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FORMULATION & EVALUATION OF ITOPRIDE HCL SUSTAINED RELEASE PELLETS *P.*

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ABSTRACT: The present work is aimed to formulate Itopride HCl sustained release pellets using ethyl cellulose N50 such as hydrophobic polymer by employing the solution/suspension layer technique. The drug excipients compatibility study was carried out by Furor Transform Infrared spectroscopy (FTIR) which reveals no interaction between drug and excipients. Total 12 batches were formulated. Six formulations were prepared by using each natural polymer like ethyl cellulose N50. All the formulations were evaluated for micromeritic properties, physical evaluation, which includes particle size analysis, percentage yield, drug content, drug entrapment efficacy, percent moisture loss and swelling index, in vitro dissolution studies, scanning electron microscopy, and drug polymer interaction studies. The formulated pellets were evaluated for various pellet properties, like hardness, bulk density, tapped density, cars index and dissolution rate. Comparative evaluation of the above-mentioned parameters established the superiority of the pellets formulated with Ethyl cellulose those formulated with different grades. The Optimized batch F3 was found to release the drug for 12 h (96.46%) and follows Higuchi Matrix model in dissolution studies, indicating the matrix-forming potential of natural polymer and diffusion controlled release mechanism.

INTRODUCTION: Oral drug delivery is the most convenient route of drug administration regardless of the inherent limitation common with it. Some of the challenges encountered are gastrointestinal erosion, drug-food interaction, poor absorption and poor patient compliance.

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To ensure optimum delivery without compromising the efficacy, potency and stability, drugs are modified by coating, matrix formation or encapsulation by considering the physicochemical properties of drug, physiology of mucosal membrane and delivery devices or matrices [1-6].

The choice of matrices depends on sustainability of drug release, stability of the matrix, safety profile, and release of molecules from the matrix, biocompatibility and biodegradability of the matrix components. Modified-release dosage forms are preparations that regulate the rate and/or time and/or site of release of the active ingredient, in order to achieve specific therapeutic objectives,

which cannot be achieved by conventional immediate release dosage forms when similarly, administered [7]. Itopride hydrochloride is an oral prokinetic agent used in the treatment of gastric motility disorders like dyspepsia of a non-ulcer/dysmotility type [8-9]. There is evidence that Itopride may have prokinetic effects throughout the gastrointestinal tract from the stomach to the end of the colon [10]. Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time [11-13].

The method used for preparing sustained release pellets was solution/suspension layering technique consists three main steps followed in this method Drug coating, Seal coating and Functional coating [14-15] five formulations of Itopride Hydrochloride pellets were prepared by using Carpool 974 P, PVP K 30, Talc, and Eudragit RS 100 5%, 10%, 15% and 20%. The pellets were characterized for colour, shapes, Angle of repose, bulk density, and compressibility index and friability test. The sustained release capsules were evaluated for weight variation test, moisture content test and drug content.

The result showed all the parameters were within the limits in case of *in-vitro* drug release, formulation F3 where tablets containing drug loaded pellets coated with 15% polymer load, the drug release at 2nd hour was found to be 30% and at 12th hour was 96%. Better release retarding effect was found which indicates that this range of polymer is sufficient enough to form barrier coat around the pellets from the results that formulation F3 is a better system for once-daily SR of Itopride hydrochloride [19-20].

MATERIALS AND METHODS: Itopride HCl was obtained as a gift sample from Cygnus chemicals Pvt Ltd, Mumbai. Ethyl cellulose and HPMC, from Dow chemical's, Chennai. Sugar spheres from Signet Chemical Corporation Pvt Ltd, Mumbai. Isopropyl alcohol was purchased from SD Fine Chemicals Ltd., Mumbai. All other reagents used were of analytical grade.

Preparation of Itopride HCl Sustained Release Pellets: Itopride HCl loaded pellets were prepared by layering a drug solution on to sugar spheres using a Coating pan by bottom spray mode. Dispersion of Itopride HCl was sprayed using the bottom spray mode. Layered beads were dried at 40^{o}C for 5– 10 min.

Preparation of Coating Solution: Itopride HCl was dissolved in Methanol. Talc was added to the above solution. A white milky solution was obtained, which was then passed through # 100 sieve.

Seal Coating: Dispersion of HPMC was sprayed using the bottom spray mode. The detailed composition of drug layering and polymer coating and the process parameter of the drug layering processes and coating are given in.

