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FORMULATION AND EVALUATION OF ITOPRIDE HYDROCHLORIDE CONTROLLED RELEASE TABLETS

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Abstract:

The aim of the present study was to develop controlled release formulation of Itopride hydrochloride to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC K 15M, HEC 2M, HPC 2M were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. From the dissolution studies it was evident that the formulation (F7) showed better and desired drug release pattern i.e., 98.68 % in 12 hours. It contains the HPC 2M polymer. It followed Zero order release kinetics mechanism.

Keywords: *Itopride hydrochloride, HPMC K 15M, HEC 2M, HPC 2M and Controlled release tablets.*

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INTRODUCTION:

Drug delivery is a technique of delivering medication to a patient in such a manner that specifically increases the drug concentration in some parts of the body as compared to others.The ultimate goal of any delivery system is to extend, confine and target the drug in the diseased tissue with a protected interaction. Every Dosage form is a combination of drug/active pharmaceutical ingredients (APIs) and the non-drug component called excipients/additives. APIs are the actual chemical components used to treat diseases. [1]

Administration of drugs into the body cavities (rectal, vaginal) can be impractical and unfeasible as they can be degraded at the site of administration (e.g., low pH in the stomach) and may cause local irritations or injury when the drug concentration is high at the site of administration. Some APIs are sensitive to the environment and can benefit from reducing the exposure to environmental factors (light, moisture, temperature and pH), or they need to be chemically stabilized due to the inherent chemical instability. APIs mostly have unpleasant organoleptic qualities (taste, smell and compliance), which reduce patient compliance. [2,3] The glidants prevent lump formation by reducing the friction between particles and improve the flowability of the tablet granules or powder. Anti-adherents stop the powder from sticking to the machines during manufacturing. Lubricants ensure the smooth surface of dosage form, by reducing the friction between the walls of the tablets and the die cavity during ejection. Flavouring agents help to mask the unpleasant odour and colourants are added to aid in recognition and aesthetics. [4] The most common dosage forms comprise tablets, capsules, pills, ointments, syrups and injections. Various routes of drug administration are tabulated in Table 1 and Figure 3. The preferred route of drug administration depends on three main factors: The part of the body being treated, the way the drug works within the body and the solubility and permeability of the drug. For example, certain drugs are prone to destruction by stomach acids after oral administration resulting in poor bioavailability. Hence, they need to be given by the parenteral route instead. Intravenous administration of drugs gives 100% bioavailability. [5]

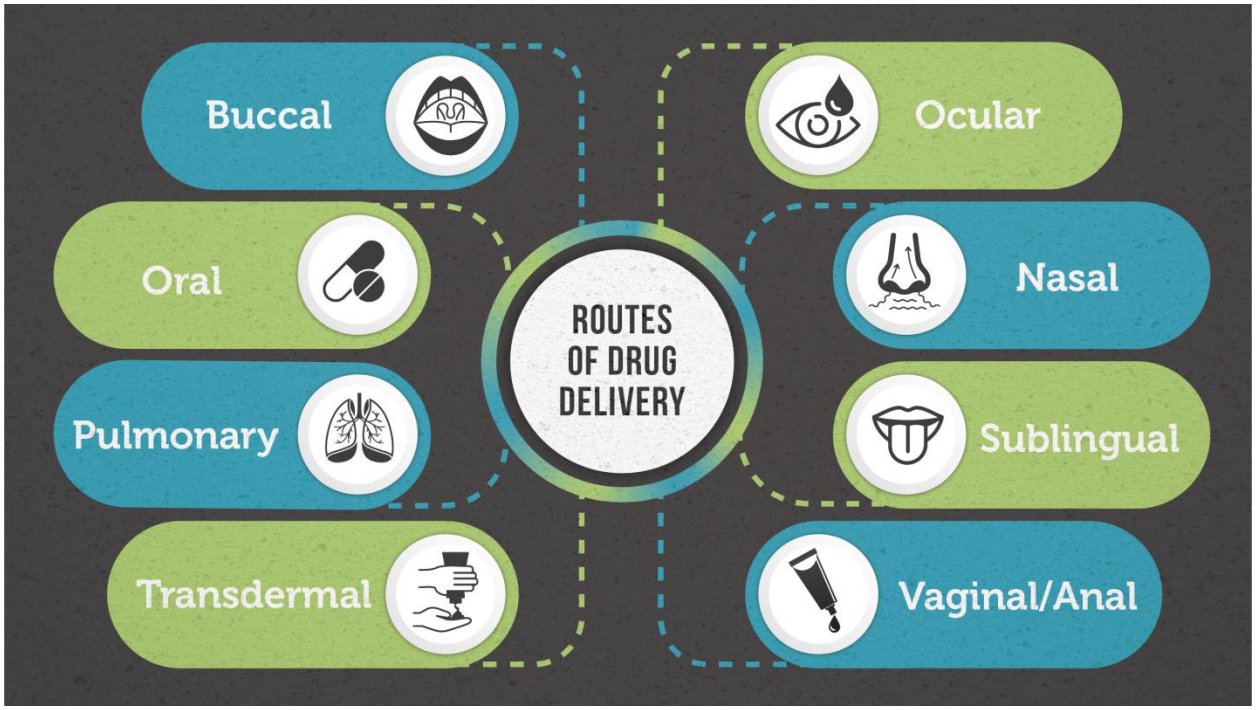


FIG 1.1: Routes of Drug delivery system

Drawback of conventional dosage form:

