Research Article

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Formulation and *in vitro* evaluation of ito pride fast dissolving tablets using novel super disintegrants

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ABSTRACT

Recent developments in Fast Dissolving tablets have brought convenience in dosing to pediatric and elderly patients who have trouble in swallowing tablets. The objective of the present study was to prepare the Fast Dissolving tablets of Itopride for the treatment of functional dyspepsia and other gastrointestinal conditions. There is a need to develop a formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling, and patient's acceptability. Hence, the present investigation was undertaken with a view to develop a Fast Dissolving tablet of Itopride which offers a new range of products having desired characteristics and intended benefits. Superdisintegrant such as FeenuGreek Seed Mucilage was optimized. The tablets were prepared by direct compression technique. The tablets were evaluated for hardness, friability, weight variation, disintegration time, and uniformity of content. Optimized formulation was evaluated by *in vitro* dissolution test, drug-excipient compatibility. It was concluded that Fast Dissolving tablets of Itopride were formulated successfully with desired characteristics which disintegrated rapidly and enhanced the patient convenience and compliance. The water absorption ratio of formulation F8 is higher and shorter wetting time than other formulations. In *vitro* drug release was satisfactory the optimized formulation F8 drug release was found to be 97.37 % at 45 min. On the basis of drug release, disintegration time and wetting studies it can be concluded that the formulation F8 is the optimum formulation.

Key words: Itopride, Fast Dissolving Tablets, Ocimum Mucilage, Gellan Gum, FeenuGreek Seed Mucilage.

INTRODUCTION

Fast disintegrating tablets are very popular nowadays as they get dissolved or easily disintegrated in mouth within few seconds of administration without the need of water[1]. Active drug is released immediately from the tablet when is placed on the tongue[2-5]. This formulation is convenient for the patients suffering from Dysphagia. FDTs have several advantages over solid and liquid dosage form like these are very easy to handle as it is a solid dosage form it can be easily transported from one place to another, They are easily administered as it is a unit dosage form and do not need water to swallow they are taken anywhere at any time and also during travelling for motion sickness. In case of FDTs there is no risk of suffocation as it does not need water to swallow and there is no chance of sticking of tablet in the mouth, FDTs have more bioavailability than conventional tablets because when it is placed in the mouth it gets easily

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dissolved in the saliva, absorbed in the oral cavity and release the active drug within few seconds increasing the bioavailability of the tablet, FDTs have quick onset of action as its absorption is very fast within few seconds, FDTs are better in taste and hence the palatability of the tablet is improved, it also improve the patient compliance.

Ideal properties of FDTs

- ✓ It should be quickly disintegrated with in seconds when placed in mouth.
- ✓ It should not require water to dissolve.
- ✓ Being a unit dosage form it should provide accurate dosing.
- ✓ Quick dissolution and absorption in the oral cavity.
- ✓ Easy to transport.
- ✓ Tablets are manufactured with conventional equipment with in low cost.
- ✓ Less sensitive to environmental condition like humidity and temperature.
- ✓ It should less fragile and should maintain its hardness.

Role of super- disintegrants in FDT

The basic approach in development of FDTs is use of disinte grant... Disintegrant play an important role in the disintegrati on and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure qu ick disintegration and high dissolution rates. Super disintegr ant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wet ability and dispersibility of the system, thus enhancing the disintegration and dissolution. Careshould be taken to taken while selecting concentration o f the super disintegrant . super disintegrates are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the con centration of the super disintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Common disintegrants used in this formulation are croscarmellose sodium (Vivasol, Ac□Di□Sol), crospovidone (Polyplasdone), carmellose (NS□300), carmellose calcium (ECG□505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have superdisintegrant property and are widely used in pharmaceutical industry .Swelling index of the super disintegrants is commonly studied in simulated saliva Volume occupied by the material at the end of 4 h should be noted and swelling index is calculated by the formula: (final volume□initial volume/initial volume) X 1008.

