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Formulation and *in vitro* Evaluation of Matrix Diffusion Controlled Release Tablets of Itopride as Model Drug

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Abstract
In the present work, an attempt has been made to develop controlled release tablets of Itopride by selecting karaya gum, HPMC K 15 M, locust bean gum as retarding polymers. All the formulations were prepared by direct compression method using 9mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation prepared with 50mg karaya gum showed maximum % drug release i.e., 98.05 % in 12 hours hence it is considered as optimized formulation. Whereas the formulations containing xanthan gum showed more retarding with increasing concentration of polymer. The formulations with HPMC K 15 M, locust bean gum was unable to produce the desired rug release pattern.

Keywords
Itopride, Karaya gum, HPMC K 15 M, Locust bean gum, controlled release

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INTRODUCTION
The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal Controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systematically, for a specific period of time. Itopride hydrochloride an ideal candidate for the controlled drug delivery systems. To reduce the frequency or administration and to improve patient compliance a controlled release formulation of Itopride is desirable.

MATERIALS
Itopride, HPMC K15M, Locust bean gum, Gumkaraya, MCC pH 102, Magnesium stearate, Talc all the chemicals used were laboratory grade.
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Methodology and Formulation

Formulation of Itopride Controlled release Tablet by Direct- Compression:

Composition of preliminary trials for Itopride Controlled release Tablet by direct compression is shown in table 1. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 9mm flat punch, B tooling. Each tablet contains 50mg of Itopride and other pharmaceutical ingredients.

Formulation No.	Itopride (mg)	HPMC K15M (mg)	Karaya gum (mg)	Locust bean gum (mg)	Mag. Stearate (mg)	Talc (mg)	MCC pH 102 (mg)
F1	50	25	-	-	4	4	QS
F2	50	50	-	-	4	4	QS
F3	50	75	-	-	4	4	QS
F4	50	-	25	-	4	4	QS
F5	50	-	50	-	4	4	QS
F6	50	-	75	-	4	4	QS
F7	50	-	-	25	4	4	QS
F8	50	-	-	50	4	4	QS
F9	50	-	-	75	4	4	QS

Table 1: Formulations of Itopride Controlled release tablets

Each tablet weight is 250 mg.

Evaluation of prepared tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability, *In-vitro* release and drug content.

RESULTS AND DISCUSSION

Determination of λ_{max} of Itopride

The λ_{max} of Itopride was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 271 nm and the same was selected for Itopride.

