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Formulation and Evaluation of Sustained Release Matrix Tablet of Itopride

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ABSTRACT

The objective of this research work was to carry out design and evaluation of sustained release matrix tablets of Itopride by use of natural and synthetic polymers. Matrix tablets were prepared by wet granulation technique by using natural polymers like Carbopol 934, Tamarind poly saccharide, Locust bean gum, Ethyl cellulose, HPMC K 100 as matrix forming agent and excipients such as Lactose, Starch 1500, Magnesium stearate, MCC 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. The release of Itopride from matrix containing lactose, micro crystalline cellulose and starch 1500 as diluents. The drug release rate was found in order of lactose > micro crystalline cellulose > starch 1500. The formulation was optimized on the basis of acceptable tablet properties and *in-vitro* drug release. The release data were fit into different kinetic models (zero-order, first-order, Higuchi's equation and Korsmeyer-Peppas equation). 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: Matrix tablets, Itopride, Carbopol 934, HPMC K 100, Ethyl cellulose.

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INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages.^[1]

Sustained release tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs.^[2] Oral drug delivery continues to rise in popularity as formulation scientists look for ways to control drug release and improve patient convenience. However, developing oral sustained release tablets for water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water-soluble drugs if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of drug on oral administration.^[3]

Hence, it is a challenging task to formulate a suitable table dosage form for prolonged delivery of highly water-soluble drugs. The most commonly used method of modulating the drug release is to include it in a matrix system.^[4]

Diffusion controlled polymeric matrix devices have been widely used as drug delivery systems owing to their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance.^[5] Many polymers have been used in the formulation of matrix based sustained release drug delivery systems. Reports were found on the use of hydrophilic polymers like hydroxy propyl methylcellulose (HPMC), sodium carboxy methylcellulose.^[6]

Carbopol's^[7] for the preparation of sustained release (SR) formulations of different drugs.

HPMC, a semisynthetic derivative of cellulose, is a swellable hydrophilic polymer. It contains methoxy and hydroxypropyl substituents on its b-o-glucopyranosyl ring backbone, which makes it very resistant to change in pH or ionic content of the dissolution medium.^[8]

Itopride is used in the treatment of gastrointestinal symptoms caused by reduced gastrointestinal motility, like feeling of gastric fullness, upper abdominal pain, anorexia, heartburn, nausea and vomiting, non-ulcer dyspepsia or chronic gastritis. Itopride hydrochloride, a novel prokinetic agent is best candidate for GERD. Central Composite design has been used to optimize the concentration of different component in the formulation of sustained release tablet. In this design, 2 factors were evaluated by using combination of different concentrations of polymer.^[9]

MATERIALS AND METHOD

The chemicals used in this study were pure drug like Itopride and polymers like HPMC K 100, Carbopol 934, Locust bean gum, Ethyl cellulose and other excipients like Lactose, Starch 1500, Magnesium stearate, MCC and talc (were procured from Yarrow chemicals, mumbai).

Pre-formulation Study:

Pre-formulation studies were conducted to confirm the compatibility of drug with polymers used. These studies were conducted by using FTIR spectrophotometer. In this method, the IR spectra of pure drug, physical mixtures containing drug and polymers (1:1) and tablet triturate were analyzed.

Evaluation of Flow Properties:

Prepared powder blend of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index.

Preparation of Itopride sustained release matrix tablets:

The core tablet was manufactured from granules prepared by conventional wet granulation method using starch. A non-aqueous granulation process was adopted to prepare itopride matrix tablets.

The detail process was as follows:

Sifting: The drug and all other ingredients were sifted through sieve # 60.

Mixing: The sifted ingredients were mixed thoroughly in a mortar with pestle for 15min

Preparation of Granules: Paste of starch (5% w/v) was added in well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve # 16.

Drying: The prepared granules were dried at 60⁰C for 1 hour in hot air oven, and then it was sifted through sieve # 22 and transferred the granules into a polybag.

Lubrication: Magnesium stearate and talc were sifted through sieve #40 and mixed with the prepared granules in a polybag for 5min.

