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Der Pharmacia Lettre, 2015, 7 (3):114-123
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Feasibility of using natural gums for development of sustained release matrix tablet of itopride

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ABSTRACT

The objective of this research work was to check feasibility of using natural gums for development of sustained release matrix tablets of Itopride in view to improve patient compliance and therapeutic action. Matrix tablets were prepared by direct compression method by using natural polymers like xanthan gum, guar gum, karaya gum, locust bean gum, neem gum as matrix forming agent and excipients such as magnesium stearate, MCC, PVP and talc were used. The dissolution medium consisted of 900 ml of 0.1 N HCl for first 2 hours and then 7.4 phosphate buffer for remaining 10 hours. All the tablet formulations showed acceptable pharmacokinetic properties and complied with in-house specifications for tested parameters. Stability studies were performed for optimised formulation as per ICH guidelines which show that formulations were stable after three months of short term stability studies. The formulation was optimized on the basis of acceptable tablet properties and in-vitro drug release. Formulation F-6 was successfully sustained the release of drug upto 12 hours. The kinetic treatment of selected optimized formulation shows that the regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics and the 'n' value lies between 0.76-0.85 (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release was Anomalous (non-Fickian) diffusion. Optimized formulation was tested for their compatibility with Itopride by FT-IR studies, which revealed that there is no chemical interaction occurred with polymer and other excipients. The drug release profile of the best formulation was well controlled and uniform throughout the dissolution studies.

Keywords: Xanthan gum, Guar gum, Karaya gum, Locust bean gum, Neem gum, Magnesium stearate, MCC, PVP, Talc, Matrix tablets, Direct compression method , Sustained release.

INTRODUCTION

The oral route is the most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In required to be administered in multiple doses and therefore have several disadvantages [1]. Extended release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs [2].

Itopride hydrochloride is an oral prokinetic agent used in the treatment of gastric motility disorder. It is benzamide derivative, absorbed from gastrointestinal tract. Itopride hydrochloride activates the gastrointestinal motility through synergism of its dopamine D_2- receptor antagonistic action and its acetylcholine esterase-inhibitory action. In addition to these actions, itopride has an antiemetic action, which is based on its dopamine D_2 -receptor antagonistic action. The short biological half-life (6 hrs), 60 % bioavailability and dosage frequency more than once a day (50 mg t.i.d.) makes the itopride hydrochloride an ideal candidate for the controlled drug delivery systems [3, 4].

The matrix tablets composed of drug and the release retarding material offers the simplest approach in designing an extended release system [5].

MATERIALS AND METHODS

The chemicals used in this study were pure drug like Itopride (Symed labs,Hyderabad) and polymers like Xanthan gum, Guar gum, Karaya gum, Locust bean gum, Neem gum (SD Fine Chem. Limited, Mumbai) and other excipients like Magnesium stearate, MCC, PVP, Talc, (Yarrowchem Products, Mumbai).

Preparation of matrix tablets

The drug and excipients of table 1 were passed through a 60 # size mesh prior to the preparation of the dosage form. The entire ingredient are weighed separately and mixed thoroughly for 10 mints to ensuring uniform mixing in geometrical ratio. 500 mg of the powder mix was accurately weighed and fed into the die of ten station rotary tablet machine (Shakti Pharmatech Pvt. Ltd Ahmedabad) and compressed at 6±0.5 Kg/cm^2 compression force using 12 mm flat punches.

Evaluation of matrix tablets [6].

The matrix tablets of itopride hydrochloride were evaluated for pre compression parameters such as angle of repose, % compressibility index, and post compression parameters such as hardness (Monsanto hardness tester), weight variation, content uniformity, percentage friability (Roche friabilator), thickness (Vernier caliper). Drug content of matrix tablets was determined by weighing and finely grinding 10 tablets of each batch. Aliquot of this powder equivalent to 150 mg of itopride hydrochloride was accurately weighed, suspended in approximately 50 ml of phosphate buffer pH 7.4 and shaken for 15 min. final volume was adjusted to 100 ml with phosphate buffer and filtered. The suitable dilutions were made and absorbance recorded at 256 nm.

***In-vitro release*[7]**

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 1.2 for first two hrs and pH 7.4 phosphate buffers for next 10 hrs, maintained at 37 $\pm$ 0.5^{0}C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 256 nm. The study was performed in triplicate.

Kinetic study [8]

The release of drug from extended release dosage form is regulated by several processes. These are extraction or diffusion of drug from matrix and erosion of matrix, alternatively the drug may be dissolved in the matrix material and then released by diffusion through membrane. In some cases, drug may be released by osmotic process. Different kinetic equations (Zero order, First order, Higuchi and Korsemeyer Peppas equation) were applied to interpret the release rate from the tablet matrix.

Fourier Transform Infrared Spectroscopy (FTIR) study[9]

FTIR spectra of the selected formulation were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were checked in the formulation spectra.