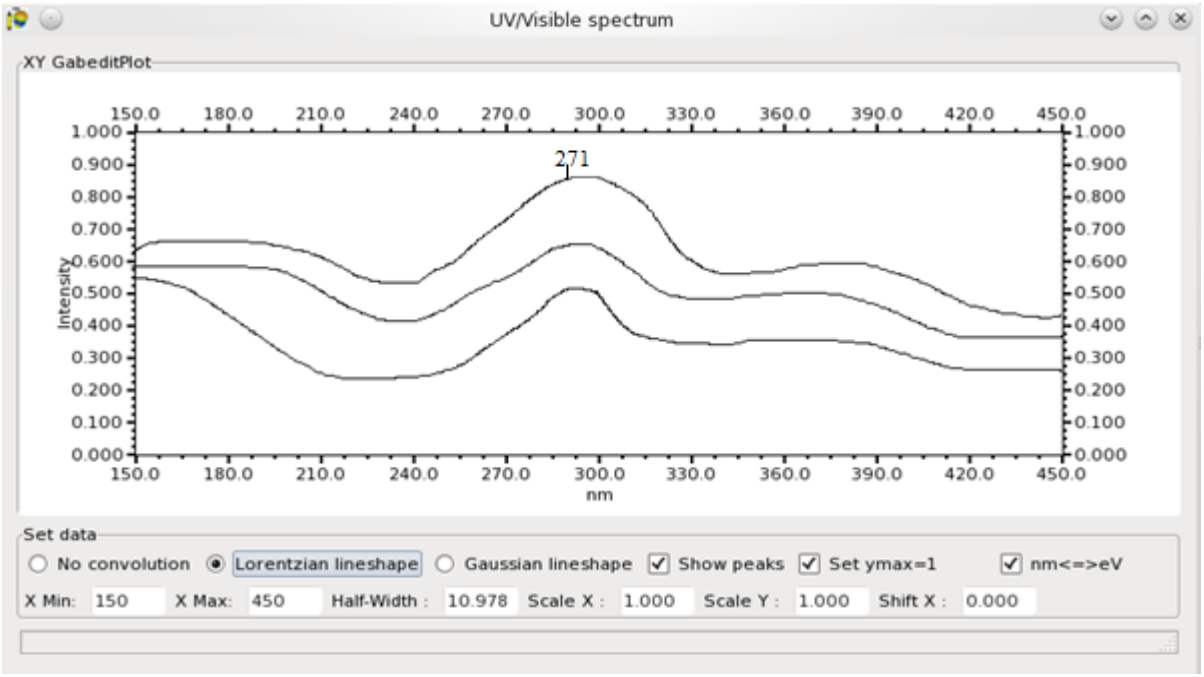

Fig 1 U.V spectrum of drug in 0.1NHCl

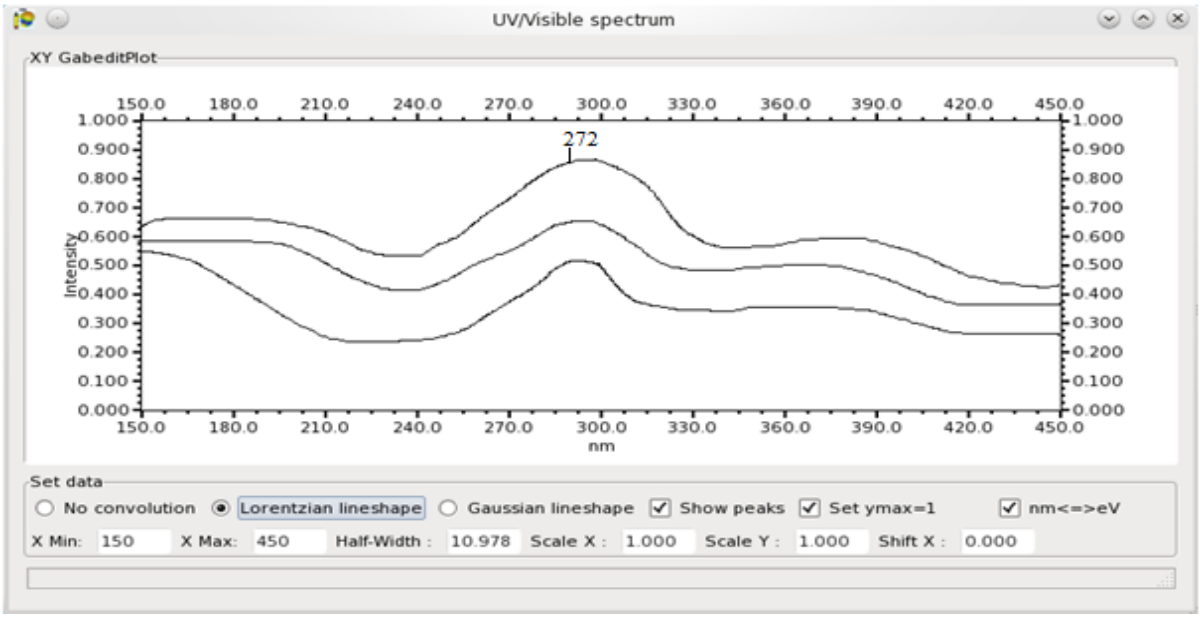

Fig 2 U.V spectrum of drug in 6.8pH

Standardization method for estimation of Itopride

Standard curves of Itopride were prepared in 0.1N HCl, and phosphate buffer (pH 6.8).

Standard graph of Itopride in 0.1N HCl

Itopride showed maximum absorbance in 0.1N HCl at 271 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 µg / ml to 10 µg / ml with regression coefficient of 0.999. Standard curve of Itopride prepared in 0.1N HCl is shown below in Table 2 and Figure 3.