Compression: Finally, tablets were compressed at 600 mg weight on a 10-station mini rotary tableting machine (Shakti Pharma tech Pvt. Ltd, Ahmedabad) with 12.1 mm flat-shaped punches natural polymer and synthetic polymers, having different concentrations (1:1, 1:2 ,1:0.5 and 1:0.25) were developed to evaluate the drug release and to study the effect of polymer concentration on drug release. (Formulation F-1 to F-10).

Table 1: Tablet composition of Itopride sustained release matrix tablets prepared with differerent release retardant natural matrices (F-1 to F-10):

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	150	150	150	150	150	150	150	150	150	150
Tamarind seed polysaccharide	300	150	75	37.5	150	75	37.5	-	-	-
Locust bean gum	-	-	-	-	-	-	-	150	75	37.5

HPMC K 100	-	150	75	37.5	-	-	-	150	75	37.5
Carbapol 934	-	-	-	-	-	-	-	-	-	-
Ethyl cellulose	-	-	-	-	150	75	37.5	-	-	-
Lactose	132	132	282	357	132	282	357	132	282	357
MCC	-	-	-	-	-	-	-	-	-	-
Starch	-	-	-	-	-	-	-	-	-	-
Magnesium stearate	12	12	12	12	12	12	12	12	12	12
Talc	6	6	6	6	6	6	6	6	6	6

Evaluation:

Hardness test:

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm².

Friability test:

Tablet strength was tested by Roche friabilator. Pre-weighed tablets were allowed for 100 revolutions (4 min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$F = \frac{(W_{\text{initial}}) - (W_{\text{final}})}{(W_{\text{initial}})} \times 100$$

Uniformity of weight:

20 tablets from each of the formulation were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, and JAPAN). The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Drug content uniformity:

Accurately weighed quantity of the powder tablet equivalent to 100mg of the drug was transferred to 100ml volumetric flask. 50ml of buffer solution of pH-7.4 was added. Mix with the aid of ultrasound for 10min, and then the volume was made up to 100ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45µm. 5ml of the filtrate was diluted to 100 ml with same buffer solution and examined under U.V Spectrophotometry at 257nm.

In Vitro Drug Release:

In-vitro drug release studies were carried out using USP dissolution apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 1.2 for first two

hours and pH 7.4 phosphate buffers for next 10 hours maintained at 37 ± 0.5 °C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Lab India, Mumbai, India) at 257 nm. The study was performed in triplicate.

RESULTS AND DISCUSSION:

The standard graph of Itopride has shown good linearity with r^2 value 0.9959 in pH 7.4 buffer solution which suggests that it obeys the “Beer-Lambert’s law”.

FTIR:

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 spectra of the pure drug and also no additional peaks were seen in the selected formulations. This confirms that no interaction between drug and excipients.