MATERIALS

Ito pride Procured From Abbott India Limited, Provided by SURA LABS, Dilsukhnagar, Hyderabad, Ocimum Mucilage, FeenuGreek Seed Mucilage procured from Green Pharmacy, Pune, Gellan Gum, Aspartame procured from Merck Specialities Pvt Ltd, Mumbai, India, Mannitol, Magnesium Stearate procured from Sigma-Aldrich, Mumbai, India, Talc procured from Ajantha Pharma, Aurangabad., India.

METHODOLOGY

Formulation development

- Drug and different concentrations of super disintegrants (Ocimum Mucilage, Gellan Gum, and FeenuGreek Seed Mucilage) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.
- The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 min.

The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations

Table 1:Formulation table showing various compositions

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Itopride	50	50	50	50	50	50	50	50	50
Ocimum Mucilage	7.5	15	22.5	-	-	-	-	-	-
Gellan Gum	-	-	-	7.5	15	22.5	-	-	-
FeenuGreek Seed Mucilage	-	-	-	-	-	-	7.5	15	22.5
Mannitol	40	40	40	40	40	40	40	40	40
Aspartame	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3	3
Total Weight	300	300	300	300	300	300	300	300	300

The tablets were prepared by using tablet compression machine .

Evaluation of tablets

Pre compression parameters:

Measurement of Micromeritic properties of powders

1.Angle of repose : tan □= h/r ……(1)

Where , h and r are the height and radius of the powder cone.

2.Bulk density: Bulk density = M/V_0 ……. (2)

V_0 = apparent unstirred volume

M= Powder mass

3.Tapped Density: Tapped density = M/V_f …… (3)

M = weight of sample powder taken

V_f = Tapped volume

4. **Compressibility index:** Carr's Index (%) = [(TD-BD)/TD] x100 …… (4)

5.Hausner's ratio: H = Pt / ρB ……..(5)

where ρT= tapped density, ρB = bulk density

Post compression parameters:

Thickness: The thickness of the tablets was determined by using Digital micrometer. 10 individual tablets from each batch were used and the results averaged.

Weight variation : Twenty tablets were randomly selected from each batch and individually weighed . The average weight and standard deviation 3 batches were calculated. It passes the test for weight variation test if not more than 2 of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the % shown. It was calculated on an electronic weighing balance

Friability: The friability values of the tablets were determined using a Roche-friabilator . Accurately weighed six tablets were placed in The Roche friabilator and rotated at 25 RPM for 4 min. Percentage friability was calculated using the following equation.

Friability = ([w_0-w]/w_0) x 100

Where w_0 = weight of tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions

Drug content

The content of drug carried out by 5 randomly selected tablets of each formulation . The 5 tablets were grinded to get powder , this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper . The drug content was analysed spectrophotometrically at 256nm using UV spectrophotometer . Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets . Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

***In vitro* dispersion time:**

Method: *In vitro* dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37±0.5°c and the time required for complete dispersion was determined.

To check for reproducibility, the measurements were carried out in triplicates (n=3). The dispersion time was recorded using a stopwatch.

Dissolution test of Itopride

Drug release from Itopride tablets was determined by using dissolution test USP 24 type II (paddle) . The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 500 ml . The whole study is being carried out at room temperature of 37˚ C and at a speed of 50 RPM.

5 ml aliquots of dissolution media were withdrawn each time intervals (5, 10,15 , 20 , 30 , min) and appropriate dilution by UV spectrophotometer . The concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies:

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1;1 ratio were to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed

properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

RESULTS AND DISCUSSION

Calibration curve of Itopride

Table 2 Standard graph values of Itopride at 256 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.154
4	0.321
6	0.499
8	0.664
10	0.852