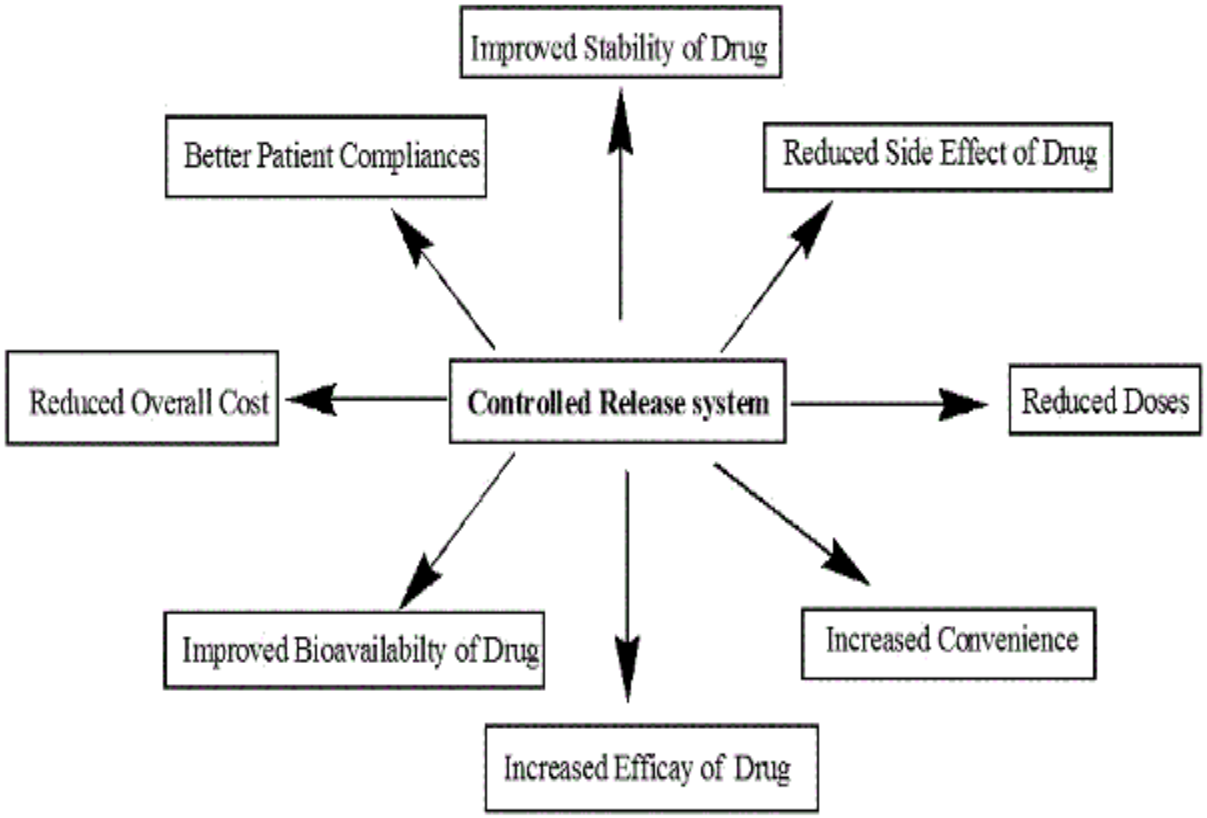
1) Poor patient compliance: Chances of missing ofthe dose of a drug.
2) The unavoidable fluctuations of drugconcentration may lead to under medication orover medication.
3) A typical peak-valley plasma concentration-timeprofile is obtained which makes attainment of Drawback of conventional dosage form.
4) The fluctuations in drug levels which causesprecipitation of adverse effects mainly the

drugwhich having the small Therapeutic Indexwhenever over medication occur.[6, 7, 8]

Controlled drug delivery is one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time.
The rationale of controlled release dosage form can be summarized as below:

- To provide a location-specific action within the GIT.
- To avoid an undesirable local action within the GIT.
- To provide a programmed drug delivery pattern.
- To increase the rate and extent of absorption/bioavailability.
- To extend the duration of action of the drug.

ADVANTAGES:



1] Therapeutic advantage:
Reduction in drug plasma level fluctuation,maintenance of a steady plasma level of the drug over aprolonged time period, ideally simulating anintravenous infusion of a drug.

2] Reduction in adverse side effects and improvement intolerability:
Drug plasma levels are maintained within a narrowwindow with no sharp peaks and with AUC of plasmaconcentration Vs time curve comparable with total AUCfrom multiple dosing with immediate release dosageform.