FTIR OF DRUG

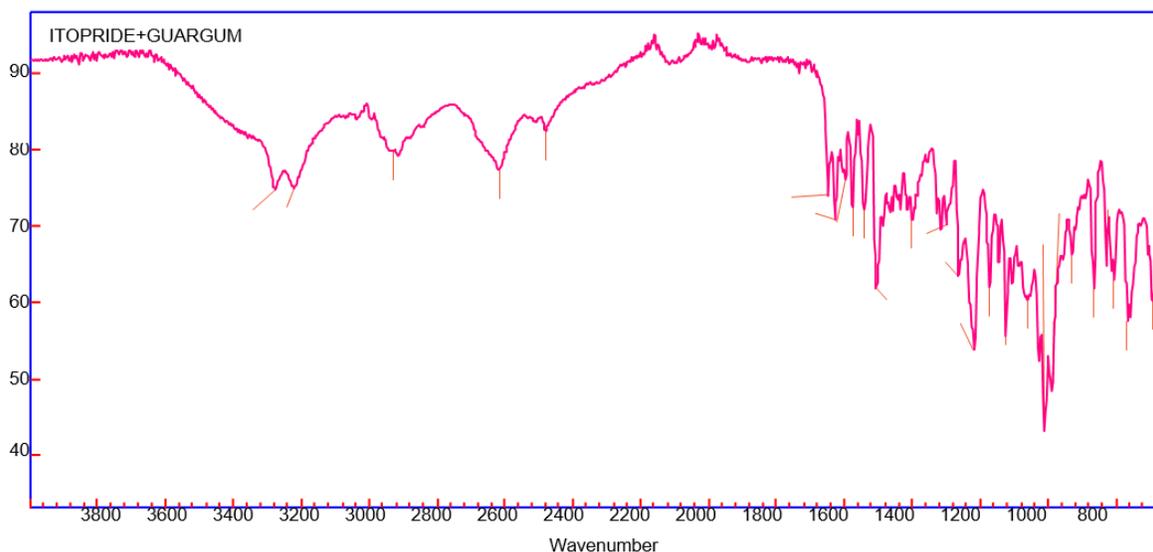


Figure 3: FT-IR of Itopride + Guar Gum

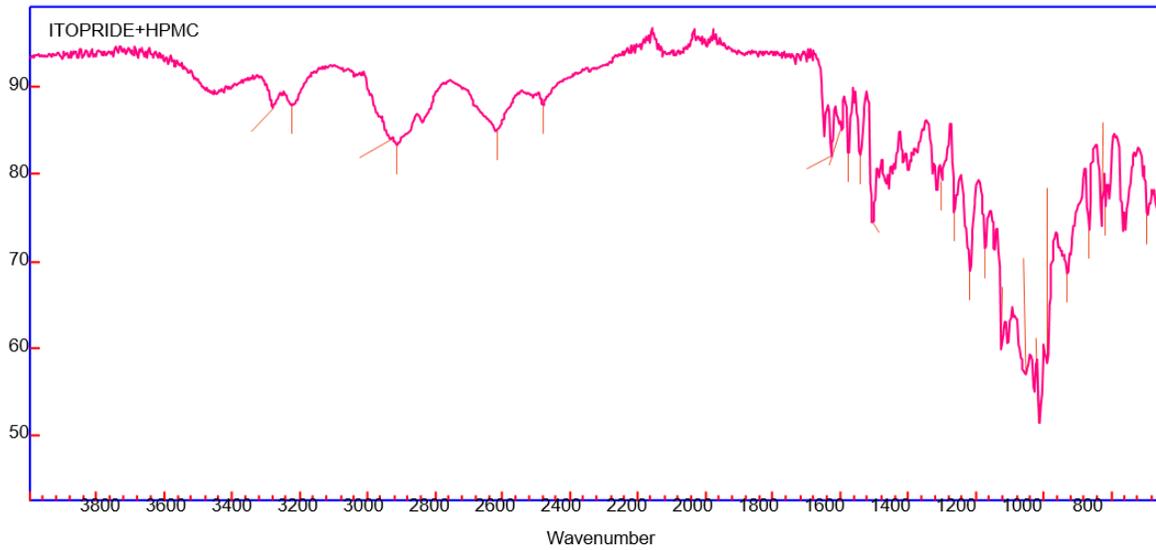


Figure 4: FT-IR of itopride + HPMC

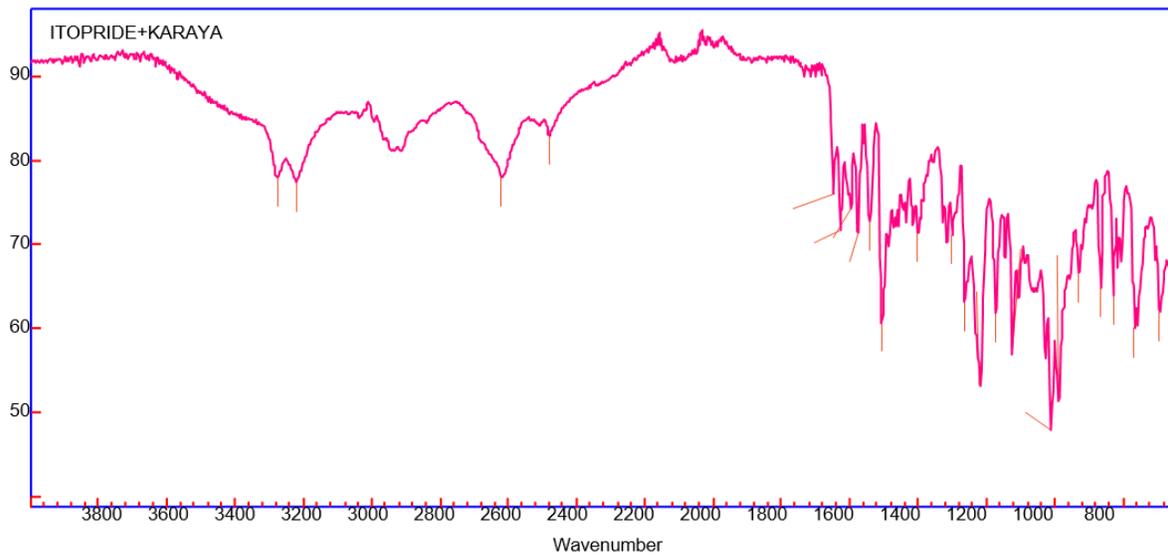


Figure 5: FT-IR of Itopride + karaya gum

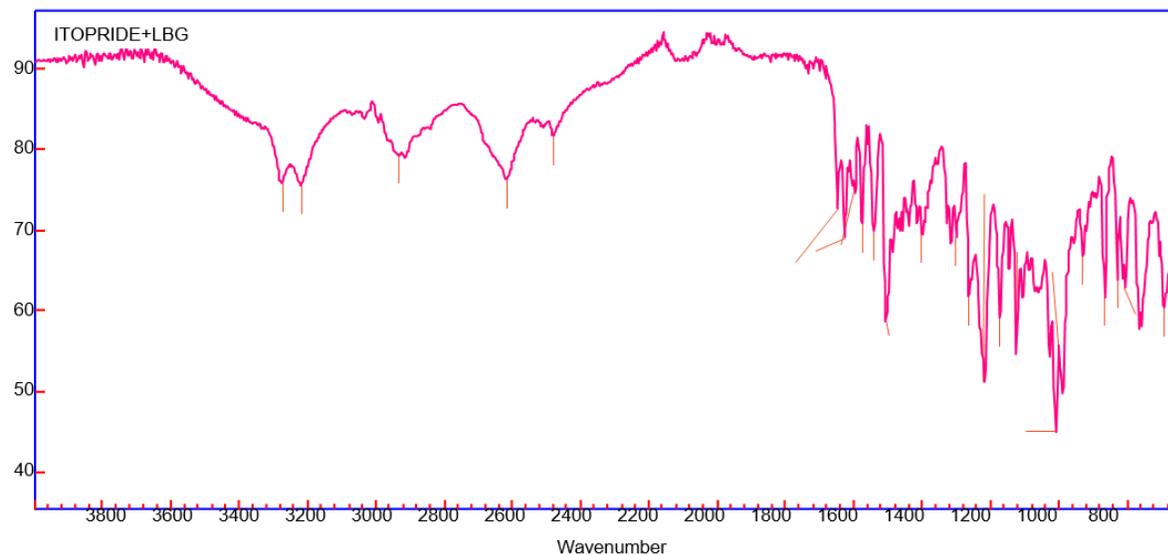


Figure 6: FT-IR of Itopride + Locust Bean Gum

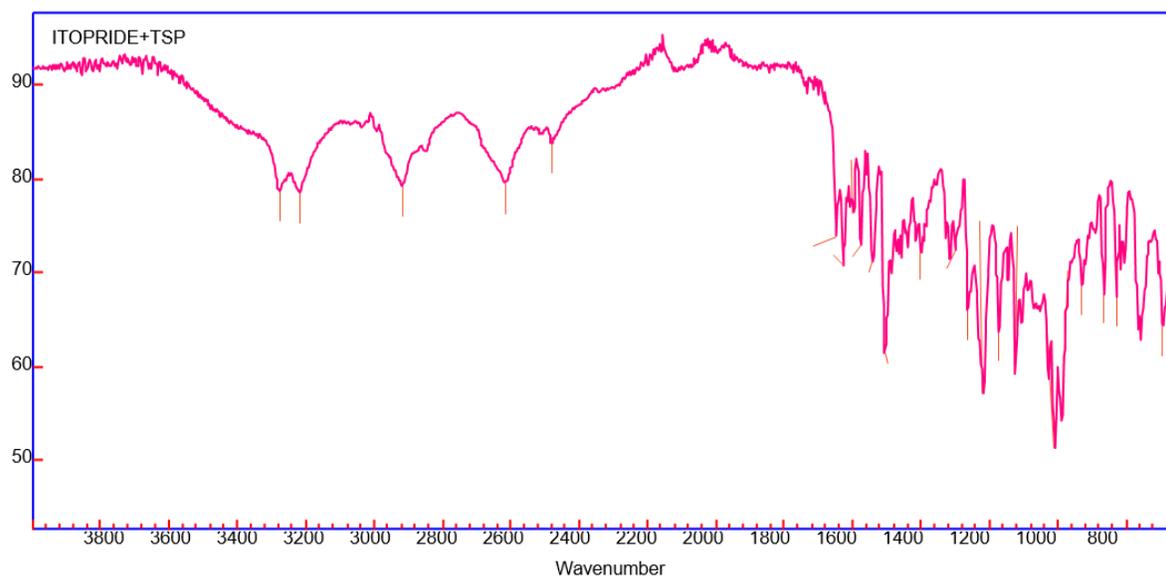


Figure 7: FT-IR of Itopride + Tamarind Seed Polysaccharide

Evaluation of Itopride Tablets:

The Itopride tablet was evaluated for hardness, thickness, friability, weight variation and drug content uniformity. The hardness was in the range of 5.7 to 6.9 kg/cm², which was in accordance with the matrix tablet. The thickness was from 3.56 to 3.90 mm suggested uniformity in thickness for matrix tablet. The friability was less than 1% indicated good handling of the layers. The weight variation results suggested uniformity in weight of layers