Table 1: Tablet composition of Itopride sustained release matrix tablets prepared with different release retardant natural matices (F-1 to F-12)

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
DRUG	150	150	150	150	150	150	150	150	150	150	150	150
XANTHAN GUM	300	-	-	-	-	150	150	150	-	-	150	-
GUAR GUM	-	300	-	-	-	-	-	150	150	150	-	150
LOCUST BEAN GUM	-	-	300	-	-	150	-	-	150	-	-	-
KARAYA GUM	-	-	-	300	-	-	150	-	-	150	-	-
NEEM GUM	-	-	-	-	300	-	-	-	-	-	150	150
MCC	10	10	10	10	10	10	10	10	10	10	10	10
PVP	25	25	25	25	25	25	25	25	25	25	25	25
MAGNESSIUM STEARATE	10	10	10	10	10	10	10	10	10	10	10	10
TALC	5	5	5	5	5	5	5	5	5	5	5	5

(-) indicates NIL

RESULTS AND DISCUSSION

All the batches were evaluated for pre and post compression parameters and found within acceptable limits. The

Carr's Index (Compressibility) of the powders was in the range of 8.54 ± 0.75 to 11.63 ± 1.63. The angles of repose of the powders were in the range of 24.19 ± 1.41 to 29.45 ± 1.52, which indicate a good flow property of the powders. Here the angle of repose was found to be below 40^{o} C this shows that the reasonable flow property of powders. The results are given in (table-2&3).

The hardness of the tablets was found to be in the range of 5.7 ± 0.33 to 6.9 ± 0.24. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 3.56 ± 0.12 to 3.90 ± 1.2. The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The results are given in (table-4).

Prepared tablets were evaluated for weight variation and the results are given in table 4. Percentage deviation from the average weight was found to be within the prescribed official limits. The drug content for all the batches was found to be in the range of 98.79 to 100.98. The results are given in (table-4).

The drug release at different time intervals was measured using an UV spectrophotometer (Labindia, Mumbai, India) at 256 nm. The results were evaluated for 12 hrs. As per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9, F-10, F-11 and F-12, showed 98.27, 98.26, 98.27, 98.26, 98.27, 98.28, 96.45, 94.62, 94.63, 96.44, 96.45, and 92.78 respectively. This showed that the drug release from the tablet was sustained for 10 to 12 hrs. The results are given in (table5&6).

Table 2: Granules properties of formulations F1 to F6 of Itopride sustained release matrix tablets

PARAMETERS	FORMULATION CODE					
	F1	F2	F3	F4	F5	F6
Angle of repose	25.20±1.32	26.22 ± 1.78	27.15±1.54	24.19±1.41	25.20±1.71	27.15±1.54
Loose bulk Density (LBD)(g/ml)	0.284±0.004	0.262±0.003	0.254±0.002	0.299±0.006	0.324±0.004	0.296±0.004
Tapped bulk density (TBD) (g/ml)	0.295±0.019	0.269±0.015	0.276±0.018	0.289±0.014	0.322±0.011	0.284±0.011
Compressibility index (%)	10.46±1.31	11.23±1.51	10.65±1.44	9.71±1.33	11.63±1.63	10.19±1.26

Table 3: Granules properties of formulations F7 to F12 of Itopride sustained release matrix tablets

PARAMETERS	FORMULATION CODE					
	F7	F8	F9	F10	F11	F12
Angle of repose	26.22±1.78	29.45±1.52	28.12±1.57	25.64±1.21	24.22±1.32	27.15±1.41
Loose bulk Density (LBD)(g/ml)	0.262±0.003	0.294±0.009	0.279±0.006	0.276±0.006	0.254±0.005	0.284±0.004
Tapped bulk density (TBD) (g/ml)	0.289±0.014	0.235±0.012	0.295±0.016	0.296±0.012	0.273±0.013	0.322±0.011
Compressibility index (%)	9.71±1.33	10.20±1.48	11.56±0.78	9.94±1.64	8.54±0.75	11.63±1.63

Table 4: Tablet properties of formulations F1 to F12 of Itopride sustained release matrix tablets

Formulation Code	Parameters				
	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug content (%)
F-1	3.56 ± 0.12	5.9 ± 0.11	0.15 ± 0.17	499.3±9.15	99.12
F-2	3.63 ± 0.17	6.06 ± 0.22	0.20 ± 0.45	498.9±9.98	99.12
F-3	3.71 ± 0.30	5.8 ± 0.14	0.31 ± 0.28	497.9±9.78	98.99
F-4	3.79 ± 0.07	6.00 ± 0.07	0.22 ± 0.12	499.5±9.91	100.65
F-5	3.82 ± 0.12	6.0 ± 0.38	0.40 ± 0.34	499.5±9.91	99.98
F-6	3.89 ± 0.10	6.7 ± 0.19	0.45 ± 0.28	499.2±9.85	99.40
F-7	3.90 ± 1.2	6.9 ± 0.24	0.32±0.09	499.1±9.19	100.90
F-8	3.66 ± 1.7	5.7 ±0.33	0.52±0.02	497.9±9.99	98.79
F-9	3.70 ± 1.48	6.9 ± 0.12	0.28±0.01	498.5±9.83	100.52
F-10	3.76 ± 1.51	6.3 ±0.45	0.41±0.06	499.8±8.97	99.99
F-11	3.80 ± 1.65	5.8 ± 012	0.39±0.04	498.6±9.59	100.98
F-12	3.86±1.29	6.6 ± 0.37	0.49± 0.08	499.1±9.87	100.08