3] Patient comfort and compliance:
Oral drug delivery is the most common and convenientfor patient and a reduction in dosing frequencyenhances compliance.

4] Reduction in Health care cost:
The total cost of therapy of the controlled releaseproduct could be comparable or lower than the
immediate release product with reduction in sideeffects. The overall expense in disease managementalso would be reduced. This greatly reduces thepossibility of side effects, as the scale of side effectsincreases as we approach the maximum safeconcentration.

Avoid night time dosing: It also good for patients toavoid the at night time.

5] Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[9,10]

Disadvantages of sustained release dosage form:

1] Dose dumping:

Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] Less flexibility in accurate dose adjustment:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

MATERIALS:

Itopride hydrochloride-Provided by SURA LABS, Dilsukhnagar, Hyderabad.,HPMC K 15-M-Merck Specialities Pvt Ltd,HEC 2M-Merck Specialities Pvt Ltd,HPC 2M-Merck Specialities Pvt Ltd,MCC-Merck Specialities Pvt Ltd,Aerosil -Merck Specialities Pvt Ltd,Magnesium Stearate-Merck Specialities Pvt Ltd

METHODOLOGY:

Organoleptic properties:

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Itopride hydrochloride Melting point

The melting point of Itopride hydrochloride was determined by capillary tube method according to the USP. A sufficient quantity of Itopride hydrochloride powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Itopride hydrochloride in the tube passed into liquid phase**.**

Determination of Itopride hydrochloride Solubility

Determination of solubility of drug by visual observation. An excess quantity of Itopride hydrochloride was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

Analytical method development:

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$

Tan θ = Angle of repose
h = Height of the cone,
r = Radius of the cone base

Formulation composition for tablets:

Formulation code	API	Polymers			Diluent	Glidant	Lubricant	Total weight
	Itopride hydrochloride	HPMC K 15M	HEC 2M	HPC 2M	MCC	Aerosil	Magnesium Stearate	
F1	50	25	-	-	Q.S	10	9	200
F2	50	50	-	-	Q.S	10	9	200
F3	50	100	-	-	Q.S	10	9	200
F4	50	-	25	-	Q.S	10	9	200
F5	50	-	50	-	Q.S	10	9	200
F6	50	-	100	-	Q.S	10	9	200
F7	50	-	-	25	Q.S	10	9	200
F8	50	-	-	50	Q.S	10	9	200
F9	50	-	-	100	Q.S	10	9	200
All the quantities were in mg								

RESULTS AND DISCUSSION:

Analytical Method

Graphs of Itopride hydrochloride were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 279 nm and 280nm respectively.

Table 8.3: Observations for graph of Itopride hydrochloride in 0.1N HCL

Conc [µg/mL]	Abs
0	0
2	0.134
4	0.242
6	0.361
8	0.457
10	0.578

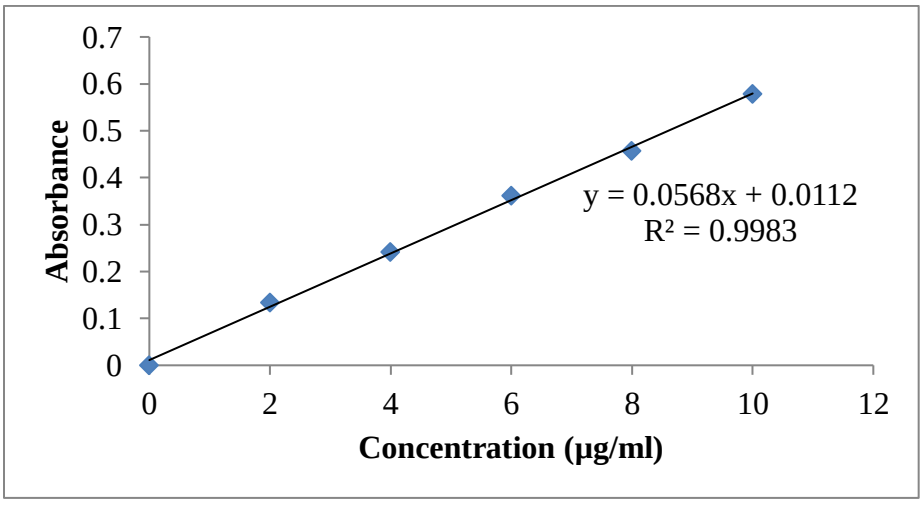


Fig 8.1: Standard curve of Itopride hydrochloride

Table : Standard graph values of Itopride hydrochloride in pH 6.8 phosphate buffer