Table 3: Tablet properties of formulations F1 to F10 of Itopride sustained release matrix tablets.

Formulation Code	Parameters Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Drug content (%)
F-1	3.56 ± 0.12	5.9 ± 0.11	0.15 ± 0.17	99.12
F-2	3.63 ± 0.17	6.0 ± 0.22	0.20 ± 0.45	100.01
F-3	3.71 ± 0.30	5.8 ± 0.14	0.31 ± 0.28	98.99
F-4	3.79 ± 0.07	6.0 ± 0.07	0.22 ± 0.12	100.65
F-5	3.82 ± 0.12	6.0 ± 0.38	0.40 ± 0.34	99.98
F-6	3.89 ± 0.10	6.7 ± 0.19	0.45 ± 0.28	100.12
F-7	3.90 ± 1.20	6.9 ± 0.24	0.32±0.09	100.90
F-8	3.66 ± 1.75	5.7 ±0.33	0.52±0.02	98.79
F-9	3.70 ± 1.48	6.9 ± 0.12	0.28±0.01	100.52
F-10	3.76 ± 1.51	6.3 ±0.45	0.41±0.06	99.99

Weight variation for tablet formulations (F-1 to F-10)

Sl. No	F-1	F-2	F-3	F-4	F-5	F6	F-7	F-8	F-9	F-10
1	601.1	600.5	599.6	600.5	599.0	600.3	600.4	599.7	601.9	600.9
2	601.3	600.6	599.4	599.9	600.5	601.2	598.9	598.2	599.2	599.8
3	601.5	600.0	600.2	601.2	600.1	600.1	600.7	599.9	600.2	599.8
4	600.2	598.2	601.3	602.4	601.3	600.9	600.4	599.6	600.3	600.2
5	600.8	599.7	602.0	600.8	600.2	599.8	602.3	600.2	602.1	500.9
6	600.5	601.1	600.8	600.9	600.4	599.8	601.7	600.1	4599.8	601.3
7	600.7	600.7	699.8	600.7	599.6	600.2	600.2	599.5	599.7	602.0
8	601.6	600.7	699.6	600.2	600.2	600.8	600.8	600.5	601.2	600.8
9	600.2	600.2	600.3	600.1	600.2	600.7	600.3	600.2	600.8	599.8
10	601.6	600.3	601.2	601.2	598.8	600.6	601.4	599.9	600.3	599.6
Average Weight	601.0	600.2	600.4	600.1	600.1	600.4	600.7	599.8	600.6	600.5
% Maximum Positive dev.	0.533	0.709	0.689	0.639	0.489	0.182	0.943	0.676	0.849	0.632