S.No.	Conc [µg/ml]	Abs
1	0	0
2	2	0.138
3	4	0.256
4	6	0.376
5	8	0.461
6	10	0.582
7	12	0.824

Table 2: Calibration data of Itopride in 0.1N HCl

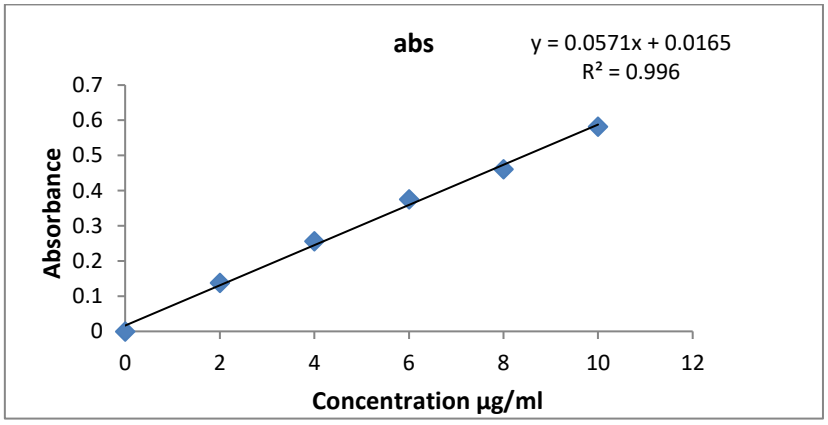

Fig 3: Standard Graph of Itopride in 0.1N HCl

Standard graph of Itopride in phosphate buffer (pH 6.8)

Itopride showed maximum absorbance in phosphate buffer (pH 6.8) at 272 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 to 10 µg/mL with regression coefficient of 0.996. Standard curve of Itopride prepared in phosphate buffer pH 6.8 is shown below.

S.No.	Conc [µg/ml]	Abs
1	0	0
2	1	0.148
3	2	0.275
4	3	0.379
5	4	0.481
6	5	0.621
7	6	0.859

