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Design and *in-vitro* evaluation of extended release matrix tablets of Itopride hydrochloride

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Abstract

This work aims at investigating different types and levels of hydrophilic matrix agents from synthetic origin, hydroxypropyl methylcellulose K100M, and from natural origin, gum karaya, in an attempt to formulate extended release matrix tablets of itopride hydrochloride. HPMC and gum karaya were used alone and in combination to know their efficacy in controlling the release rate of a highly water soluble drug itopride hydrochloride. Itopride hydrochloride is the prokinetic agent which improves GI motility by a dual mode of action, dopamine D_2 receptor blockade and acetyl cholinesterase inhibitory action. The tablets, prepared by direct compression, were subjected to physical characterization. Physicochemical interactions between the drugs with excipients were determined by using FTIR and DSC which revealed that there is no interaction between drug with excipients. All the precompression and postcompression parameters were found within acceptable limits. From the obtained data it was concluded that, the release rate was strongly influenced by the concentration of the polymers. The formulation F1, F6 and F8 showed the maximum drug release up to 24 h. The mathematical treatment of in vitro drug release data suggest that, selected formulations close to zero order and showed non-Fickian (anomalous) release as all values of release exponent (n) are between 0.5-0.89.

Keywords: Extended release; Itopride hydrochloride; Hydrophilic polymers, Direct compression; *In-vitro* release

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INTRODUCTION

The oral route is the most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long term therapy for the treat of chronic disease conditions, conventional formulations are

required to be administered in multiple doses and therefore have several disadvantages [1]. Extended release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs [2].

Itopride hydrochloride is an oral prokinetic agent used in the treatment of gastric motility disorder. It is benzamide derivative, absorbed from gastrointestinal tract. Itopride hydrochloride activates the gastrointestinal motility through synergism of its dopamine D_2 receptor antagonistic action and its acetylcholine esterase-inhibitory action. In addition to these actions, itopride has an antiemetic action, which is based on its dopamine D_2 -receptor antagonistic action. The short biological half-life (6 hrs), 60 % bioavailability and dosage frequency more than once a day (50 mg t.i.d.) makes the itopride hydrochloride an ideal candidate for the controlled drug delivery systems [3, 4].

The matrix tablets composed of drug and the release retarding material offers the simplest approach in designing an extended release system [5]. Because of their simplicity and cost-effectiveness, hydrophilic gel matrix tablets are widely used for oral controlled release dosage forms. Hydrophilic polymers form a gel like structure around the tablet core which controls the release of drug. In present work HPMC K100M and gum karaya were used alone and in combination in different concentration to retard the release up to 24 hrs, and to investigate the effect of polymer concentration and their combinations on the *in-vitro* release of the water soluble itopride hydrochloride.

MATERIALS AND METHODS

Materials

Itopride Hydrochloride was received as gift sample from Alkem Labs. Ltd., Mumbai., Hydroxypropyl methylcellulose K1000M (HPMC K100M) was obtained as gift from Colorcon Asia Pvt. Ltd., Goa. and gum karaya was obtained from Krystal colloids, Mumbai.

Methods

Preparation of matrix tablets

The matrix tablets of itopride hydrochloride were prepared by employing hydrophilic polymers from synthetic (hydroxypropyl methylcellulose with different viscosity grades) and natural origins (gum karaya) alone and in combination by direct compression method using 12mm concave-faced punch of 10 station Rimek compression machine. For the preparation of tablets previously sieved ingredients are mixed, according to the formulae specified in the Table (1), by using the well closed plastic bottle for 20 min. Magnesium stearate and Aerosil 200 were added to above mixture as flow promoters and mixed for 10 min. In all formulations the amount of itopride hydrochloride was kept constant at 150mg.

Evaluation of matrix tablets [6].

The matrix tablets of itopride hydrochloride were evaluated for precompression parameters such as angle of repose, % compressibility index, Hausner's ratio and postcompression parameters such as hardness (Monsanto hardness tester), weight variation, content uniformity, percentage friability (Roche friabilator), thickness (vernier caliper). Drug content of matrix tablets was

determined by weighing and finely grinding 10 tablets of each batch. Aliquot of this powder equivalent to 150 mg of itopride hydrochloride was accurately weighed, suspended in approximately 50 ml of phosphate buffer pH 7.4 and shaken for 15 min. final volume was adjusted to 100 ml with phosphate buffer and filtered. The suitable dilutions were made and absorbance recorded at 258 nm.