S. No.	Concentration(µg/ml)	Absorbance* (at 290 nm)
1	0	0
2	2	0.128
3	4	0.232
4	6	0.347
5	8	0.459
6	10	0.581

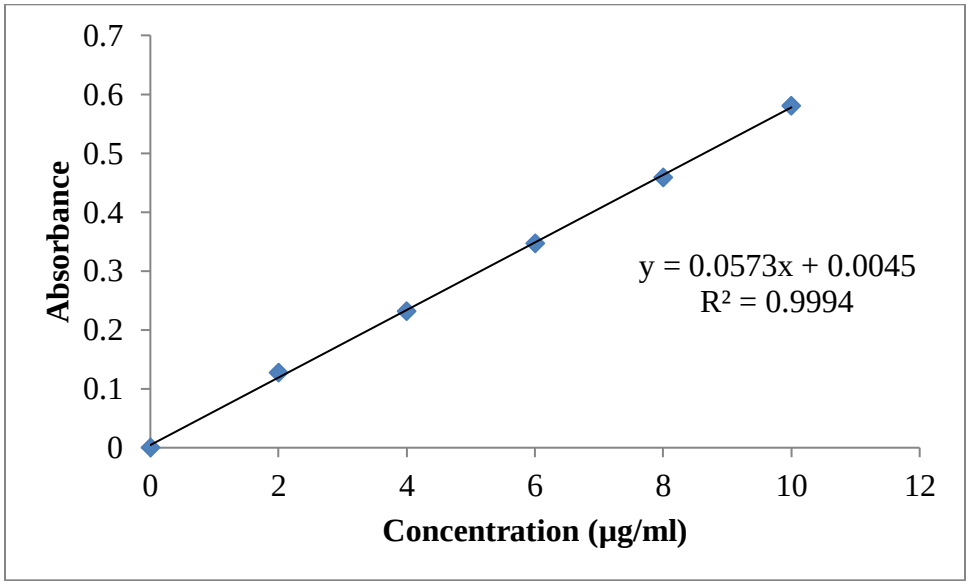


Fig 8.2: Standard curve of Itopride hydrochloride

Preformulation parameters of powder blend

Table : Pre-formulation parameters of Core blend

Table 8.3: Pre-compression parameters					
Formulations	**Bulk Density(gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Θ)**
F1	28.76	0.5770	0.6817	17.71	1.111
F2	28.48	0.5648	0.6741	14.46	1.146
F3	28.16	0.5715	0.6979	17.14	1.276
F4	28.80	0.5782	0.6722	15.82	1.129
F5	28.51	0.5650	0.6757	17.59	1.257
F6	28.20	0.5622	0.6688	17.21	1.186
F7	28.95	0.5592	0.6714	16.96	1.237
F8	28.60	0.5665	0.6833	16.65	1.263
F9	28.32	0.5531	0.6765	17.32	1.294

Quality Control Parameters for tablets:

Tablet quality control tests such as weight variation, hardness, friability, thickness and drug release studies in different media were performed on the compression tablet.

Table 8.6: *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	198.15	5.1	0.47	4.12	98.16
F2	200.25	5.4	0.34	4.49	99.45
F3	199.39	4.7	0.51	4.77	96.77
F4	197.52	5.2	0.48	4.25	99.21
F5	200.10	4.5	0.55	4.56	97.55
F6	196.57	5.8	0.32	4.81	98.80
F7	198.61	4.3	0.59	4.38	99.38
F8	199.72	5.6	0.46	4.66	97.62
F9	197.95	5.9	0.33	4.97	99.94

***In Vitro* Drug Release Studies**

Table 8.7: Dissolution Data of Itopride hydrochloride Tablets

TIME (H)	CUMULATIVE % OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
In dissolution media 0.1 N HCL									
1	21.13	12.94	11.79	21.91	19.79	11.81	21.65	11.91	13.72
2	24.72	25.37	24.15	24.66	21.15	24.80	24.63	24.50	26.77
In dissolution media 6.8 Phosphate Buffer									
3	42.45	28.52	27.86	37.55	24.86	27.52	27.35	27.46	31.05
4	45.79	33.42	32.70	39.68	37.70	32.58	32.21	29.89	34.85
5	53.68	46.34	35.50	42.82	39.50v	35.85	45.76	42.03	42.87
6	66.56	59.48	43.40	55.75	42.40	43.12	58.76	55.70	45.02
7	79.17	60.19	56.33	68.19	55.33	46.05	63.32	58.76	53.57
8	82.82	61.96	59.17	73.62	58.17	51.73	76.23	63.98	56.76
9	85.62	64.82	62.21	76.26	63.60	54.92	89.93	66.12	62.07
10	88.37	77.44	65.98	81.89	66.75	62.60	90.30	71.95	65.59
11	93.15	82.65	71.59	84.58	79.16	65.84	91.82	74.34	68.93
12	91.36	95.92	84.25	87.25	82.64	76.18	98.68	87.28	78.31