Table 3. CalibrationdataofItoprideinpH6.8 phosphate buffer

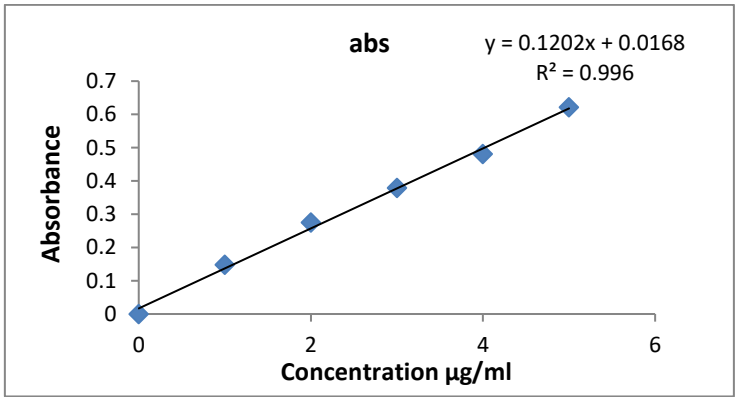

Fig 4: Graph of ItoprideinpH6.8 phosphate buffer

FTIR Graphs

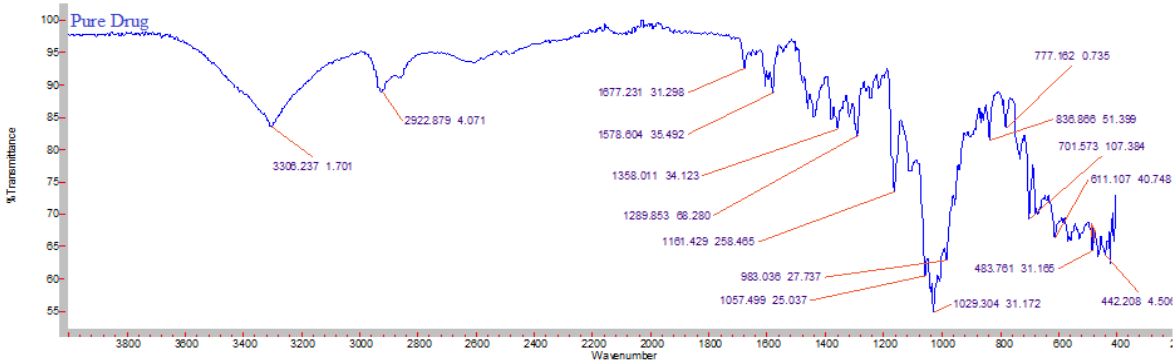

Fig 5: FTIR spectrum of pure drug

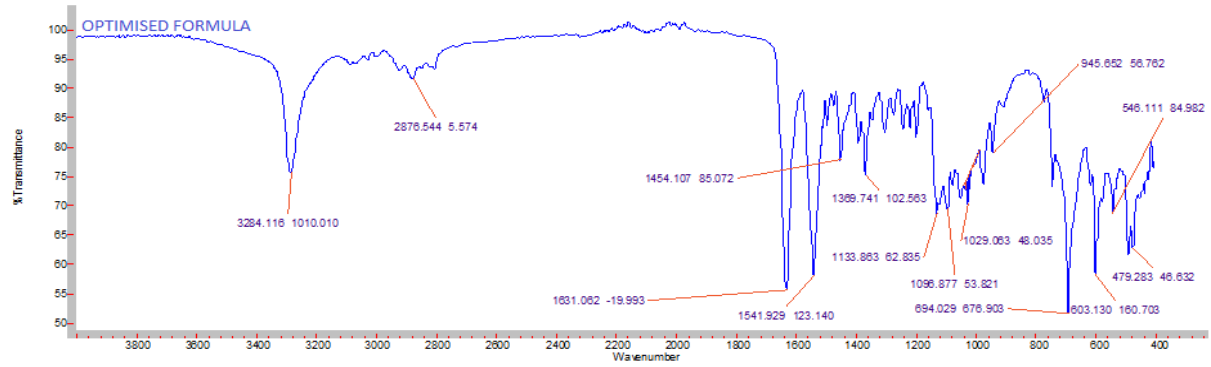

Fig 6 FTIR spectrum of optimized formula

S.NO	Wave-number-in-formulation-(cm^{-1})		Characteristic-Wave-number-range-(cm^{-1})	Bond-nature-and-bond-attributed
	Pure drug	Optimised-formulation		
1	2922	2876	3300-2500	O-H-stretching Carboxylic acids
2	1677	1631	1760-1690	C=O-stretching Carboxylic acids
3	1578	1541	1600-1400	C-C-stretch-in-ring-aromatics
4	1358	1369	1320-1000	C-O-stretch-Esters
5	611	603	1000-650	=C-H-bend-Alkenes

Table 4 Interpretation-of-FTIR-results

Evaluation Parameters for Controlled release tablets of Itopride:

Table 5 Pre-compression parameters:

Formulation Code	Angle of Repose (degrees)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's Ratio
F1	25.11±0.18	0.49±0.28	0.54±0.22	16.21±0.29	0.86±0.03
F2	25.67±0.22	0.52±0.19	0.52±0.38	16.87±0.38	0.98±0.28
F3	25.54±0.47	0.50±0.22	0.58±0.47	17.11±0.77	0.64±0.11
F4	25.43±0.29	0.51±0.56	0.54±0.33	17.67±0.38	1.12±0.87
F5	25.34±0.85	0.52±0.38	0.57±0.29	16.92±0.33	1.2±0.28
F6	24.22±0.47	0.53±0.33	0.56±0.21	17.65±0.28	1.06±0.22
F7	25.18±0.87	0.54±0.17	0.59±0.28	16.43±0.16	0.76±0.21
F8	24.22±0.38	0.58±0.22	0.67±0.22	17.97±0.01	1.15±0.98
F9	25.05±0.33	0.55±0.38	0.52±0.98	17.54±0.01	1.17±0.01

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 0.49 to 0.58 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52 to 0.67 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations have shown the hausner ratio ranging between 0.64 to 1.17 indicating the powder has good flow properties.

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Thickness(mm)	Friability (%loss)	Drug content (%)
F1	252.5±0.21	4.5±0.12	3.1±0.18	0.50±0.18	99.76±0.38
F2	255.4±0.18	4.5±0.45	2.9±0.98	0.51±0.11	99.45±0.33
F3	248.6±0.12	4.4±0.28	3.0±0.56	0.51±0.23	99.34±0.19
F4	250.6±0.29	4.5±0.56	3.2±0.34	0.55±0.41	99.87±0.26
F5	259.4±0.57	4.4±0.76	2.9±0.56	0.56±0.51	99.14±0.45
F6	250.7±0.29	4.5±0.35	3.2±0.31	0.45±0.28	98.56±0.57
F7	252.3±0.18	4.1±0.44	3.2±0.36	0.51±0.44	98.42±0.92
F8	251.2±0.22	4.3±0.37	3.1±0.12	0.49±0.38	99.65±0.33
F9	248.3±0.57	4.5±0.29	3.1±0.44	0.55±0.23	99.12±0.47

Table 6 Post compression Parameters:

Physical characteristics:

The physical characteristics of Itopride tablets (F1 to F9) such as weight variation, thickness, hardness, friability and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Hardness

A difference in tablet hardness reflects difference in tablet density and porosity. The hardness of tablets was found to be in the range of 4.1±0.44Kg/cm^2 to 4.5±0.56 Kg/cm^2

Percentage friability

Percentage friability of all formulations was found to be in the range of 0.45±0.28% to 0.56±0.51%. This indicates good handling property of the prepared tablets.