Coating of the drug layered Pellets: The drug layered pellets were coated in a fluidized bed coater using the bottom spray mode with Ethyl cellulose at different coating levels each respectively. The non aqueous solvents contain the Isopropyl alcohol (IPA). The final coating solution was sprayed onto a drug-loaded sugar spheres to achieve the desired % of the coating solution.

Evaluation of drug loaded Itopride HCl sustained release pellets [16, 17, 18]:

Micromeritic Properties: The flow properties of drug loaded microspheres were studied by determining various parameters like the Bulk density, Tapped density, Angle of repose, Carr's consolidation Index, Hausner's Ratio.

Evaluation of Physical Properties of Pellets:

a. **Friability test:** Friability is the loss of weight of pellets in the container/package, due to removal of fine particles from the surface. Roche Friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. 5 g pellets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the pellets were exposed to rolling, resulting from free fall of pellets within the chamber of the friabilator. After 100 rotations (4 minutes), the pellets were taken out from the friabilator and intact pellets

were again weighed collectively after removing fines using sieve # 44 sieve. Permitted percentage friability limit is 0.8%.

The percent friability was determined using the following formula.

$$\text{Percent friability} = \frac{(W1 - W2)}{W1} \times 100$$

Whereas W1 = weight of the pellets before test. W2 = weight of the pellets after test.

b. **Particle size distributions:** This practice was done for the pellets obtained after functional coating to check average size of the pellets. 100 gms of the pellets are shifted in to sieve shaker where a series of sieves was placed (#10, #16, # 25 and #36). The machine was run for 5 minutes, all the meshes were taken out and retained granules were collected by respective mesh and the % retention of pellets by that mesh was calculated. Average particle size was determined. A graph was plotted taking average particle size on X – axis and percent weight undersize on Y – axis.
c. **Drug content estimation:** Weighed the pellets equivalent to 100 mg was crushed in mortar and transferred to 100 ml flask. The powder was dissolved in 3 ml of 0.1N HCl and volume was made up with 0.1N HCl. The sample was mixed for 5 minutes, after which it was filtered through what man filter paper. The filtered solution after appropriate dilution (1 ml to 10 ml) with 0.1N HCl were analyzed by validated UV spectrophotometric method at λ_{max} 258nm.
d. ***In-vitro* dissolution studies:** The dissolution study was carried out in 0.1N HCl using dissolution test apparatus - II. In this study, the pellets were placed inside the 900 ml dissolution medium and speed and paddle was set at 100 rpm. Samples (5 ml) withdrawn at a time interval of 1, 2, 4, 6, 8, 10, 12 hours and same value of fresh medium were replaced. The samples were analysed for drug content against 0.1N HCl as blank at λ_{max} 258.0 nm. The percentage drug release was plotted against time to determine the release profile.
e. **Mechanism of Drug Release:** To know the mechanism of drug is from the formulations the data were treated according to first order (log cumulative percentage of drug remaining vs time) Higuchi's (cumulative percentage drug release vs. square root of time) and Korsemeyer (log cumulative percentage drug release vs log time) equations along with zero order (cumulative amount of drug release vs time). Korsemeyer and Peppas model was fitted into the following equation.

$$M_T/M\mu = K.T^n$$

Where, $M_T/M\mu$ is the fraction of drug release, K=the release rate constant, T=release time, n= diffusion exponent.

If n=0.45 the release is Fickian diffusion, if n>0.45 the release is non Fickian diffusion

Stability Studies: Optimised formulation were packed and stored in ICH certified stability chambers maintained at 25°C and 60% RH.40°C and 75% RH for three months. The pellets are withdrawn periodically and evaluated for the friability, color, diameter, drug content and in-vitro release studies.

Scanning electron microscopy for the optimised formulation: Morphological characterisation of the pellets was done by taking scanning electron micrograph in (JEOL JSM Model 5200).cross-sectional view were obtained by cutting the pellets with a razor blade. The samples were coated to 200 A^0 thickness with gold-platinum using (place model 3 sputter coater) prior to microscopy working distance of 20nm.a tilt of 0^o and accelerating voltage of 15 kv were the operating parameters. Photographs were taken within range of 20-500 magnification.

Drug-Excipient Compatibility:

FTIR Studies: Infrared spectroscopy was conducted using thermo Nicolet nexus 670 spectrophotometer and the spectrum was recorded in the wave length region of 4000 to 500 cm^{-1}. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compress into discs by applying a pressure.

The pellet was placed in the light path and the spectrum was obtained.