Each value represents as mean±SD of three determinants.

Table 5: Percentage drug release of formulations (F1 – F6)

Time (hrs)	FORMULATION CODE					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
1	13.2	7.8	13.2	9.6	17.4	16.8
2	20.51	18.70	25.94	29.56	33.18	18.69
3	29.67	35.09	38.75	48.43	44.22	24.19
4	33.34	44.23	51.49	53.96	51.52	38.71
5	38.79	51.52	57.60	65.45	64.84	46.06
6	42.44	61.22	68.49	74.57	72.75	59.38
7	44.27	68.51	78.20	83.67	85.47	66.69
8	59.37	81.82	87.91	92.77	90.97	73.97
9	74.53	85.52	94.60	94.63	92.81	87.28
10	83.67	89.16	96.45	98.26	96.44	94.6
11	96.39	94.61	98.27	-	98.27	98.26
12	98.27	98.26	-	-	-	98.28

Table 6: Percentage drug release of formulations (F7 - F12)

Time (hrs)	FORMULATION CODE					
	F-7	**F-8**	**F-9**	**F-10**	**F-11**	**F-12**
1	15	15	13.2	24	11.4	14.4
2	22.32	24.13	31.37	27.75	20.51	31.37
3	27.87	31.50	40.59	44.8	33.29	42.40
4	48.42	44.82	52.11	53.94	36.98	46.08
5	53.96	52.13	59.41	66.66	49.67	53.95
6	60.63	59.41	64.88	72.76	63.02	63.04
7	70.32	70.31	72.75	80.04	70.33	70.33
8	78.21	72.78	76.42	89.13	76.40	72.78
9	85.5	78.23	83.68	90.99	90.92	74.61
10	89.16	87.31	90.81	94.01	92.81	80.05
11	94.61	90.98	92.81	94.03	94.63	85.51
12	96.45	94.62	94.63	96.44	96.45	92.78