Weight variation

The average weight of the tablet is 250mg. The pharmacopoeial limit for percentage deviation is ±5%. The weights of all tablets were ranged from 248.3±0.57mg to 259.4±0.57mg.

Thickness

The thickness of tablets was found to be in the range of 2.9±0.98 mm to 3.2±0.36mm.

Drug content

All the tablet formulations shown good uniformity in drug content and they contain 98.42±0.92 to 99.65±0.33% of Itopride which is within the specified limit. The results were shown in the table no: 9

Invitro Dissolution studies:

Invitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 6 hours. The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7,8,9,10,11 & 12 hours respectively.

Time (hrs)	F1	F2	F3
0	0	0	0
0.5	4.13±0.43	3.19±0.51	4.23±0.46
1	9.42±0.39	10.16±0.46	8.45±0.57
2	13.76±0.72	15.87±0.43	14.71±0.51
3	22.15±0.45	23.82±0.57	18.32±0.81
4	29.61±0.57	29.13±0.39	26.65±0.43
5	38.12±0.63	38.05±0.45	33.84±0.57
6	48.25±0.81	46.18±0.72	39.19±0.39
7	57.31±0.46	58.37±0.63	45.52±0.45
8	63.14±0.64	65.04±0.81	56.17±0.72
9	69.15±0.51	71.15±0.64	61.26±0.63
10	73.19±0.46	74.38±0.57	68.14±0.46
11	78.12±0.43	79.09±0.49	72.58±0.58
12	83.92±0.57	86.95±0.46	78.72±0.36

Table 7: Dissolution Data of F1, F2, F3 Formulations

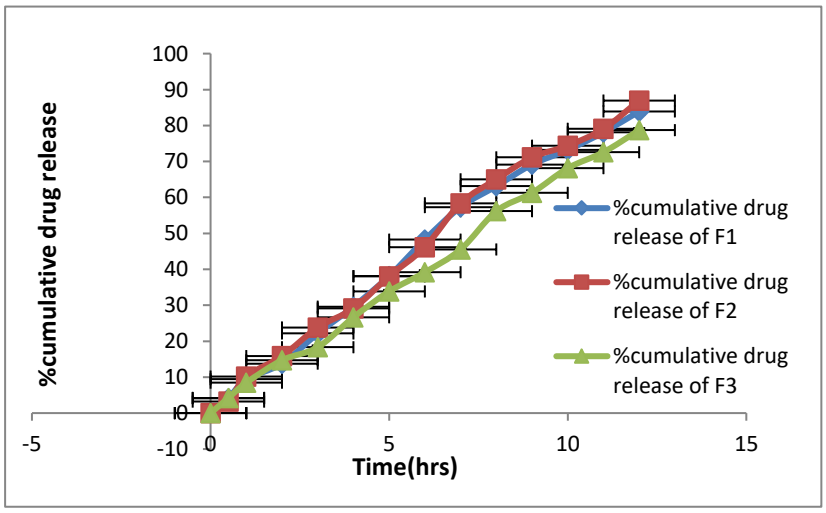

Fig 7: Dissolution profile of formulations prepared with HPMCK15M polymer

Time (hrs)	F4	F5	F6
0	0	0	0
0.5	2.16±0.64	5.12±0.57	2.39±0.72
1	7.14±0.57	9.26±0.46	12.45±0.64
2	13.06±0.64	15.62±0.57	18.68±0.46
3	19.57±0.51	24.84±0.81	24.28±0.57
4	28.13±0.46	31.46±0.64	35.19±0.51
5	35.82±0.81	39.85±0.51	44.57±0.46
6	42.85±0.43	46.53±0.46	56.18±0.81
7	48.93±0.57	53.91±0.63	64.21±0.63
8	56.37±0.39	62.75±0.43	73.18±0.57
9	65.43±0.45	73.48±0.45	81.45±0.72
10	72.39±0.72	82.17±0.39	85.21±0.43
11	76.54±0.63	93.85±0.57	87.65±0.45
12	84.26±0.46	98.05±0.72	91.67±0.39