RESULT AND DISSCUSSION: Itopride HCl exerts antiemetic action because of its dopamine D2 receptor Antagonistic action at CTZ. It also acts by inhibiting the dopamine D2 receptor at the parasympathetic nerve ends and there by increases the release of acetylcholine and decreases the metabolism of Acetylcholine by inhibiting the enzyme acetyl cholinesterase (ACHE). The objective of the present study was to develop a sustained release formulation of Itopride HCl with a view to increase the bioavailability as well as its complete utilization by sustaining the dose. For this purpose ethyl cellulose was used as the retarding polymer.

Preformulation Studies: Drug-excipient interactions play a vital role with respect to biological performance and formulation stability. FTIR spectroscopy was used to study the physical and chemical inter actions between drug and excipients. The characteristic absorption peaks obtained for the drug alone and in the presence of polymer (1:1) are depicted in **Figure 5-8** From the spectra, it is clear that the main drug peaks and the frequencies of peaks observed were within the standard range. This indicates that the drug was compatible with the formulation components. The following characteristics peaks were observed with Itopride HCl.

C=O (stretching) 1737.37cm^{-1}. (Carboxylic acid).
C=O Stretching 1630.46cm^{-1} (Amide)
C=O (Stretch) 1601.48cm^{-1}. (Aldehyde)
C-H (Bending) 830.99cm^{-1} (Aromatic)