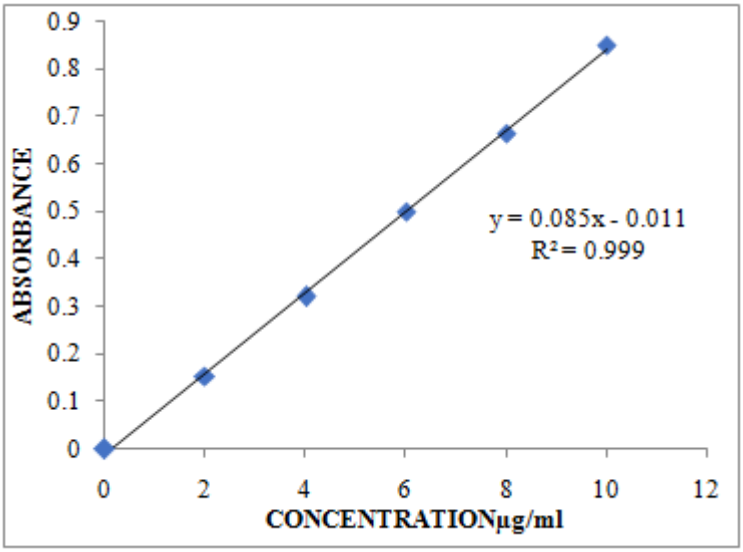

Fig 1: Standard curve of Itopride

Evaluation :

Characterization of precompression blend :

The precompression blend of Itopride were characterized with respect to angle of repose , bulk density , tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28˚,Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all batches indicating good flow properties.

Table 3: Physical properties of precompression blend

Formulation code	Angle of repose (□)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	37.6	0.3217	0.3911	17.74	1.2157
F2	36.7	0.3439	0.4244	18.96	1.2340

F3	35.5	0.3911	0.4639	15.6	1.1860
F4	36.6	0.3117	0.3836	18.7	1.2307
F5	32.5	0.5937	0.6785	12.5	1.1428
F6	28.5	0.5588	0.6064	7.84	1.08
F7	37.8	0.2977	0.3562	16.41	1.19
F8	36.5	0.4830	0.5937	18.64	1.22
F9	27.7	0.5699	0.6125	6.95	1.07

All the values represent n=3

Evaluation of tablets

Physical evaluation of Itoprideimmediate release tablets

The results of the weight variation , hardness , thickness , friability , and drug content of tablets are given in table . All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit . The hardness of the tablets ranged from 1.54 - 2.04 kg/cm^2 and the friability values were < than 0.561 % indicating that the tablets were compact and hard . The thickness of the tablets ranged from 1.86 - 2.24 cm . All the formulations satisfied the content of the drug as they contained 98-100% of Itoprideand good uniformity in drug content was observed . Thus all physical attributes of the prepared tablets were found to be practically within control limits .

Table 4: Physical evaluation of Itopride

Formulation code	Average Weight (mg)	Thickness(cm)	Hardness(Kg/cm^2)	Friability (%)	Content uniformity(%)
F1	299.27	3.12	1.54	0.65	99.18
F2	298.34	3.05	1.85.	0.72	99.57
F3	296.45	2.86	1.73	0.68	100.78
F4	297.79	2.95	2.04	0.57	99.46
F5	300.65	3.13	2.02	0.60	98.84
F6	299.72	3.24	1.93	0.58	99.75
F7	299.38	2.98	1.93	0.63	98.32
F8	298.32	2.99	1.99	0.66	99.22
F9	300.86	3.14	1.98	0.59	99.68

Table 5: Evaluation of post compression parameters of ItoprideOral Disintegrating Tablets

Formulation	Disintegration time*(seconds)	Wetting time* (seconds)	*In vitro* dispersion time*(sec)	%Water absorption ratio*
F1	22	35	32	23.44
F2	17	22	29	39.09
F3	14	19	25	53.70
F4	44	55	33	32.89
F5	39	42	37	45.12
F6	30	38	39	58.81
F7	52	36	27	63.08
F8	11	20	23	96.64
F9	34	28	19	74.97