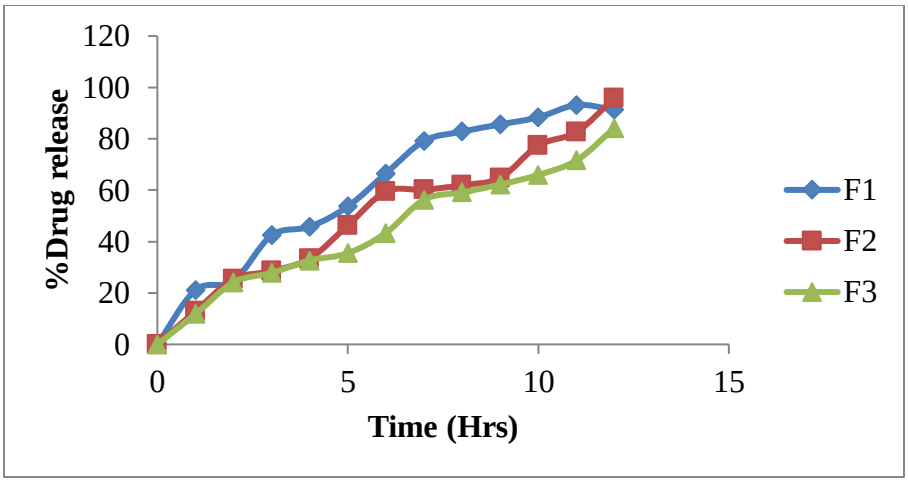


Fig 8.3: Dissolution profile of Itopride hydrochloride (F1, F2, F3 formulations)

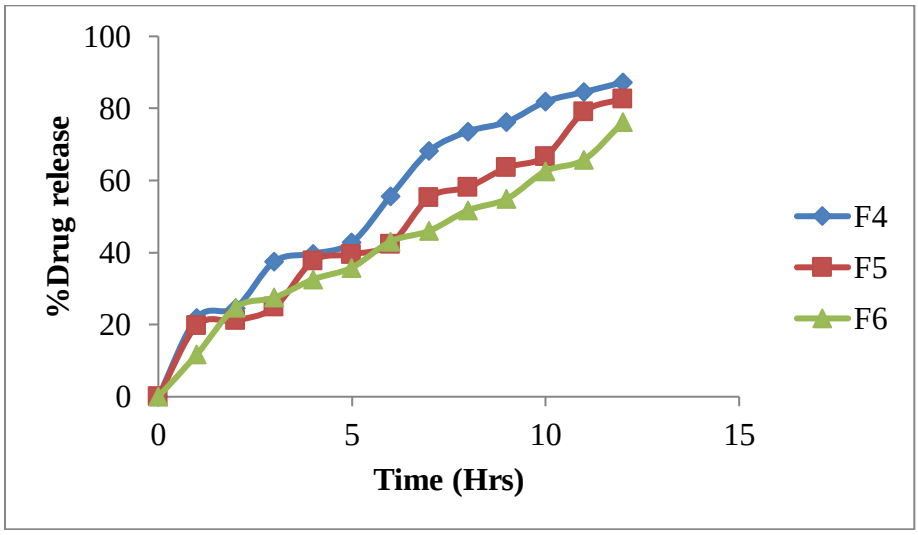


Fig 8.4: Dissolution profile of Itopride hydrochloride (F4, F5, F6 formulations)

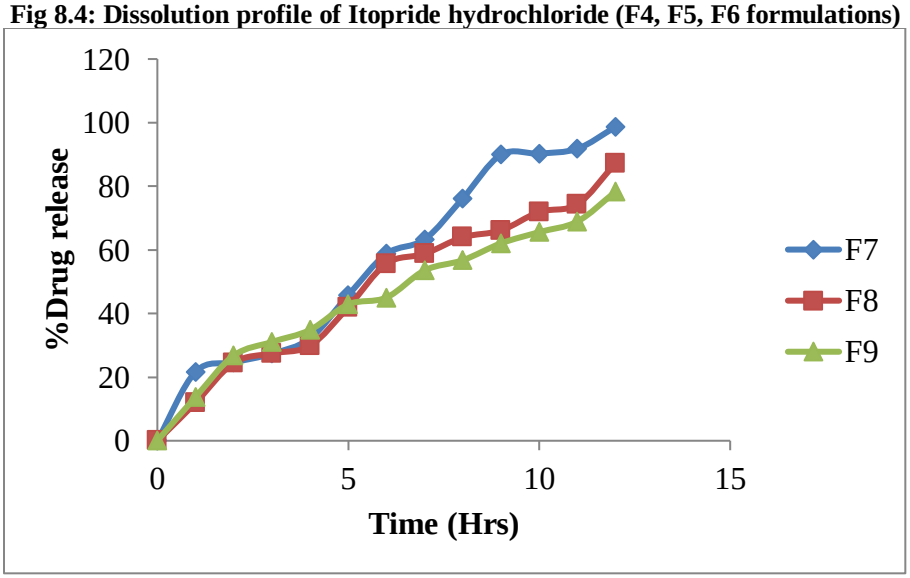


Fig 8.5: Dissolution profile of Itopride hydrochloride (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with HPMC K 15M as polymer were retarded the drug release Less than 12 hours.

