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## RESEAECH ARTICLE

# 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 were unable to produce the desired rug release pattern.

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

## ARTICLE INFO

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#### **1. 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.

#### 2. Materials and Methods

**Materials:** Itopride, HPMC K15M, Locust bean gum, Gumkaraya, MCC pH 102, Magnesium stearate, Talcall the chemicals used were laboratory grade.

#### Methodology& 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 poly bag. 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.

#### **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.

#### 3. Results and Discussions

#### Determination of $\lambda$ max of Itopride:

The  $\lambda$  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: UV spectrum of drug in 0.1NHCl





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#### 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 HCI:

Itopride showed maximum absorbance in 0.1N HCl at 271 nm. The solution obeyed Beer-Lambert's law for concentration range of 1  $\mu$ g / ml to 10  $\mu$ g / 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.



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  $10\mu g$  /mL with regression coefficient of 0.996. Standard curve of Itopride prepared in phosphate buffer pH 6.8 is shown below.



Fig 4: Graph of Itopride in pH6.8 phosphate buffer

#### **FTIR Graphs:**



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#### **Pre Compression Parameters:**

Tablet powder blend was subjected to various preformulation 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 has shown the hausner ratio ranging between 0.64 to 1.17 indicating the powder has good flow properties.

#### **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  $4.1\pm0.44$ Kg/cm<sup>2</sup> to  $4.5\pm0.56$  Kg/cm<sup>2</sup>

#### Percentage friability:

Percentage friability of all formulations was found to be in the range of  $0.45\pm0.28\%$  to  $0.56\pm0.51\%$ . 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  $\pm 5\%$ . The weights of all tablets were ranged from 248.3 $\pm 0.57$ mg to 259.4 $\pm 0.57$ mg.

#### Thickness:

The thickness of tablets was found to be in the range of  $2.9\pm0.98$  mm to  $3.2\pm0.36$ mm.

#### Drug content:

All the tablet formulations shown good uniformity in drug content and they contain  $98.42\pm0.92$  to  $99.65\pm0.33\%$  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 International Journal of Chemistry and Pharmaceutical Sciences

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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.



Fig 7: Dissolution profile of formulations prepared with HPMCK15M polymer



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



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





Fig 13: First order release kinetics graph

time

4

2

1.700

0

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







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 Karava 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 Locustbean 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 analyze 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.

Formulation No.	Itopride (mg)	HPMC K15M (mg)	Karaya gum (mg)	Locustbean 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 No 1: Formulations of Itopride Controlled release tablets

8

6

Each tablet weight is 250 mg

Table No 2: Calibration data of Itopride in 0.1N HCl

S.No.	Conc [µg/ml]	Abs			
1	0	0			
2	2	0.138			
3	4	0.256			
4	6	0.376			

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5	8	0.461
6	10	0.582
7	12	0.824

#### Table No 3:CalibrationdataofItoprideinpH6.8 phosphate buffer

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 No 4: Interpretation-of-FTIR-results

S.No	Wave number in	formulation (cm <sup>1</sup> )	Characteristic	Dond nature and
	Pure drug	Optimised formulation	Wave number range (cm <sup>1</sup> )	bond attributed
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 No 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	$0.49{\pm}0.28$	$0.54{\pm}0.22$	16.21±0.29	$0.86{\pm}0.03$
F2	25.67±0.22	0.52±0.19	$0.52{\pm}0.38$	16.87±0.38	$0.98{\pm}0.28$
F3	25.54±0.47	$0.50{\pm}0.22$	$0.58{\pm}0.47$	17.11±0.77	$0.64{\pm}0.11$
F4	25.43±0.29	$0.51 \pm 0.56$	$0.54{\pm}0.33$	$17.67 \pm 0.38$	$1.12{\pm}0.87$
F5	25.34±0.85	$0.52{\pm}0.38$	0.57±0.29	16.92±0.33	$1.2 \pm 0.28$
F6	24.22±0.47	0.53±0.33	0.56±0.21	$17.65 \pm 0.28$	$1.06 \pm 0.22$
F7	25.18±0.87	0.54±0.17	$0.59{\pm}0.28$	16.43±0.16	0.76±0.21
F8	24.22±0.38	0.58±0.22	0.67±0.22	$17.97 \pm 0.01$	$1.15\pm0.98$
F9	25.05±0.33	$0.55 \pm 0.38$	$0.52{\pm}0.98$	$17.54 \pm 0.01$	$1.17\pm0.01$

#### Table No 6: Post compression Parameters

Formulation	Weight	Hardness		Friability	Drug content (%)
codes	variation(mg)	(kg/cm2)	Thickness(mm)	(%loss)	
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

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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	$15.87 \pm 0.43$	14.71±0.51
3	22.15±0.45	23.82±0.57	$18.32 \pm 0.81$
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 No 7: Dissolution Data of F1, F2, F3 Formulations

 Table No 8: Dissolution Data of F4,F5,F6 Formulations

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	$13.06 \pm 0.64$	$15.62 \pm 0.57$	$18.68 \pm 0.46$
3	19.57±0.51	$24.84{\pm}0.81$	$24.28 \pm 0.57$
4	28.13±0.46	$31.46 \pm 0.64$	35.19±0.51
5	35.82±0.81	39.85±0.51	$44.57 \pm 0.46$
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	$73.48 \pm 0.45$	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 No 9: Dissolution Data of F7, F8, F9 Formulations

Time(hrs)	F7	F8	F9
0	0	0	0
0.5	$1.31 \pm 0.57$	3.71±0.46	$2.09 \pm 0.57$
1	6.43±0.46	9.43±0.57	8.51±0.51
2	$11.52 \pm 0.69$	$13.52 \pm 0.51$	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	$37.04 \pm 0.72$	45.26±0.57
6	51.42±0.46	46.83±0.63	54.32±0.39
7	59.65±0.72	$54.62 \pm 0.57$	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	$78.49 \pm 0.43$	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 No 10: Release kinetics data for optimised formulation

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

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15.62	2	1.414	1.194	0.301	1.926
	3	1.732	1.395	0.477	1.876
31.46	4	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 No 11: Stability studies for optimized formulation F5				
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 <sup>2</sup> )	4.4±0.76	4.4±0.54	4.4±0.43	4.4±0.32
Friability (%)	0.56±0.51	$0.56{\pm}0.49$	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 No 12: Dissolution studies-data of Formulation F5 after three months

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

#### 4. 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 were 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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