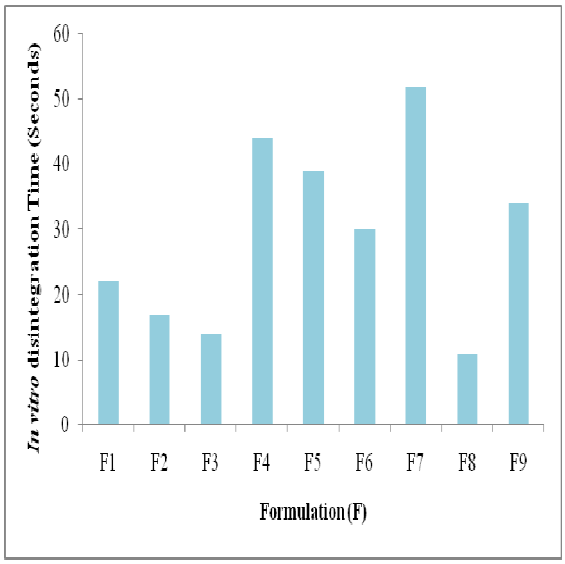

Figure 2:*In vitro* Disintegration time graph

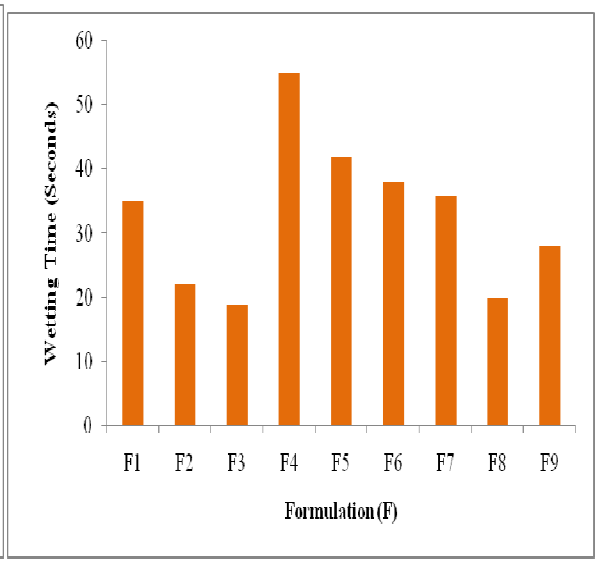

Figure 3:Wettingtime graph

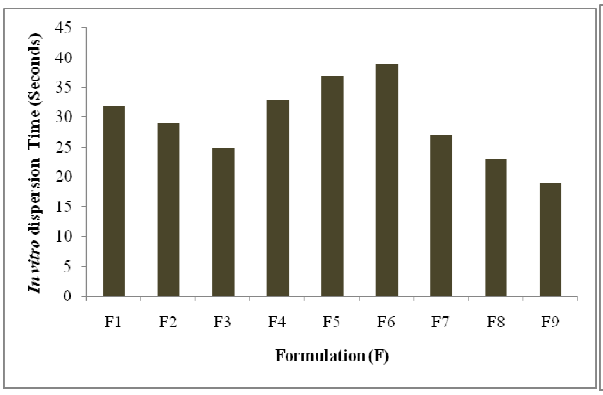

Figure 4: *In vitro* Dispersion Time

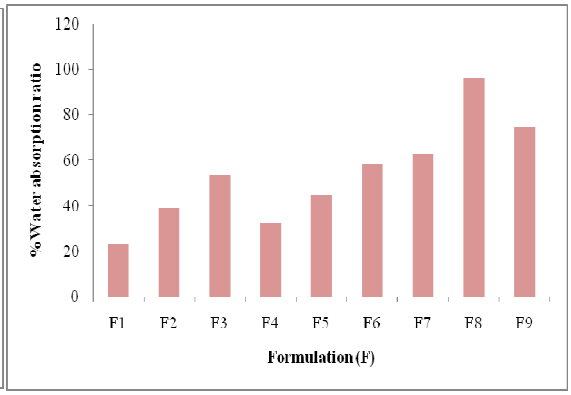

Figure 5: Water absorption ratio graph

Invitro release studies

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C . Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 256nm. after appropriate dilution by using UV spectrophotometer at 256nm.

Table 6: *I*n vitro data for formulation F1-F3.

TIME (MIN)	% DRUG RELEASE		
	F1	F2	F3
0	0	0	0
5	18.1	15.41	22.3
10	25.5	31.21	34.09
15	39.6	42.90	56.5
20	50.53	50.35	72.32
25	59.21	65.89	88.24
30	62.30	70.65	90.37
45	87.35	91.06	94.82