Whereas the formulations prepared with higher concentration of HEC 2M retarded the drug release up to 12 hours in the concentration 25 mg. In higher concentrations the polymer was unable to retard the drug release up to 12 hours.
The formulations prepared with HPC 2M showed good retardation capacity of drug release (98.68%) up to 12 hours in concentration 25 mg whereas high concentrations (50 mg, 100 mg) not retard the drug release up to 12 hours.
Only HPC 2M low concentrations (25 mg) retards the drug release up to 12 hours and the drug release 98.68 % respectively. In this HPC 2M releases the more drug release when compared to HEC 2M and HPMC K 15M. So F7 Formulation considered as optimised formulation.

Hence from the above dissolution data it was concluded that F7 formulation was considered as optimised formulation because good drug release (98.68 %) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
21.65	1	1.000	1.335	0.000	1.894	21.650	0.0462	-0.665	78.35	4.642	4.279	0.363
24.63	2	1.414	1.391	0.301	1.877	12.315	0.0406	-0.609	75.37	4.642	4.224	0.418
27.35	3	1.732	1.437	0.477	1.861	9.117	0.0366	-0.563	72.65	4.642	4.173	0.469
32.21	4	2.000	1.508	0.602	1.831	8.053	0.0310	-0.492	67.79	4.642	4.077	0.564
45.76	5	2.236	1.660	0.699	1.734	9.152	0.0219	-0.340	54.24	4.642	3.785	0.856
58.76	6	2.449	1.769	0.778	1.615	9.793	0.0170	-0.231	41.24	4.642	3.455	1.187
63.32	7	2.646	1.802	0.845	1.564	9.046	0.0158	-0.198	36.68	4.642	3.323	1.319
76.23	8	2.828	1.882	0.903	1.376	9.529	0.0131	-0.118	23.77	4.642	2.875	1.766
89.93	9	3.000	1.954	0.954	1.003	9.992	0.0111	-0.046	10.07	4.642	2.159	2.482
90.3	10	3.162	1.956	1.000	0.987	9.030	0.0111	-0.044	9.7	4.642	2.133	2.509
91.82	11	3.317	1.963	1.041	0.913	8.347	0.0109	-0.037	8.18	4.642	2.015	2.627
98.68	12	3.464	1.994	1.079	0.121	8.223	0.0101	-0.006	1.32	4.642	1.097	3.545