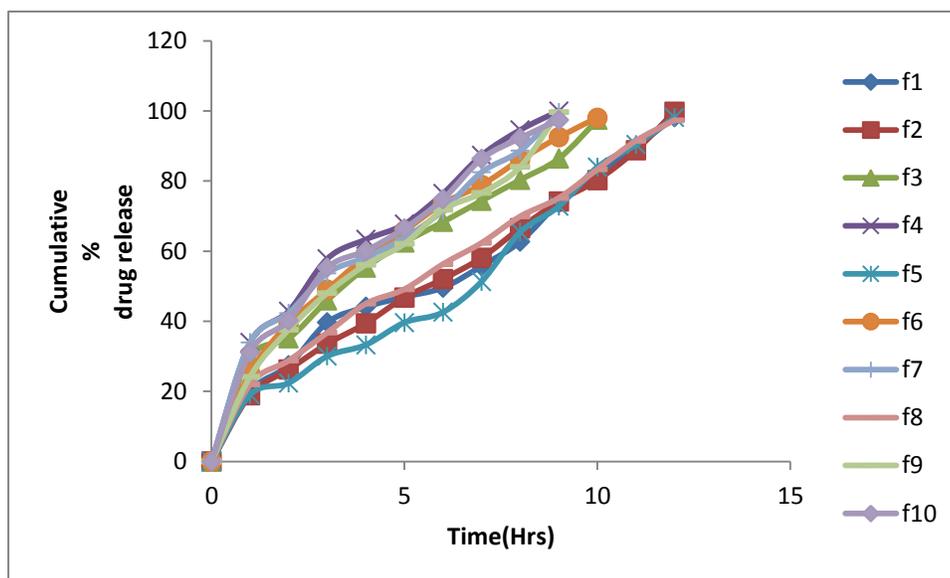
***In vitro* Drug Release Studies:**

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer, maintained at $37 \pm 0.5^{\circ}\text{C}$. The drug release at different time intervals was measured using an UV spectrophotometer (Lab India, Mumbai, India) at 257 nm.

Table: 5: Percentage drug release of formulations (F1 – F9)

Time (hrs)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
1	19.839	18.894	29.659	33.924	19.038	25.366	33.965	21.943	24.162	31.162
2	27.376	26.218	35.091	42.858	22.366	39.300	42.306	28.779	37.596	40.202
3	39.630	33.550	45.943	57.813	30.011	49.049	53.658	36.724	48.047	55.261
4	44.081	39.392	55.303	63.333	33.259	58.409	58.209	44.982	56.105	60.113
5	46.930	46.739	62.461	67.674	39.615	65.768	63.764	49.134	62.060	66.469
6	49.581	52.049	68.318	76.419	42.567	73.629	71.625	56.294	71.825	74.831
7	55.739	58.110	74.376	87.311	51.330	78.885	82.492	62.352	76.580	86.300
8	62.699	66.533	80.334	94.553	65.404	86.045	88.650	69.913	84.041	92.258
9	73.767	74.205	86.392	99.970	72.765	92.504	99.600	75.170	99.666	97.414

10	82.029	80.266	97.460	83.933	98.061	83.332
11	89.791	88.797		90.392		91.494
12	98.253	99.796		98.153		97.352