Table 8: Dissolution Data of F4, F5, F6 Formulations

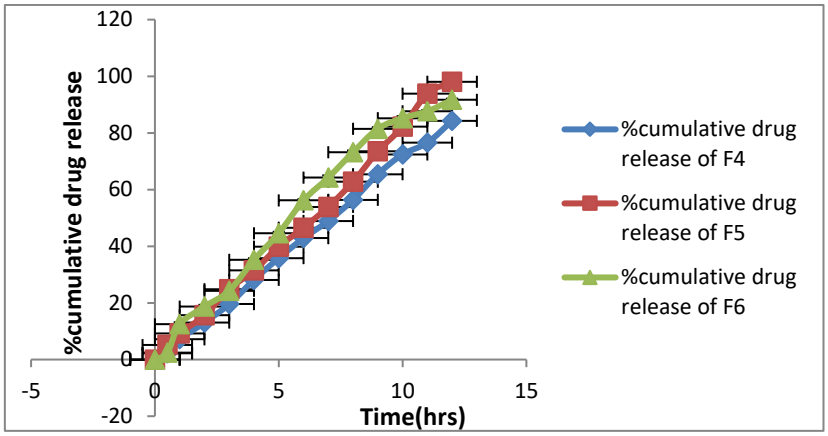

Fig 8: Dissolution profile of formulations prepared with Karaya gum polymer

Time (hrs)	F7	F8	F9
0	0	0	0
0.5	1.31±0.57	3.71±0.46	2.09±0.57
1	6.43±0.46	9.43±0.57	8.51±0.51
2	11.52±0.69	13.52±0.51	15.72±0.64
3	21.63±0.64	21.64±0.46	27.63±0.72
4	33.58±0.81	29.24±0.81	36.48±0.63
5	42.06±0.51	37.04±0.72	45.26±0.57
6	51.42±0.46	46.83±0.63	54.32±0.39
7	59.65±0.72	54.62±0.57	62.49±0.45
8	63.98±0.63	63.71±0.39	67.82±0.43
9	71.62±0.57	71.53±0.45	72.84±0.81
10	77.05±0.39	78.49±0.43	78.06±0.46
11	85.13±0.45	86.94±0.64	84.51±0.49
12	92.64±0.43	88.52±0.39	86.63±0.57

Table 9: Dissolution Data of F7, F8, F9 Formulations

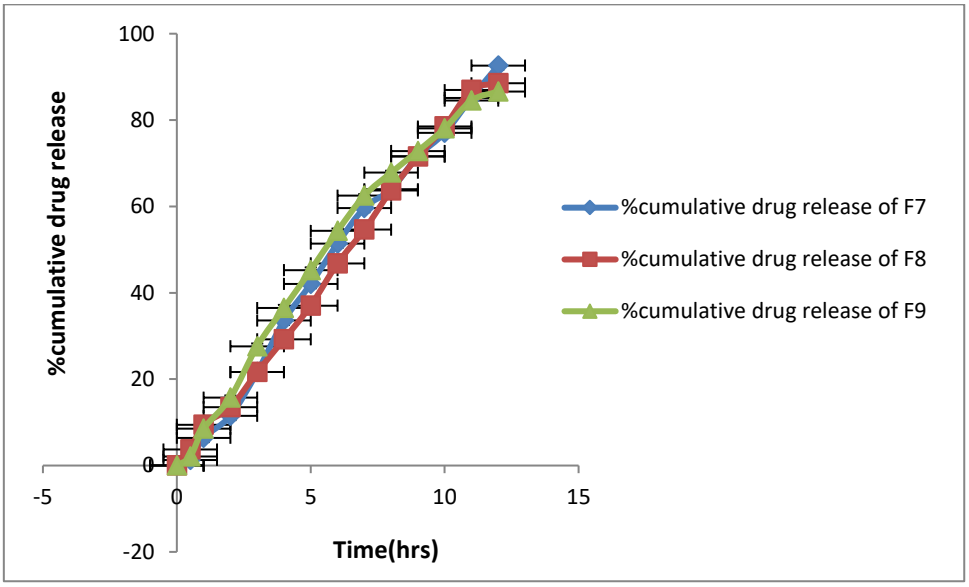

Fig 9: Dissolution profile of formulations prepared with Locust bean gum as polymer

