0.72	1.95	4.69	9.37	15.57
$GRFX_4$	0.68	1.84	4.42	8.84	14.69
$GRFX_5$	0.46	1.24	2.98	5.96	9.91
$GRFX_6$	0.45	1.21	2.90	5.80	9.63
$GRFX_7$	0.61	1.65	3.97	7.93	13.18
$GRFX_8$	0.58	1.59	3.82	7.63	12.68
$GRFX_9$	0.51	1.38	3.31	6.62	10.99
Urispas	0.52	1.40	3.36	6.72	11.16