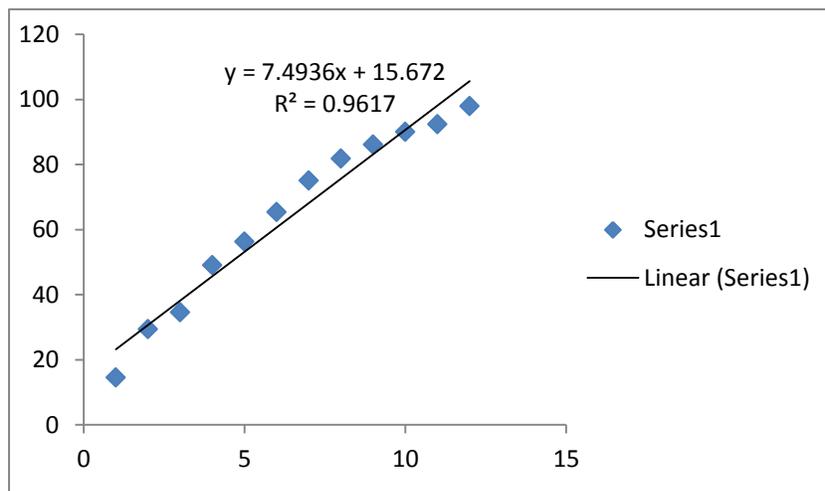


***In-vitro* dissolution profile of F1 to F10**

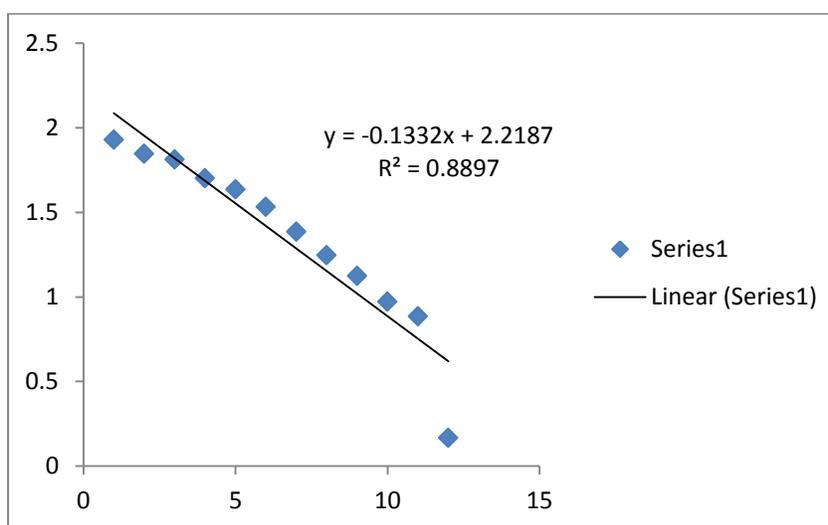
Release Kinetics:

Model fitting for formulation F-2

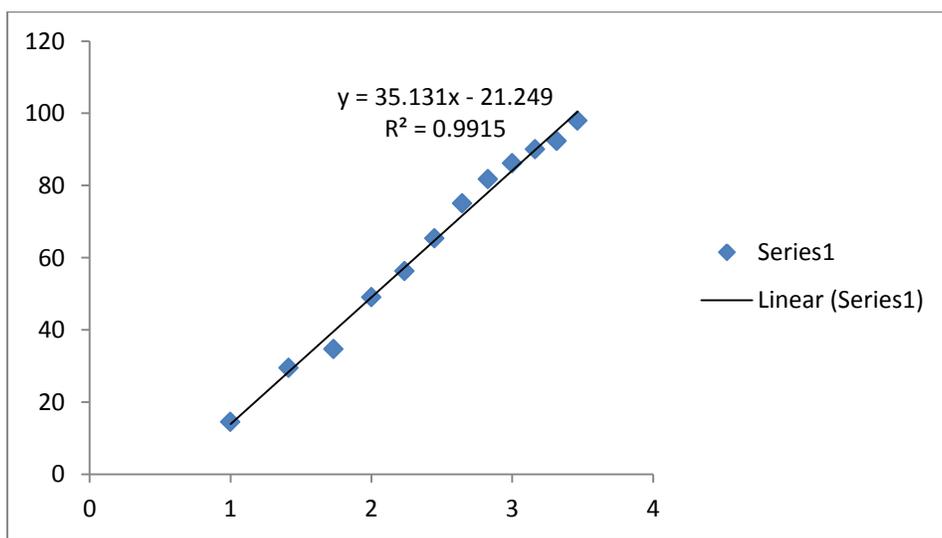
Time(hrs)	% CDR	Log of % drug unreleased	Log time	SQRT	Log % CDR
1	14.511	1.928	0	1	1.161
2	29.439	1.845	0.301	1.414	1.468
3	34.624	1.811	0.477	1.732	1.539
4	49.054	1.701	0.602	2	1.690
5	56.294	1.634	0.698	2.236	1.750
6	65.361	1.531	0.778	2.449	1.815
7	75.072	1.386	0.845	2.645	1.875
8	81.778	1.246	0.903	2.828	1.912
9	86.121	1.123	0.954	3	1.935
10	90.036	0.971	1	3.162	1.954
11	92.339	0.884	1.041	3.316	1.965
12	97.938	0.167	1.079	3.464	1.990