From the above dissolution results, it was observed that all the formulations drug release is sustained for up to 12 hours. In case of formulations prepared with HPMC K15M (F1-F3), percentage of drug release is not more than 86.95±0.46% within 12 hours. In case of formulations prepared with Karaya Gum (F4-F6), percentage of release was up to 98.05±0.72% in case of F5, which contains 50 mg of polymer, and it was also observed that as the polymer concentration increases drug release was reduced. In case of formulations prepared with Locust bean Gum (F7-F9), percentage of release was not more than 92.64±0.43%. Hence, it was evident that the formulation F5 is best formulation with desired drug release pattern extended up to 12 hours with complete drug release.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
5.12	**0.5**	0.458	0.709	1.987	1.977
9.26	1	1.000	0.967	0.000	1.958
15.62	2	1.414	1.194	0.301	1.926
	3	1.732	1.395	0.477	1.876
31.46		2.000	1.498	0.602	1.836
39.85	5	2.236	1.600	0.699	1.779
46.53	6	2.449	1.668	0.778	1.728
53.91	7	2.646	1.732	0.845	1.664
62.75	8	2.828	1.798	0.903	1.571
73.48	9	3.000	1.866	0.954	1.424
82.17	10	3.162	1.915	1.000	1.251
93.85	11	3.317	1.972	1.041	0.789