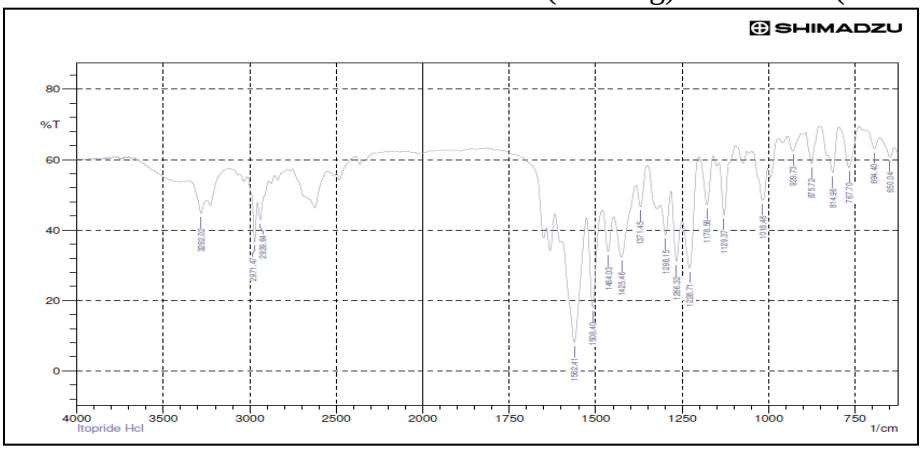

FIGURE 5: INFRARED SPECTRUM OF ITOPRIDE HCl

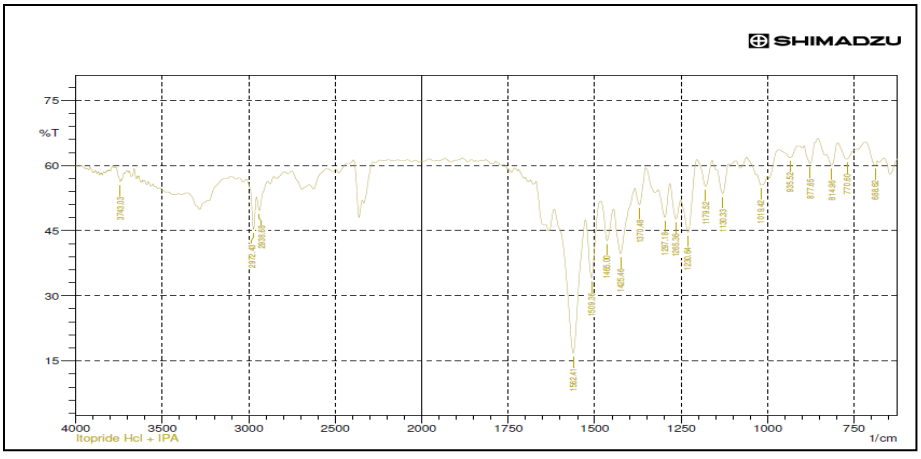

FIGURE 6: INFRARED SPECTRUM OF ITOPRIDE HCl +IPA

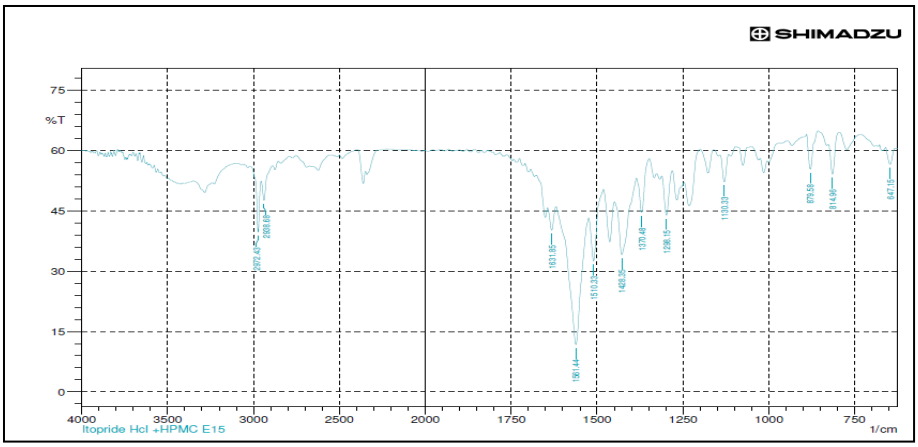

FIGURE 7: INFRARED SPECTRUM OF ITOPRIDE Hcl +HPMC E 15

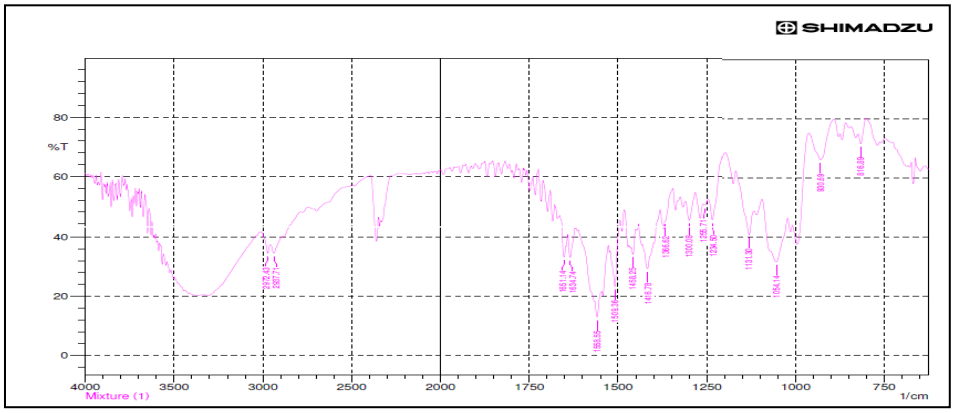

FIGURE 8: INFRARED SPECTRUM OF MIXTURE (1)

Studies on Itopride HCl coated with Ethyl cellulose: The formulated pellets were subjected to different parameters and results were represented in the (**Table 1).** From the results it was observed that the bulk density was found to be between 0.923-0.964 gm/ml and tapped density ranged between 0.893 to 0.899 gm/ml. The other micromeritic properties such as Carr's index, Hausner's ratio revealed no significant differences. Angle of repose was to be between 22.78 to 33.82 indicating the good flow properties. The drug content of the all formulations was within the range of 99.16to99.59%ensurin Uniformity of drug content in the formulations. The percentage friability of prepared pellets within the limits (<1%).

TABLE 1: MICROMERITIC PROPERTIES OF ITOPRIDE HCl SUSTAINE RELEASE PELLETS (MEAN ± S.D., N=3)

Formulation code	Loose Bulk density (gm/c)	Tapped density (gm/cc)	Hausner's ratio	Angle of repose	Carr's index
F1	0.954±0.0013	0.895±0.0012	0.938±0.0024	25.17±0.0012	6.592±0.0023
F2	0.935±0.0018	0.899±0.0024	0.961±0.0013	26.10±0.0011	4.004 ±0026
F3	0.923±0.0021	0.898±0.0026	0.972±0.0014	33.82±0.0016	2.78±0.0035
F4	0.945±0.0016	0.897±0.0025	0.949±0.0024	27.92±0.0017	5.351±0.0034
F5	0.964±0.0017	0.893±0.0023	0.926±0.0020	22.78±0.0011	7.950±0.0020