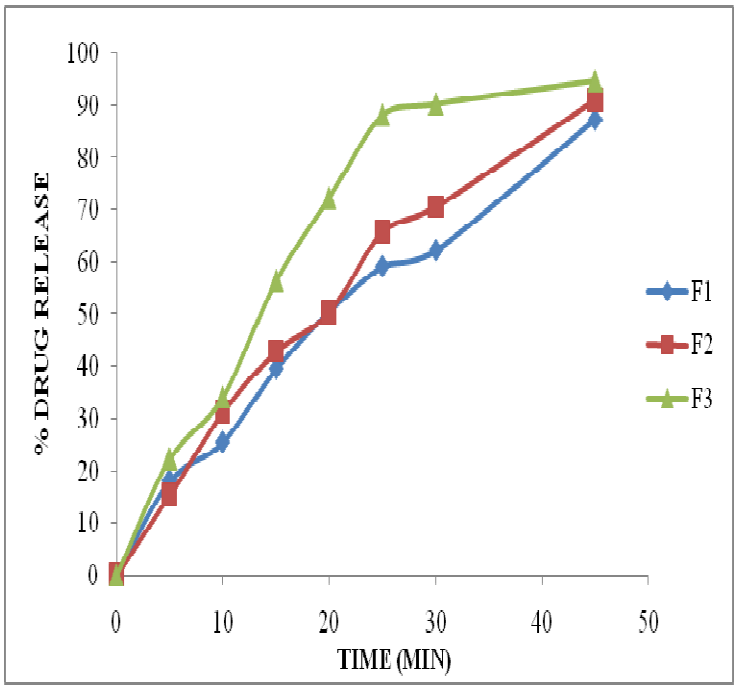

Fig 6: *I*n vitro dissolution data for formulation F1-F3

Table 7: *I*n vitro dissolution data for formulations F4-F6

TIME(MIN)	% DRUG RELEASE		
	F4	F5	F6
0	0	0	0
5	11.04	20.55	21.72
10	21.71	29.80	34.15
15	40.23	42.39	50.22
20	48.42	50.09	59.98
25	56.90	64.04	70
30	61.70	69.49	74.13
45	67.56	80.30	91.58

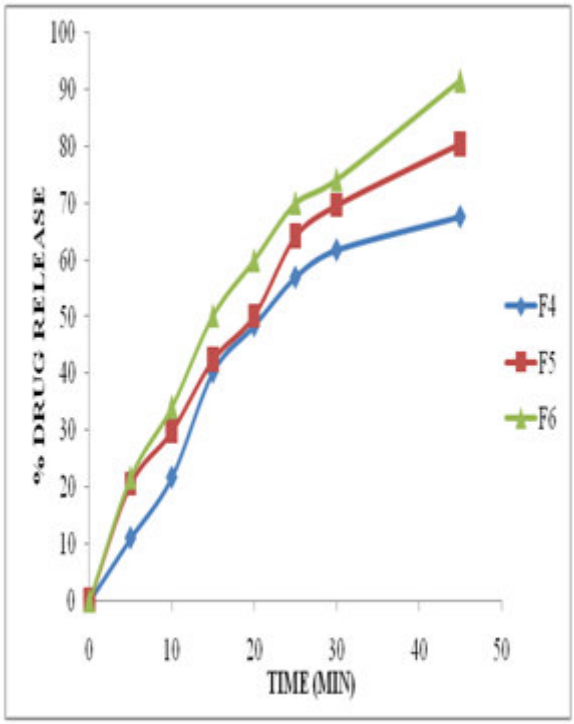

Fig 7: *In vitro* dissolution data for formulations F4-F6

Table 8: *In vitro* dissolution data for formulations F7-F9

TIME (MIN)	% DRUG RELEASE		
	F7	F8	F9
0	0	0	0
5	18.62	16.41	25.43
10	26.84	33.78	31.60
15	42.13	75.61	56.53
20	48.94	82.21	61.01
25	57.54	85.80	78.87
30	69.47	91.02	85.36
45	81.44	97.37	94.73