Table 10: Release kinetics data for optimised formulation

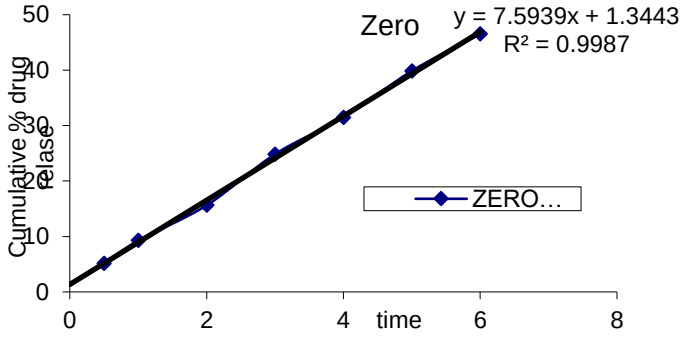

Fig 10: Zero order release kinetics graph

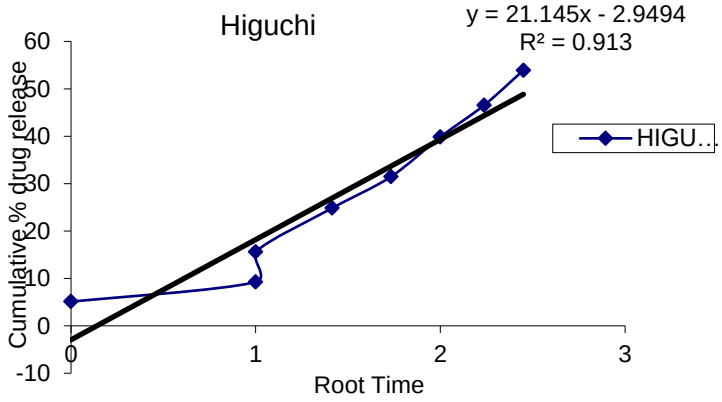

Fig 11: Higuchi release kinetics graph

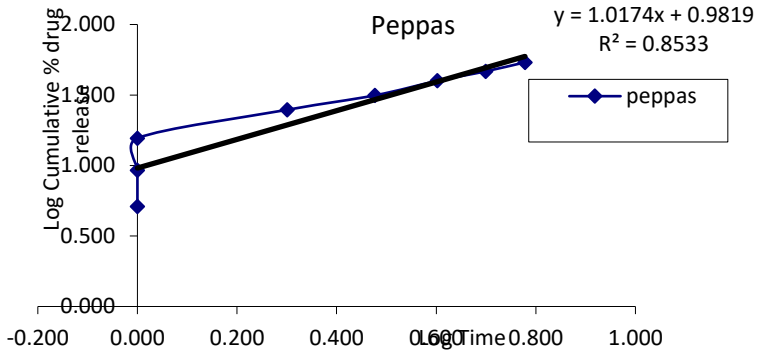

Fig 12: Kars mayer peppas graph

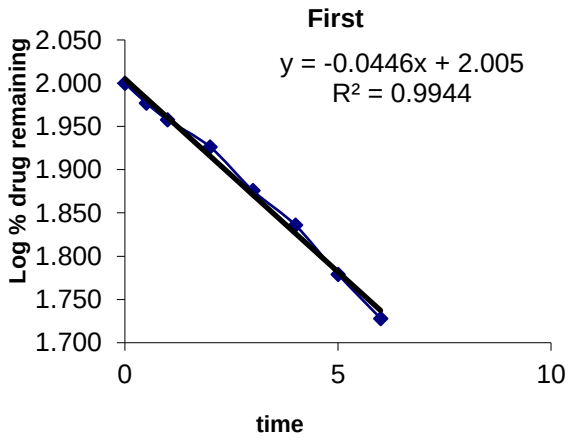

Fig 13: First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed Zero order release mechanism.

Stability Studies

Parameters Tested	Initial	After 1 month	After 2 months	After 3months
Weight (mg) variation	259.4±0.57	259.3±0.43	259.4±0.35	259.2±0.08
Thickness (mm)	2.9±0.56	2.9±0.32	2.9±0.27	2.9±0.26
Hardness -(kg/cm^2)	4.4±0.76	4.4±0.54	4.4±0.43	4.4±0.32
Friability (%)	0.56±0.51	0.56±0.49	0.56±0.32	0.56±0.23
Drug content (%)	99.14±0.45	99.14±0.41	99.14±0.35	99.14±0.29
Maximum %CDR	98.05±0.72	98.05±0.65	98.05±0.54	98.02±0.43

Table 11. Stability studies for optimized formulation F5.

Time (hrs)	% Cumulative drug release
0	0
0.5	5.09±0.52
1	9.23±0.41
2	15.59±0.54
3	24.82±0.81
4	31.43±0.63
5	39.82±0.49
6	46.52±0.45
7	53.89±0.62
8	62.74±0.43
9	73.46±0.45
10	82.15±0.38
11	93.82±0.55
12	98.02±0.43

Table 12. Dissolution studies-data of Formulation F5 after three months

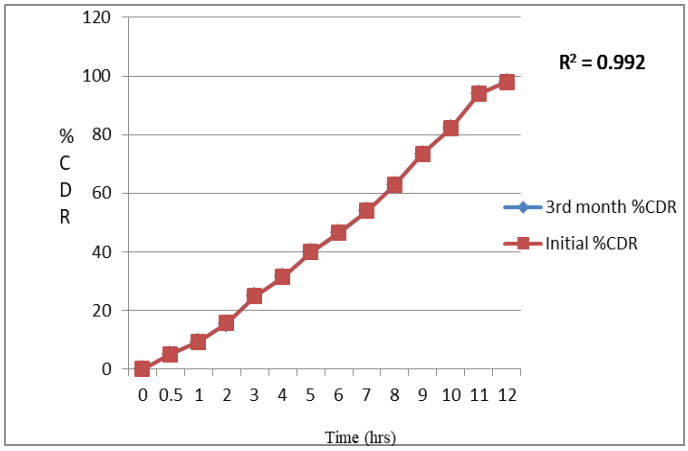

Fig 14: Comparison of-Dissolution-profiles-of-formulation F5

The stability studies for F5 were performed at temperature 40± 0.5°C & 75% relative humidity and the results are listed, from the results it indicates the selected formulation was stable.

CONCLUSION

In the present work, an attempt has been made to develop controlled release tablets of Itopride by selecting karaya gum, HPMC K 15 M, locust bean gum as retarding polymers. All the formulations were prepared by direct compression method using 9mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation

prepared with 50mg karaya gum showed maximum % drug release i.e., 98.05 % in 12 hours hence it is considered as optimized formulation. Whereas the formulations containing xanthan gum showed more retarding with increasing concentration of polymer. The formulations with HPMC K 15 M, locust bean gum was unable to produce the desired rug release pattern. From the stability results, it was concluded that the selected formulation F5 is stable. Based on the results it is claimed that the formulations can be suitable for Industrial application after pilot plant scale up techniques.

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