***In-vitro* Dissolution studies:** The release profiles of Itopride HCl from pellet coated with ethyl cellulose was shown in (**Table 3 & Fig. 1)**. The entire pellet disintegrates during the dissolution test, and no gel like structure remained, indicating complete dissolution at different coating

levels. As the coating level increased, the drug release decreased. The reduction in the release rate with increasing coating level may be due to the increased diffusion path length with increase in the thickness of the coat. The effect of coating level on release of Itopride HCl from pellets coated with ethyl cellulose was shown in (**Fig. 2)**. Uncoated Itopride HCl pellets disintegrate rapidly in dissolution medium and release their drug content within 10 min. For instant at higher coating level such as 12% coating, only about 21% of Itopride HCl was released in 2 hr, whereas those Pellets coated to weight increases of 9%, 6% and 3% released 29%, 30% and 31% of drug respectively. It is observed from the results that the coating levels had a major effect on the ultimate rate of drug release and the duration of the release. The entire pellet remained intact during the dissolution test indicating that the ethyl cellulose coating layer controlled the drug release. Generally, in dosage forms that have a water insoluble polymer as the rate controlling membrane since diffusion through the membrane controls the overall release rate of the drug the layer properties and geometry, such as coating porosity, internal structure (tortuosity) and coating thickness may be critical factors in determining the release rate of drug.

TABLE 2: WEIGHT DISTRIBUTIONS of PELLETS of BATCH F3 (MEAN ± S.D., N=3)

Sieve no.	Nominal mesh aperture size in µm.	aperture size (passed/retained)	Mean size opening, µm.	Weight powder undersize	%weight weight retained on smaller sieve	Weight size Nxd
10	1700	1700/pan	1700	0	0	0
16	1000	1700/1000	1350	1.77	1.77	1.77
25	600	1000/600	800	3.67	3.67	2936.0
36	425	600/425	512.5	94.56	94.56	48462.0
					Σ (n) =100	Σ (nd) =537.8

TABLE 3: DISSOLUTION DATA OF ITOPRIDE HCl PELLETS FORMULATION WITH VARIOUS CONCENTRATIONS OF ETHYLCELLULOSE (MEAN ± S.D., N=3

Time (hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	20.34±0.386	18.89±0.379	16.45±0.375	16.09±0.376	18.7±0.375
2	45.86±0.435	31.6±0.381	30.47±0.387	29.51±0.367	21.74±0.370
4	68.57±0.345	40.25±0.371	60.58±0.371	45.14±0.380	40.32±0.365
6	90.45±0.347	67.52±0.345	67.08±0.382	58.25±0.378	55.16±0.378
8	98.56±0.346	78.23±0.340	70.15±0.387	66.5±0.386	65.84±0.375
10	--	86.96±0.350	83.30±0.311	74.54±0.374	71.03±0.370
12	--	95.42±0.380	96.46±0.321	86.30±0.382	78.19±0.387

TABLE 4: DISSOLUTION KINETICS OF ITOPRIDE HCl PELLETS FORMULATED WITH VARIOUS CONCENTRATIONS OF ETHYL CELLULOSE (MEAN ± S.D., N=3)

Formulation Code	Zero order	First order	Higuchi	Peppas	K value mg/hr	$T_{50\%}$	$T_{90\%}$	Slope (n)
F1	0.940	0.992	0.976	0.832	8.21	8.21	6.04	0.521
F2	0.914	0.986	0.963	0.850	7.95	7.95	10.34	0.513
F3	0.980	0.993	0.988	0.966	8.03	8.03	10.80	0.562
F4	0.953	0.898	0.984	0.979	7.19	7.19	12.07	0.589
F5	0.946	0.954	0.971	0.970	6.51	6.51	12.67	0.576