Swelling behavior of matrix tablets [7].
The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 20 ml of phosphate buffer pH 7.4. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The % weight gain by the tablet was calculated by formula:

$$\%\text{Swelling index} = \frac{M_t - M_0}{M_t} \times 100$$

Where, M_t – weight of tablets at time‘t’; M_0 – weight of tablets at time ‘0’.

***In –vitro* drug release study** [8]
In vitro drug release studies for the prepared matrix tablets were conducted for a period of 24 hours using USP type-II (Paddle) dissolution apparatus (Electro lab, Mumbai.) at 37±0.5^{o}C and 75 rpm speed using pH 1.2 buffer for initially 2 hrs and later phosphate buffer of pH 7.4 up to 24 hrs as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 258 nm for itopride hydrochloride by a UV-Visible spectrophotometer. The amount of drug present in the samples was calculated. All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviation less than three indicating reproducibility of results. The plot of cumulative percentage drug release against time (hrs) is shown in figure 1.

Kinetic study [9]
The release of drug from extended release dosage form is regulated by several processes. These are extraction or diffusion of drug from matrix and erosion of matrix, alternatively the drug may be dissolved in the matrix material and then released by diffusion through membrane. In some cases, drug may be released by osmotic process. Different kinetic equations (Zero order, First order, Higuchi and Korsemeyer Peppas equation) were applied to interpret the release rate from the tablet matrix.

Fourier Transform Infrared Spectroscopy (FTIR) study
The compatibility between drug and polymer was detected by IR spectra (Shimadzu 8400, Japan). The pellets were prepared on KBr- press (spectra lab,). The spectra were recorded over the number range of 4000 to 500cm^{-1}.

Differential scanning Calorimetry (DSC) study

Thermograms were obtained by using a Diamond DSC (Mettler Star SW 8.10) at a heating rate 10^{o} C/min over a temperature range of 0-275^{o}C. The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 25 ml/min for maintaining inert atmospheres.

Table 1: Formulation table of Itopride Hydrochloride tablets

Formulation code	Drug	HPMC K100M	Gum Karaya	MCC	PVP	Aerosil	Mg. Stearate	Total weight
F1	150	210	-	231	-	3	6	600
F2	150	240	-	201	-	3	6	600
F3	150	270	-	171	-	3	6	600
F4	150	-	210	207	24	3	6	600
F5	150	-	240	177	24	3	6	600
F6	150	-	270	147	24	3	6	600
F7	150	105	105	231	-	3	6	600
F8	150	120	120	201	-	3	6	600
F9	150	135	135	171	-	3	6	600

All quantities are in mg.

RESULTS AND DISCUSSION

All the batches were evaluated for pre and post compression parameters and found within acceptable limits. Plain itopride hydrochloride drug exhibited angle of repose value of (47.07± 0.28^{0}) indicating poor flow property. It was further supported by high compressibility index value (33.52±0.21%) and Hausner's ratio (1.61±0.07) as shown in table 2. The flow property of plain itopride hydrochloride was improved by addition of lubricants and directly compressing agent MCC. Hardness of the tablets was found in the range of 5.6-7.6 kg/cm^2, thickness 5.96-6.11mm, percentage weight loss in the friability test was less than 0.6% in all batches and all batches contained itopride HCl within 100 ± 5 % of the labeled content as shown in table 3. The swelling index of formulations are directly proportional to the concentration of the polymer, as polymer concentration increases there is increase in swelling index as polymer absorbs buffer and swells as shown in fig 1. Erosion of surface layer of matrix tablet was found in case of gum karaya matrix tablets

Release profile indicated that, increasing the polymer concentration from 35 to 45% w/w has drastically retarded the release of itopride hydrochloride. The direct relationship was observed between concentration, swelling index and cumulative percent drug release Formulation containing 35% w/w HPMC K100M (F1) showed complete release of drug in 24 hrs in controlled manner as compare to gum karaya which requires higher concentration 45% w/w (F6). Combination of gum karaya with HPMC K100M, 20% w/w each, (F8) gave controlled release up to 24 hrs as shown in fig 2-4. This is due to the increase in gel strength of tablets.