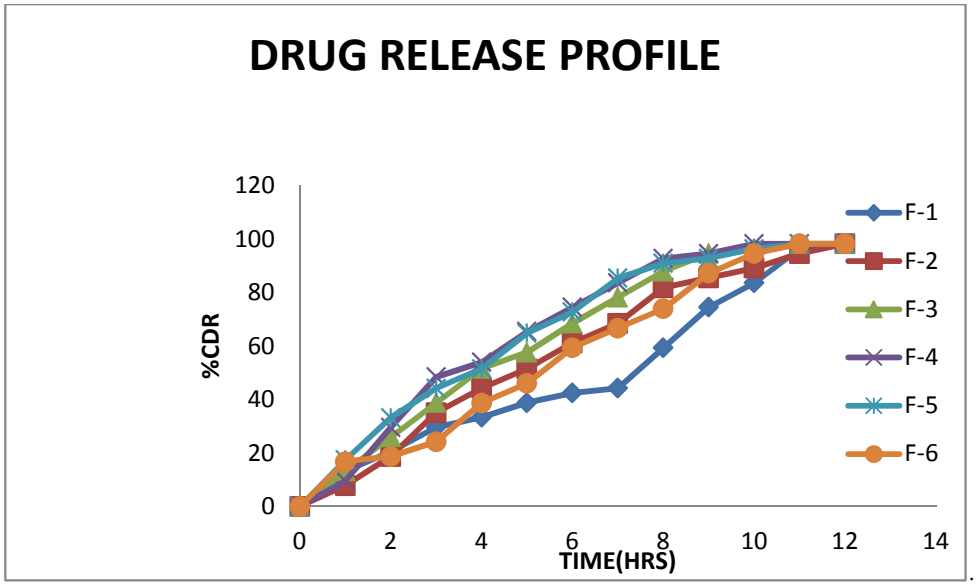

Figure.1: *In Vitro* release Profile of F-1 to F-6 Formulations

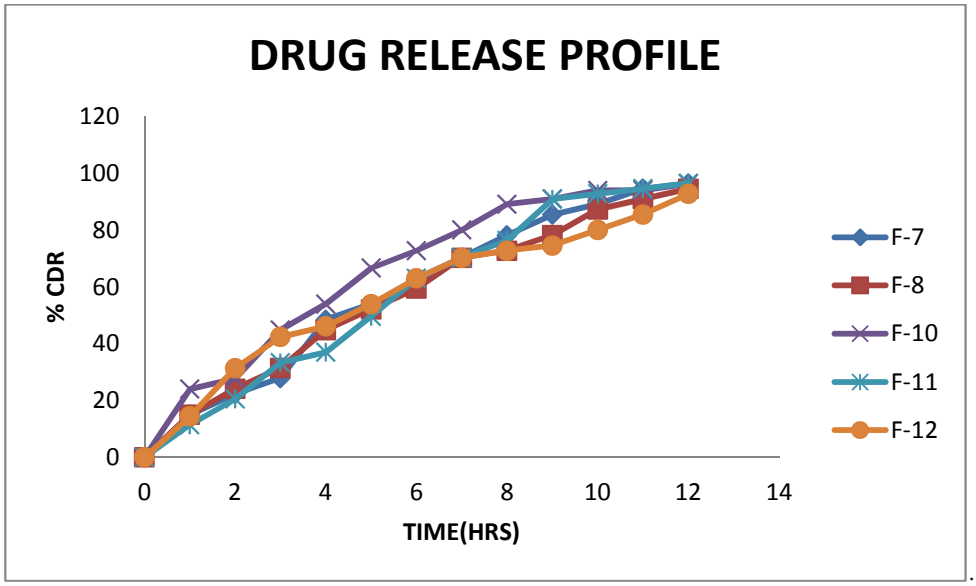

Figure.2: *In Vitro* release Profile of F-7 to F-12 Formulations

Different models like Zero order, First order, Higuchi's and Peppas or Korsemeyer et al's plots were drawn. The regression coefficient (R^2) value for Zero order, First order, Higuchi's and Peppas or Korsemeyer et al's plots (Figure36-39) for best formulation F-6 were found to be 0.980, 0.867, 0.963, and 0.953 respectively. The slope (*n*) value of Peppas or Korsemeyer et al's plots for best formulation F-6 were found to be 0.83. The 'n' value lies between 0.76-0.85 (korsemeyer-Peppas model) demonstrating that the mechanism controlling the drug release was Anomalous (non-fickian) diffusion. Thus orally sustained itopride matrix tablets, delivers the drug through a complex mixture of diffusion, swelling and erosion.The regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics. The results are given in (table-7&8).

Table 7: Model fitting for formulation F-6

Time(hrs)	% CDR	Log of % drug unreleased	Log time	SQRT	Log % CDR
1	16.8	1.920123	0	1	1.225309
2	18.69	1.910143	0.30103	1.414214	1.271609
3	24.19	1.879726	0.477121	1.732051	1.383635
4	38.71	1.787389	0.60206	2	1.587823
5	46.06	1.731910	0.69897	2.236068	1.663323
6	59.38	1.608739	0.778151	2.44949	1.773640
7	66.69	1.522574	0.845098	2.645751	1.824060
8	73.97	1.415474	0.90309	2.828427	1.869055
9	87.28	1.104487	0.954243	3	1.940914
10	94.6	0.732393	1	3.162278	1.975891
11	98.26	0.240549	1.041393	3.316625	1.992376
12	98.28	0.235528	1.079181	3.464102	1.992465