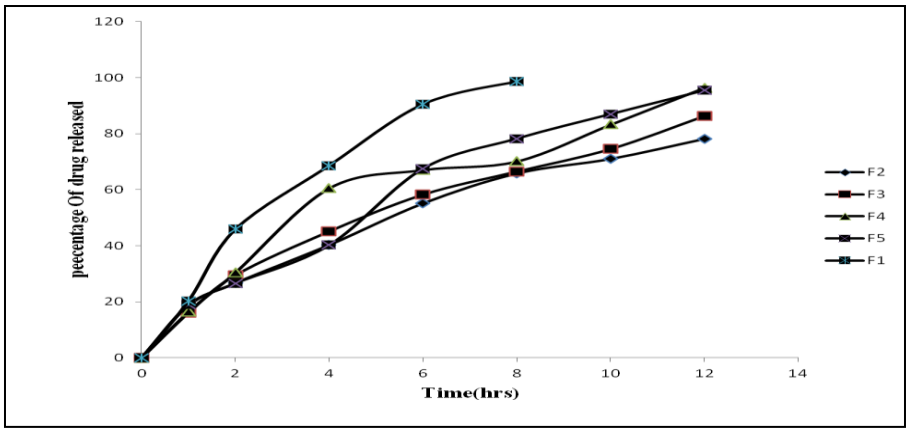

FIGURE 1: DISSOLUTION PROFILE OF ITOPRIDE HCl PELLETS

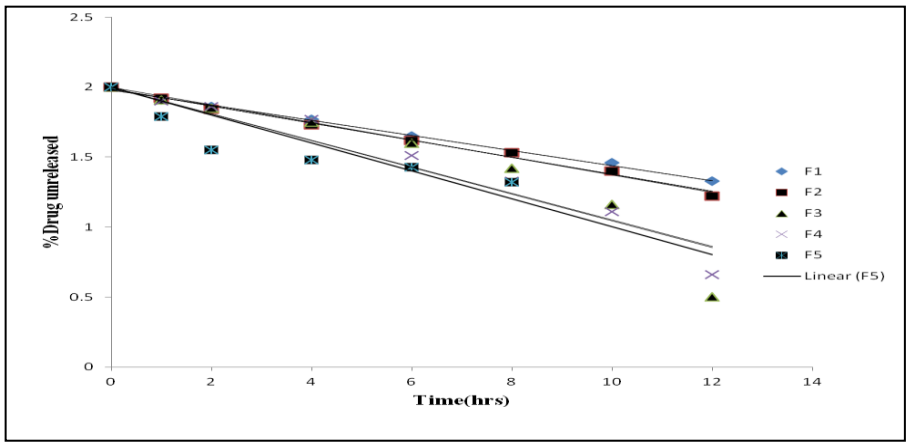

FIGURE 2: FIRST ORDER PLOTS FOR ITOPRIDE HCl PELLETS

Kinetics of *in-vitro* Dissolution: The drug release followed first order kinetics shown in (**Fig 2)**. As the graph was drawn between the log percent of drug unreleased verses time were found to be linear. To ascertain the mechanism of drug release data was subjected to Higuchi shown in (**Fig 3)** & Korsemeyer Peppas equations shown in (**Fig 4)**. From the regression coefficients the plots shows highest linearity with first order followed by Higuchi model. The value of release exponent 'n' for various formulations ranged from **0.513 to 0.589** indicating that the release mechanism was non- fickian diffusion.