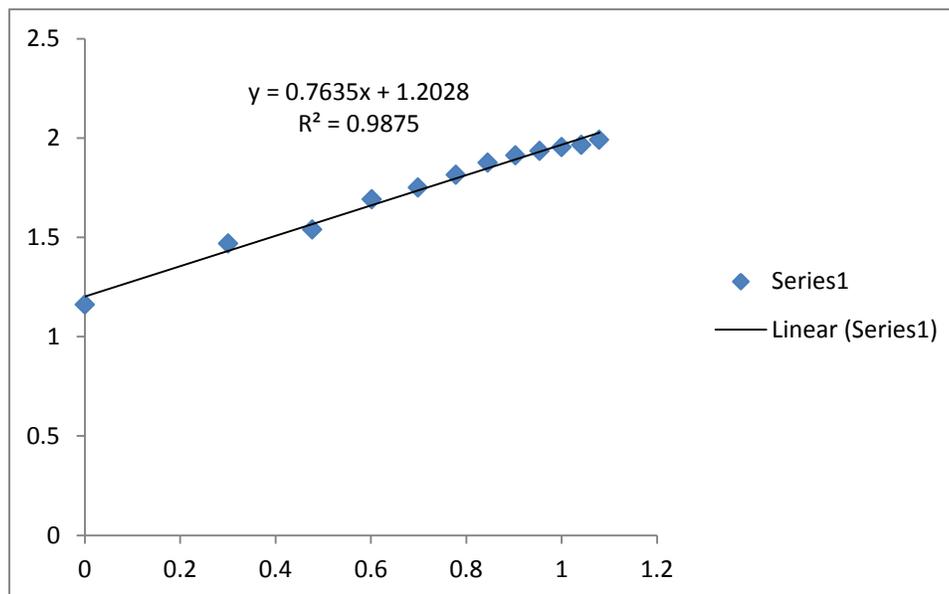
Zero order plots for the formulation F-2 (Time in hours on x-axis and %CDR on y-axis)



First order plot for the formulation F-2 (Time-hours on x-axis and Log of % drug unreleased on y-axis)



Higuchi's plot for the formulation F-2 (SQRT time on x-axis and %CDR on y-axis)



Korsmeyer's plot for the formulation F-2 (Log time on x-axis and Log % CDR on y-axis)

CONCLUSION:

In this study sustained release matrix tablet of Itopride was prepared by wet granulation technique using natural and synthetic polymers like Carbopol 934, tamarind poly saccharide, karaya gum, locust bean gum, ethyl cellulose, HPMC K 100, were used as retardant. It was found that increase in the concentration in polymeric ratio decreases the drug release. Itopride hydrochloride, a novel prokinetic agent is best candidate for Gastro esophageal reflux disease (GERD). Itopride 50mg is given thrice in a day given. By developing the sustained release formulation of Itopride hydrochloride, the frequency drug administration can be reduced to once a day and one can obtain good therapeutic response. The prepared formulation is usually taken on an empty stomach about an hour before meals and efficient to overcome Gastro esophageal reflux disease (GERD) for 24 hr.

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