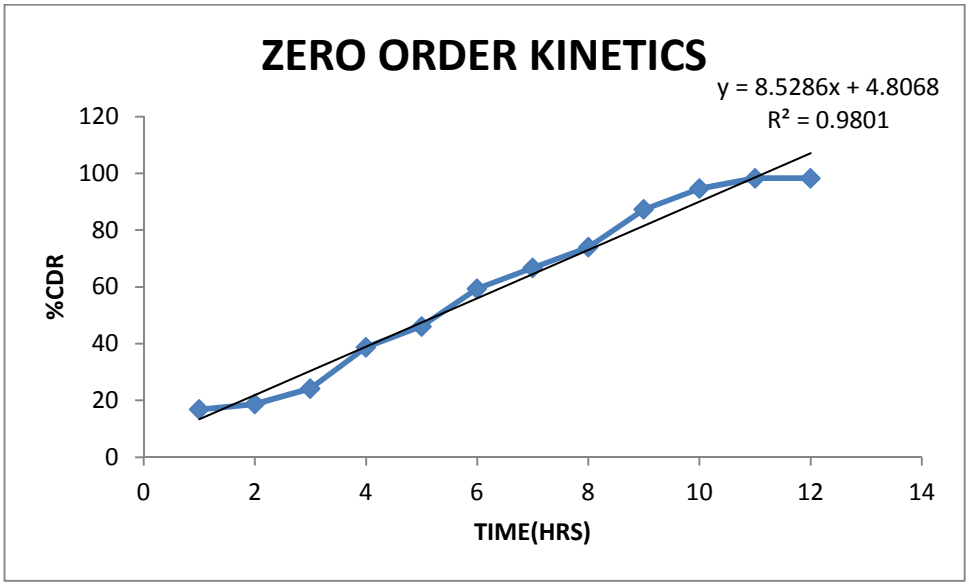

Figure.3: Zero order kinetic of *in vitro* release data of formulation F -6

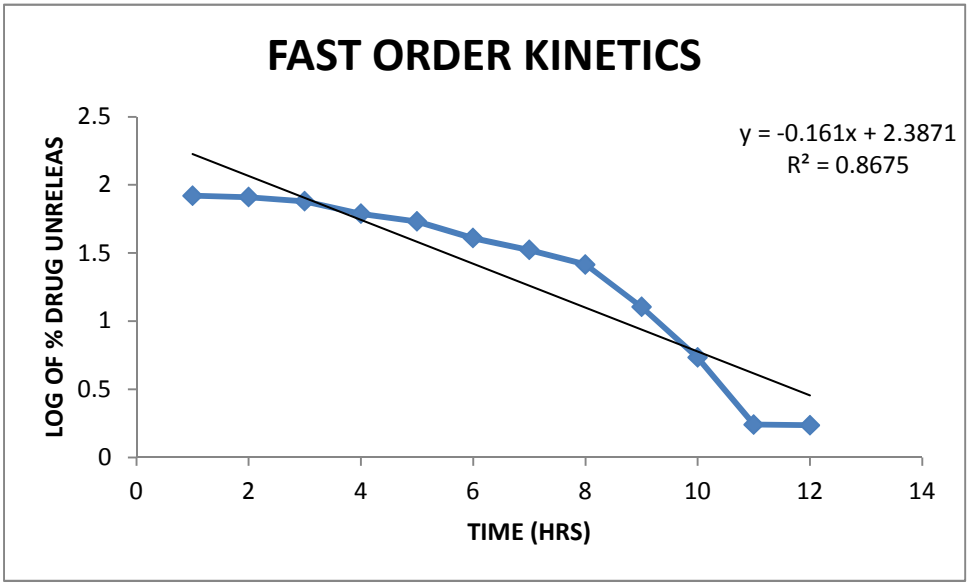

Figure.4: First order kinetic of *in vitro* release data of formulation F -6

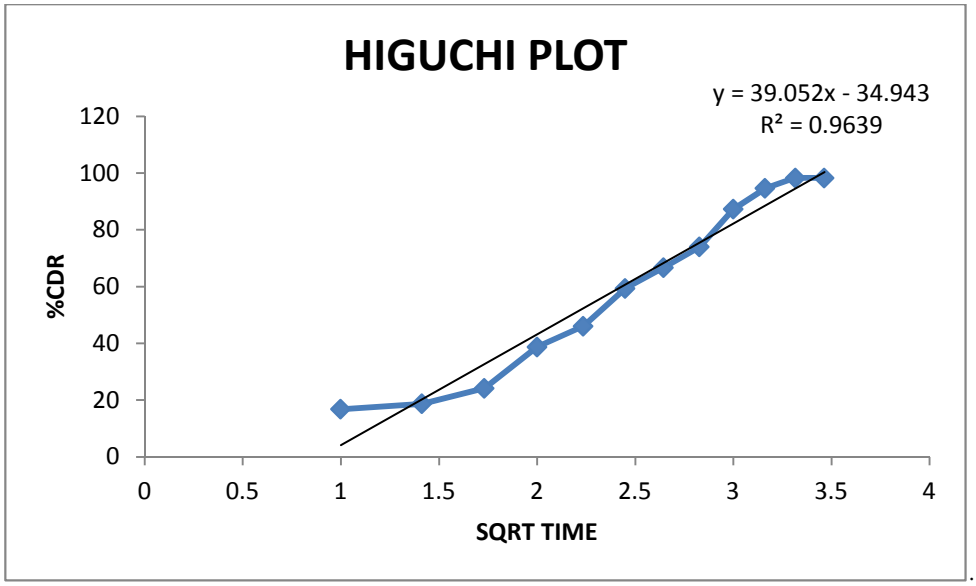

Figure.5: Higuchi plot of *in vitro* release data of formulation F -6

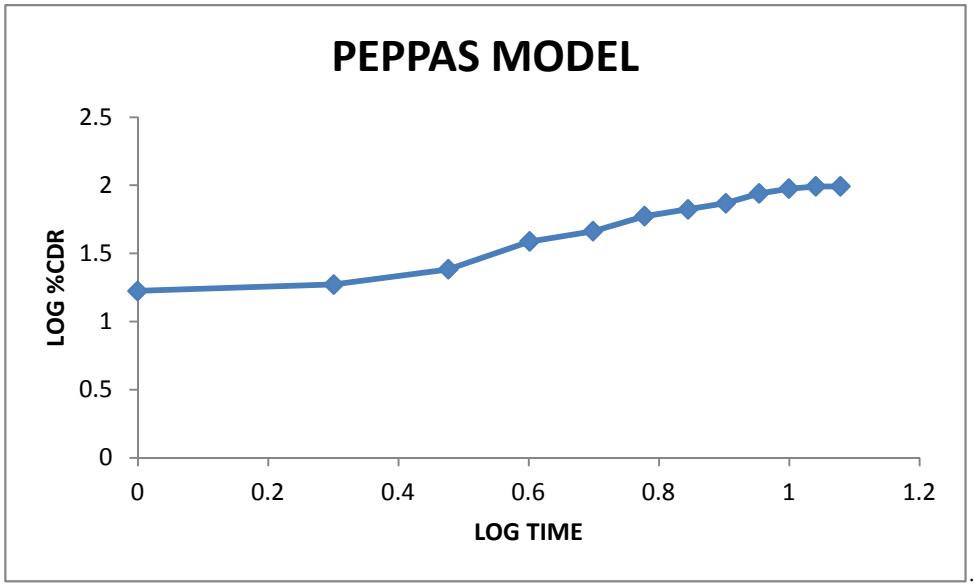

Figure.6: Peppas model of *in vitro* release data of formulation F -6

Table 8: Correlation coefficients of different kinetic models for sustained release matrix tablet of Itopride

FORMULATION	ZERO RDER R^2	FIRST ORDER R^2	HIGUCHI R^2	PEPPAS	
				R^2	n value
F1	0.989	0.840	0.975	0.991	0.812
F2	0.990	0.778	0.995	0.974	0.799
F3	0.995	0.843	0.978	0.997	0.842
F4	0.990	0.778	0.969	0.993	0.832
F5	0.993	0.771	0.974	0.990	0.798
F6	0.980	0.867	0.963	0.953	0.839
F7	0.999	0.775	0.990	0.978	0.859
F8	0.997	0.799	0.983	0.983	0.849
F9	0.980	0.607	0.987	0.961	0.761
F10	0.865	0.845	0.912	0.987	0.845
F11	0.987	0.798	0.843	0.798	0.798
F12	0.789	0.745	0.877	0.899	0.792

Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and

also no additional peaks were seen in the selected formulations (figures: 7-12). This confirms that no interaction between drug and excipients.