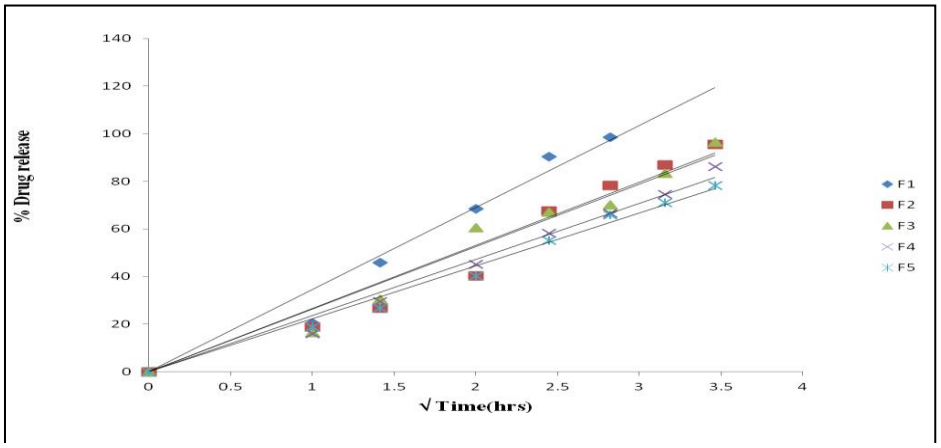

FIGURE 3: HIGUCHI PLOTS OF ITOPRIDE HCl PELLETS

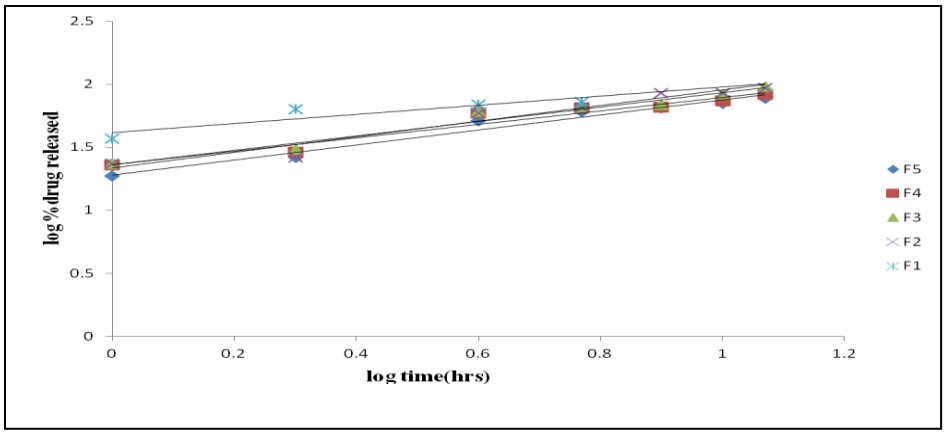

FIGURE 4: KORSEMEYER PEPPAS PLOTS OF ITOPRIDE HCl PELLETS

Morphological Study (SEM) on Optimized Pellets: The morphological studies carried by using the scanning electron microscopy. In this study the pellet was observed under different magnifications (X35, 150, and 350). The scanning electron microscopy (**Fig 9, 10, &11)** shows the pellets being the spherical in shape.

The surface depression was observed. The ethyl cellulose shows more rough surface which is due to the density of the matrix and it justifies sustained action.

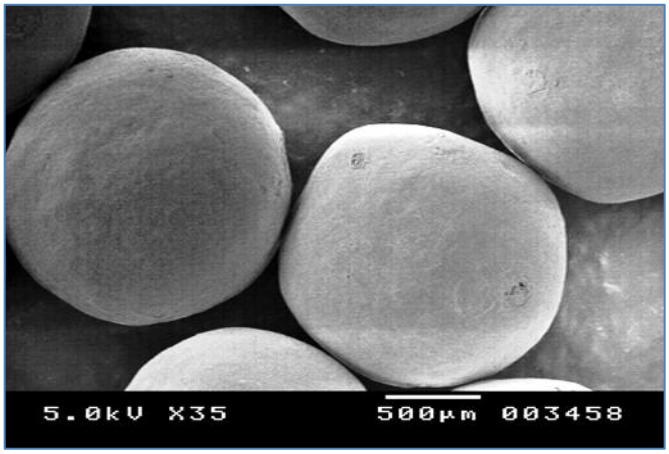

FIGURE 9: SEM PHOTOGRAPH OF OPTIMISED (F3) ITOPRIDE HCl PELLETS (35X)

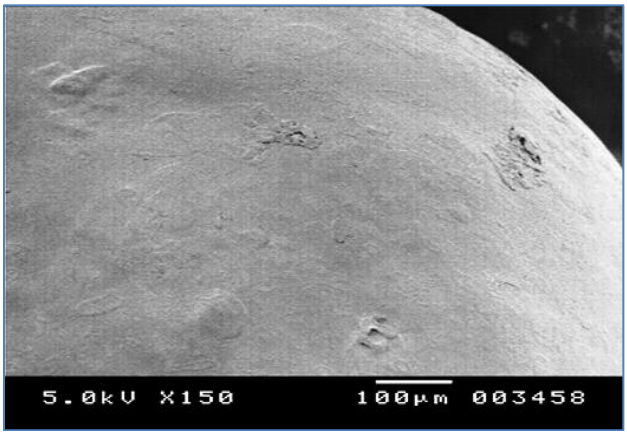

FIGURE 10: SEM PHOTOGRAPH OF OPTIMISED (F3) ITOPRIDE HCl PELLET (150X)

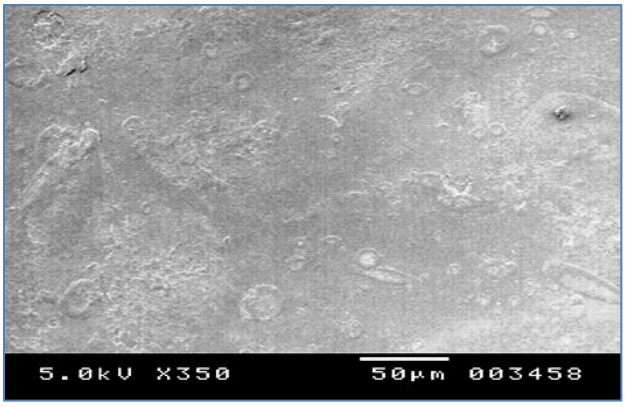

FIGURE 11: SEM PHOTOGRAPH OF OPTIMISED (F3) ITOPRIDE HCl PELLET (350X)

Stability Studies: Optimised formulation were packed and stored in ICH certified stability chambers maintained at I) 25°C and 60%±5% RH II) 40°C and 75%±5% RH for three months.the results are shown in **Table 5-8.** It was found to be there is no changes in the physical and chemical parameters of Itopride HCl Pellets of formulation F3 after three month at 25°C/60%±5% RH, 40°c /75%±5% RH. There is no significant difference in the percentage of drug release of Itopride HCl Pellets of formulation F3 after three month at 25°C/60%±5% RH, 40°C /75%±5% RH.