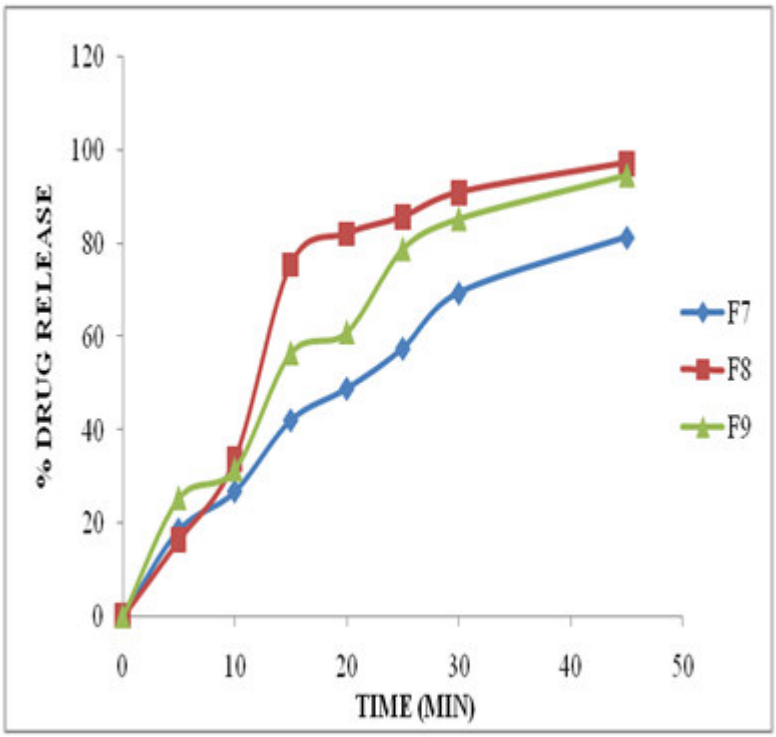

Fig 8:*In vitro* dissolution data for formulations F7-F9

Among all the formulations F8 formulation containing drug and FeenuGreek Seed Mucilage showed good result that is 97.37 % in 45 minutes, at the concentration of 22.5 mg. Hence from all the formulations it is evident that F8 formulation is the better formulation

Drug-Excipient compatibility studies by FTIR studies

Itopride was mixed with various proportions of excipients showed no colour change at the end of two months , providing no drug –excipient interactions.

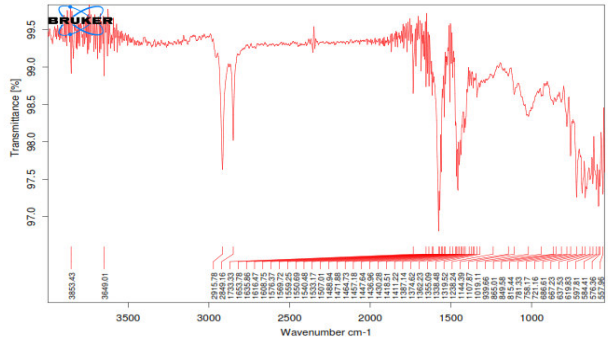

Fig 9:FTIR spectra of pure drug

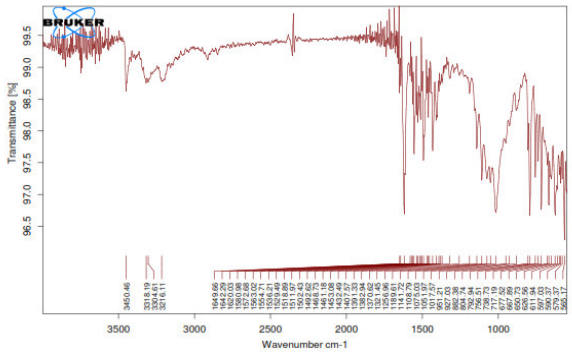

Fig 10: FTIR spectra of optimized formulation

CONCLUSION

The standard curve of Itopride was obtained and good correlation was obtained with R^2 value of 0.999 , the medium selected was pH 6.8 phosphate buffers.

The precompression blend of Itopride was characterized with respect to angle of repose , bulk density , tapped density, Carr's index and Hausner's ratio. Angle of repose and Carr's index values were precompression blend of all the batches indicating good to fair floability and compressibility. Hausner's ratio was all batches indicating good flow properties .

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Among all the formulations F8 formulation containing drug and FeenuGreek Seed Mucilage Powder showed good result that is 97.37 % in 45 minutes. Hence from all the formulations it is evident that F8 formulation is the better formulation.

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