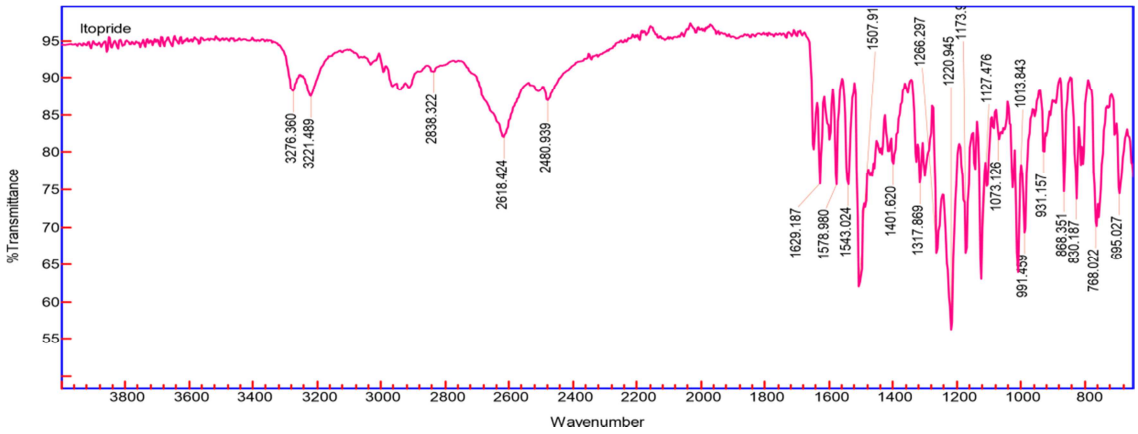

Figure 7: FT-IR of Itopride

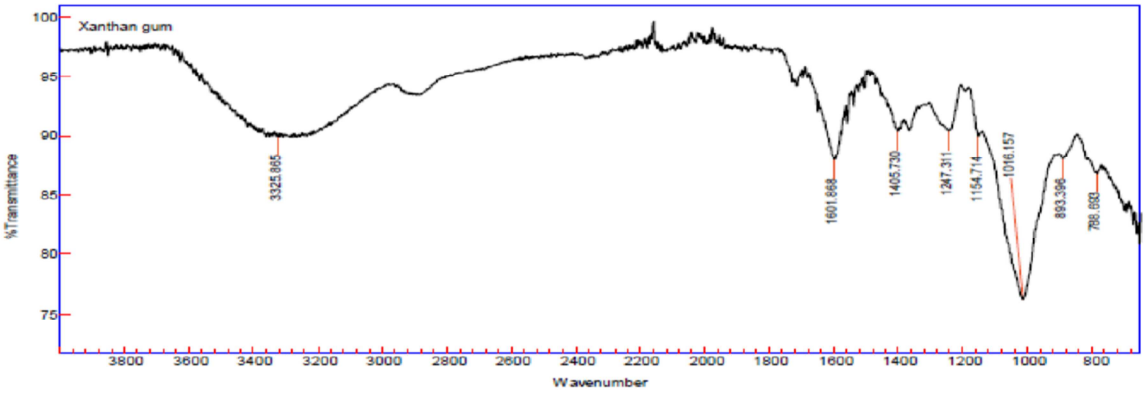

Figure 8: FT-IR of Xanthan gum

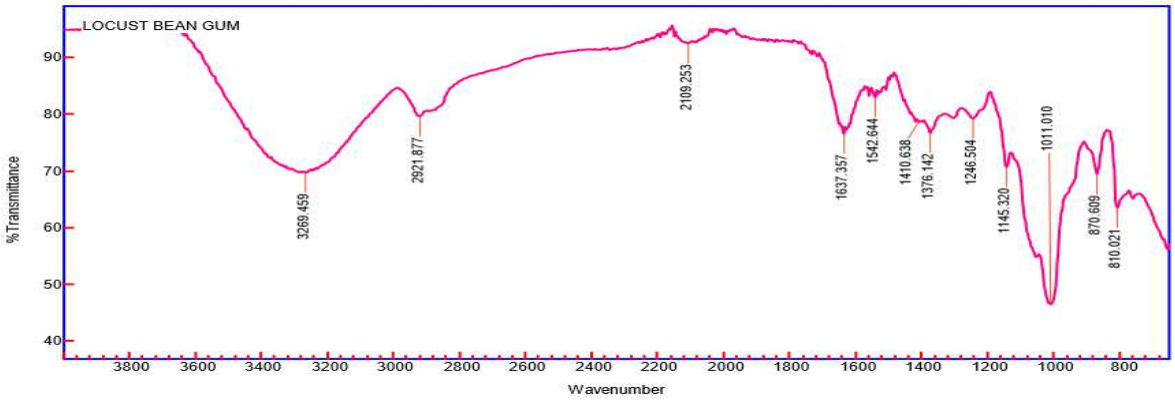

Figure 9: FT-IR of Locust bean gum

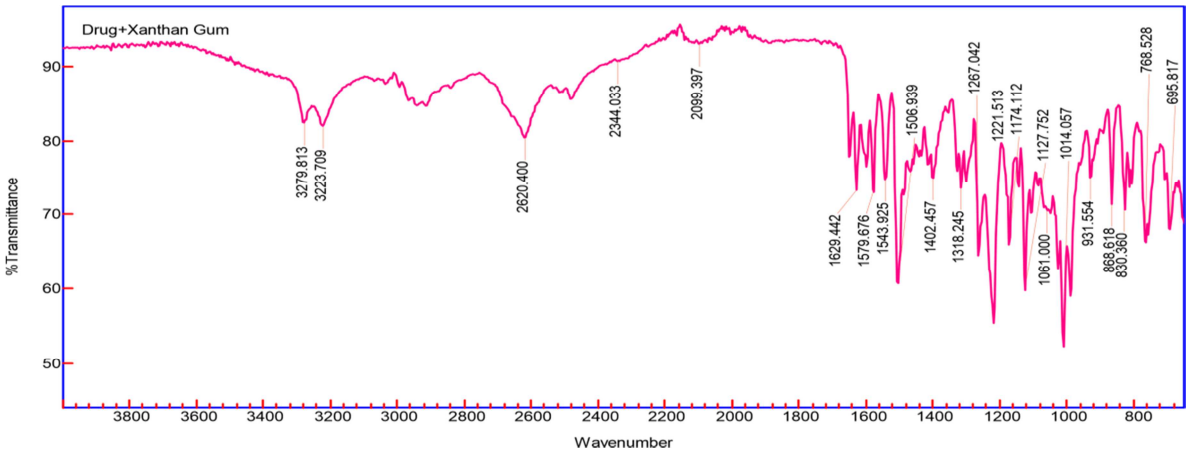

Figure 10: FT-IR of Itopride+Xanthan gum

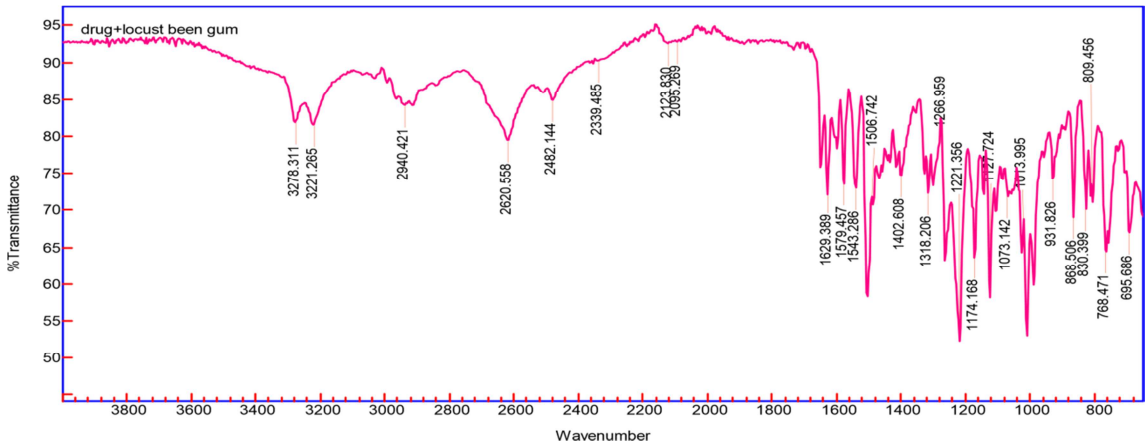

Figure 11: FT-IR of Itopride+Locust bean gum

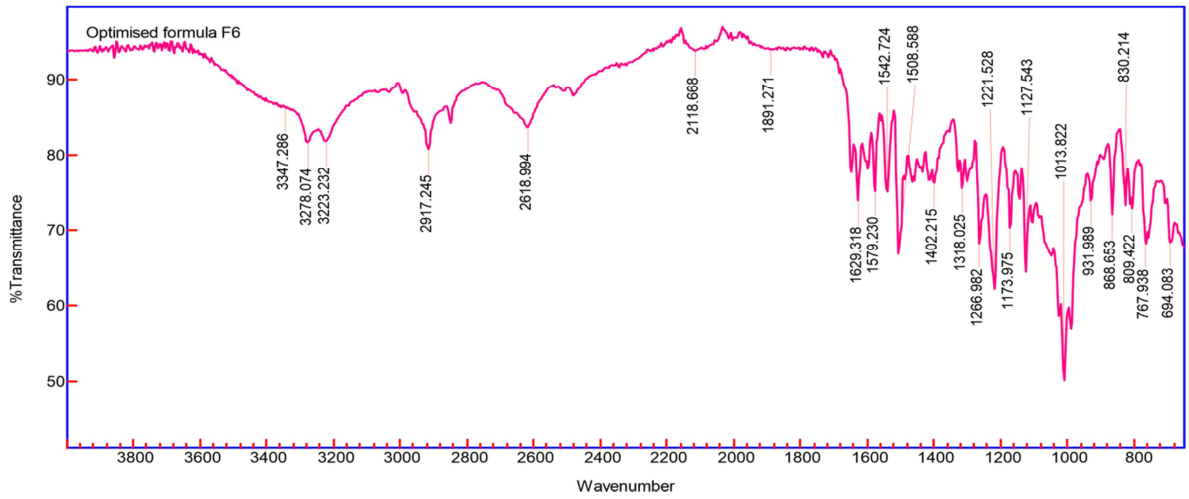

Figure 12: FT-IR of Optimised Formulation F6

Stability Study:

Stability studies were carried out on selected formulations (F6) as per ICH guidelines. There was no significant changes in drug content, physical stability, hardness, friability and drug release (Table 9-11) for the selected

formulation F-6 after 90 days at 40^0C ± 0.5^0 / 75% ± 5% RH. Therefore the main objective of the study to design and evaluate the matrix tablets of a Itopride drug using natural polymers as a retardant was achieved.

Table 9: Physical appearance of all optimised formulation with excipients after stability studies

Temp. and relative humidity	F6							Parameters
	Days							
	0	15	30	45	60	75	90	
40°C± 0.5°C / 75% ± 5% RH	No change in physical appearance							Physical appearance

Table 10: Percentage Drug content of the optimised formulation prepared with, locust bean gum and xanthan gum after stability period

NO. of Days	%Drug content
0	99.4
30	98.9
60	98.7
90	98.6

Table 11: *In vitro* % drug release of F6 after the stability period

Time in hr	F6	
	At 0 day	After 90 days
0	0	0
1	16.8	15.8
2	18.69	17.44
3	24.19	23.56
4	38.71	37.60
5	46.06	45.05
6	59.38	58.37
7	66.69	65.68
8	73.97	72.89
9	87.28	86.27
10	94.60	93.60
11	98.26	97.15
12	98.27	97.26

CONCLUSION

All the tablet formulations showed acceptable pharmacotechnical properties like hardness, friability, thickness, weight variation, drug content uniformity etc. and complied with in-house specifications for tested parameters. To develop sustained release matrix tablet the polymer were used individually and in combination. Among all, the xanthan gum and locust bean gum (1:1) release almost all amount of drug incorporated in the period of 12 hrs. Thus, formulation F-6 was found to be the most promising formulation on the basis of acceptable tablet properties and in-vitro drug release.

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