TABLE 5: PHYSIO CHEMICAL PARAMETERS OF ITOPRIDE HCl PELLETS OF FORMULATION: (Mean± S.D; n=3) condition: room temp: 25°C, Relative Humidity: 60%

PARAMETER	INITIAL	AFTER 1 MONTH	AFTER 2 MONTHS	AFTER 3 MONTHS
Description	Sunset yellow colored spherical shaped pellets	Sunset yellow colored spherical shaped pellets	Sunset yellow colored spherical shaped pellets	Sunset yellow colored spherical shaped pellets
Diameter (µm)	537.87	537.87	537.87	537.87
Friability	0.39	0.39	0.39	0.39
Drug Content Uniformity	99.40	99.39	99.38	99.38

TABLE 6: PHYSIO CHEMICAL PARAMETERS OF ITOPRIDE HCl PELLETS OF FORMULATION: (Mean± S.D; n=3) condition: room temp: 40°C, Relative Humidity: 75%

PARAMETER	INITIAL	AFTER 1 MONTH	AFTER 2 MONTHS	AFTER 3 MONTHS
Description	Sunset yellow colored spherical shaped pellets	Sunset yellow colored spherical shaped pellets	Sunset yellow colored spherical shaped pellets	Sunset yellow colored spherical shaped pellets
Diameter (µm)	537.87	537.87	537.87	537.87
Friability	0.39	0.39	0.39	0.39
Drug Content Uniformity	99.40	99.39	99.38	99.38

TABLE 7: DISSOLUTION PROFILES OF ITOPRIDE HCl PELLETS FROM FORMULATION: (Mean± S.D; n=3) condition: room temp: 25°C, Relative Humidity: 60%

TIME (hrs)	INITIAL	AFTER 1MONTH	AFTER 2 MONTHS	AFTER 3 MONTHS
0	0	0	0	0
1	16.45±0.375	16.44±0.375	16.44±0.375	16.43±0.375
2	30.47±0.387	30.46±0.387	30.46±0.387	30.45±0.387
4	60.58±0.371	60.57±0.371	60.57±0.371	60.56±0.371
6	67.08±0.382	67.06±0.382	67.05±0.382	67.03±0.382
8	70.15±0.387	70.14±0.387	70.13±0.387	70.12±0.387
10	83.30±0.311	83.29±0.311	83.28±0.311	83.24±0.311
12	96.46±0.321	96.45±0.321	96.44±0.321	96.42±0.321

TABLE 8: DISSOLUTION PROFILES OF ITOPRIDE HCl PELLETS FROMFORMULATION: (Mean± S.D; n=3) condition: room temp: 40°C, Relative Humidity: 75%

TIME (hrs)	INITIAL	AFTER 1 MONTH	AFTER 2 MONTHS	AFTER 3 MONTHS
0	0	0	0	0
1	16.45±0.375	16.44±0.375	16.44±0.375	16.43±0.375
2	30.47±0.387	30.46±0.387	30.46±0.387	30.45±0.387
4	60.58±0.371	60.57±0.371	60.57±0.371	60.56±0.371
6	67.08±0.382	67.06±0.382	67.05±0.382	67.03±0.382
8	70.15±0.387	70.14±0.387	70.13±0.387	70.12±0.387
10	83.30±0.311	83.29±0.311	83.28±0.311	83.24±0.311
12	96.46±0.321	96.45±0.321	96.44±0.321	96.42±0.321

CONCLUSION: The present investigation focused on the improvement of absorption and oral bioavailability of Itopride HCl along with sustained action. To meet the above criteria extended release tablets of Itopride HCl were formulated with hydrophobic rate controlling polymers such as Ethyl cellulose as key excipients. The hydrophobic polymers selected were more reliable as they released the drug slowly, extending it over a long period of time.

Alternating concentrations of Ethyl cellulose have a significant influence on the release rate of drug. The drug release from all the formulations followed first order kinetics and Higuchi's mechanism. The *in-vitro* dissolution profiles of **F3** were found to be better formulation. Therefore, it may be concluded that the extended release formulations are suitable delivery system for Itopride HCl and may be used for effective management in GERD.

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