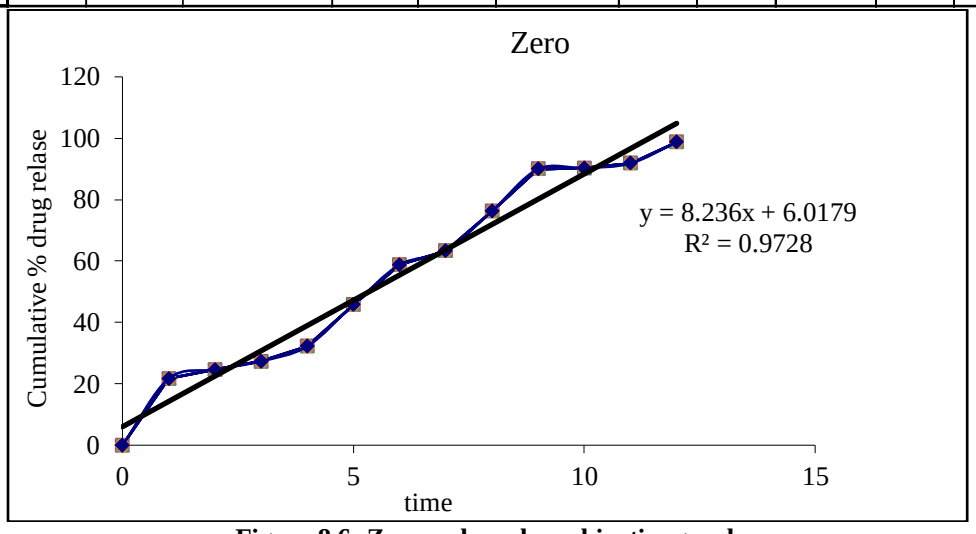


Figure 8.6: Zero order release kinetics graph

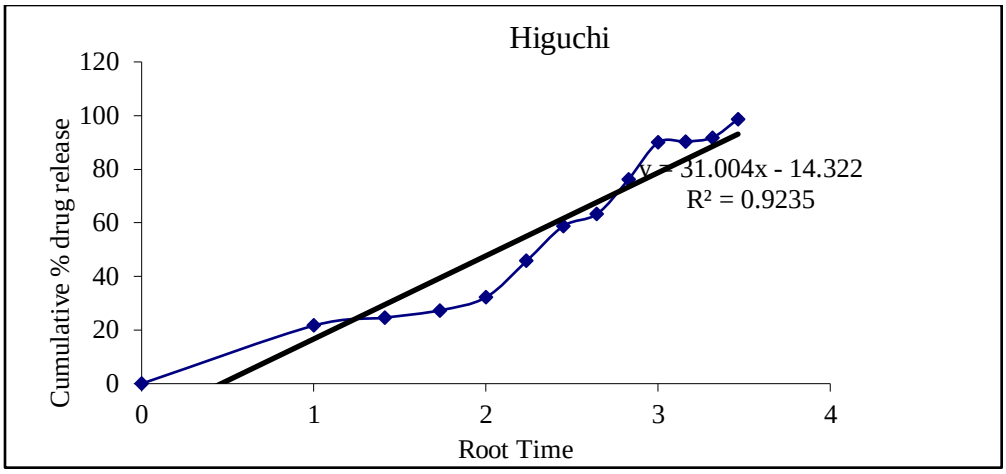


Figure 8.7: Higuchi release kinetics graph

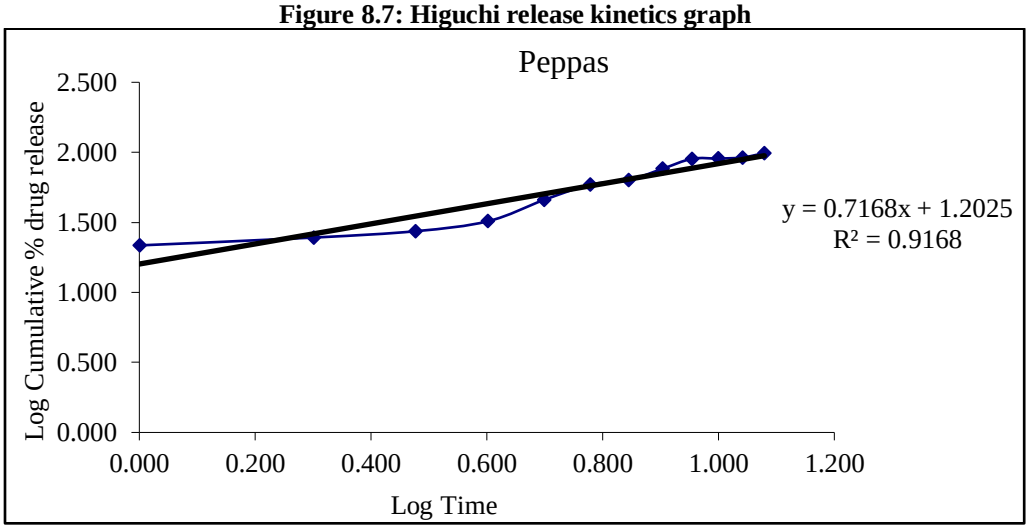


Figure 8.8: Peppas release kinetics graph

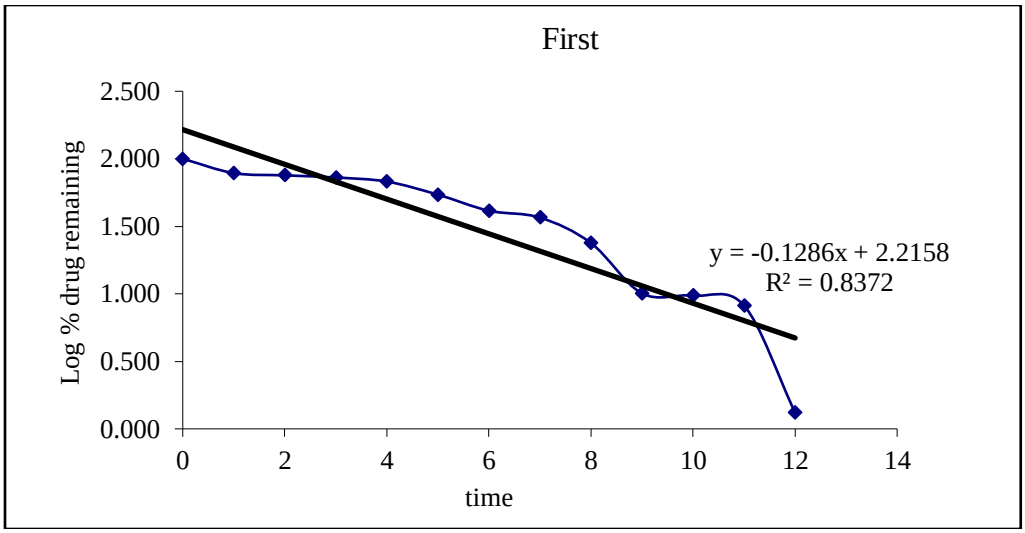


Figure 8.9: First order release kinetics graph

Optimised formulation F7 was kept for release kinetic studies. From the above graphs it was evident that the formulation F7 was followed **Zero order release** mechanism.

Fourier Transform-Infrared Spectroscopy:

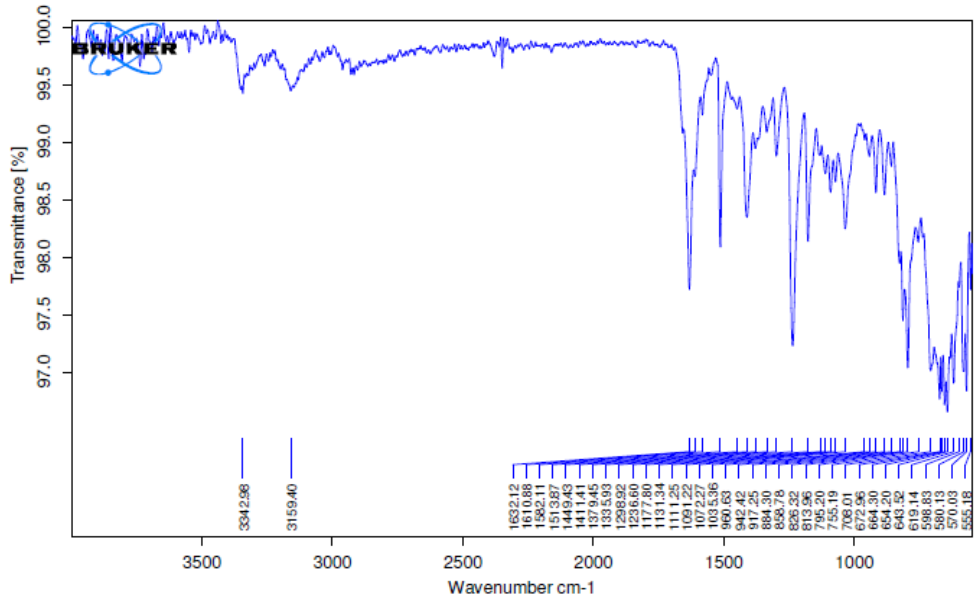


Figure 8.10: FT-TR Spectrum of Itopride hydrochloride pure drug

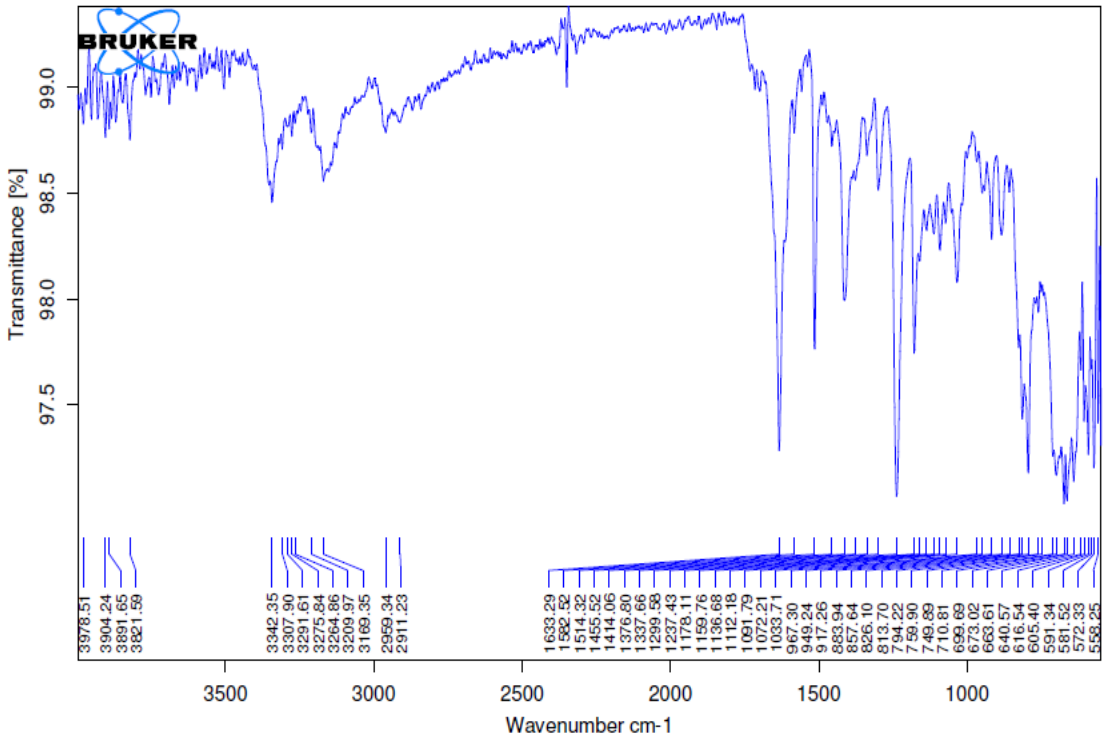


Figure 8.11: FT-IR Spectrum of Optimised Formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Itopride hydrochloride is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug

CONCLUSION:

The present investigation was carried out for controlling the drug release up to 12 hrs. For controlling the drug release polymers used such as HPMC K 15M, HEC 2M, HPC 2M.

From the investigation studies were found following:

- Standard graph was given that regression analysis R^2 value was 0.998 in 0.1 N HCl and 0.999 in pH 6.8 phosphate buffer.
- FTIR results were shown good compatibility between drug and excipients.
- All the pre and post compression studies such as Bulk density, Tapped density, Angle of repose, Carr's index, Hausners ratio, Weight variation, Thickness, Hardness, Drug content was found to be within limits.
- *In vitro* drug release studies revealed that among all formulations F7 formulation was considered as optimised formulation which contains HPC 2M as polymer in the concentration of 25 mg.
- Drug release kinetic studies were done for optimised formulation. It was followed Zero order release kinetics.

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