Table 2. Evaluation of precompression parameters

Formulation code	Angle of repose (θ)	Compressibility (%)	Hausner's ratio
F1	25.16 ± 0.32	14.12 ± 0.28	1.17 ± 0.02
F2	25.10 ± 0.25	14.56 ± 0.31	1.19 ± 0.03
F3	25.72 ± 0.30	15.26 ± 0.49	1.21 ± 0.08
F4	25.36 ± 0.23	14.67 ± 0.32	1.19 ± 0.06
F5	26.38 ± 0.19	15.12 ± 0.14	1.22 ± 0.04
F6	26.06 ± 0.34	15.56 ± 0.25	1.24 ± 0.07
F7	25.72 ± 0.26	15.42 ± 0.41	1.23 ± 0.03
F8	27.52 ± 0.14	15.23 ± 0.18	1.22 ± 0.05
F9	26.17 ± 0.12	15.11 ± 0.30	1.21 ± 0.01
Plain Itopride HCl	47.07 ± 0.28	33.52 ± 0.21	1.61 ± 0.07

All values are expressed as mean ± SD.

Table 3. Evaluation of postcompression parameters

Formulation code	Hardness test* (kg/cm^2)	Friability** (%)	Weight variation*** (%)	Thickness** (mm)	Drug content* (%)
F1	7.5 ± 0.33	0.20 ± 0.09	1.47 ± 0.19	6.09 ± 0.04	98.25 ± 0.67
F2	7.6 ± 0.34	0.22 ± 0.14	1.18 ± 0.16	6.07 ± 0.01	98.86 ± 0.81
F3	7.1 ± 0.46	0.31 ± 0.08	1.67 ± 0.75	6.11 ± 0.03	95.68 ± 0.66
F4	5.9 ± 0.31	0.50 ± 0.05	1.59 ± 0.49	5.92 ± 0.03	97.35 ± 0.72
F5	5.6 ± 0.30	0.51 ± 0.09	1.34 ± 0.27	5.98 ± 0.02	98.12 ± 0.42
F6	5.7 ± 0.42	0.50 ± 0.03	1.73 ± 0.74	6.02 ± 0.01	97.34 ± 0.65
F7	6.9 ± 0.62	0.35 ± 0.07	1.11 ± 0.52	6.02 ± 0.05	97.67 ± 0.95
F8	7.3 ± 0.54	0.37 ± 0.04	2.11 ± 0.32	5.96 ±0.03	95.86 ± 0.47
F9	7.3 ± 0.35	0.36 ± 0.05	1.56 ± 0.23	6.04 ± 0.03	98.19 ± 0.34

All values are expressed as mean ± SD**, ***n=5, **n=10, ***n=20.

FT-IR and DSC study revealed no interaction between drug and excipients used. The IR spectra of formulations F1, F6 and F8 have shown the characteristic absorption bands for the different functional group and bonds present in the drug molecule with negligible changes in the positions of the bands in comparison with the IR spectrum of the pure drug. Similarly DSC thermogram of pure drug gave sharp melting endotherm at 198.23^{o}C. There was no shift in the endotherm of drug-excipients mixtures indicating compatibility of the drug with all the excipients as shown in fig 5 and 6.

Kinetic study revealed that the prepared hydrophilic matrix tablets showed non-Fickian (anomalous) release, as the values of release exponent (n) lies between 0.5384-0.7265 with correlation coefficient (r^2) values > 0.9598, indicating that coupled diffusion, polymer swelling and relaxation were involved in the release process. The results are indicated in table 4.

Table 4. Mathematical modeling and drug release kinetics of extended release tablets of Itopride Hydrochloride

Formulation code	Zero order		First order		Highuchi		Korsmeyer-peppas	
	n	r^2	n	r^2	n	r^2	n	r^2
F1	3.6876	0.9815	-0.0496	0.8631	19.286	0.9657	0.6139	0.9677
F2	3.5624	0.9801	-0.0405	0.9131	18.706	0.9725	0.6066	0.9733
F3	2.9955	0.9786	-0.0270	0.9359	15.825	0.9625	0.5384	0.9676
F4	5.0198	0.9681	-0.0611	0.9185	23.020	0.989	0.6690	0.9952
F5	4.2848	0.9826	-0.0604	0.8363	21.143	0.9729	0.7265	0.9852
F6	3.843	0.9782	-0.0598	0.8195	20.163	0.9687	0.6193	0.9658
F7	4.1377	0.9522	-0.0517	0.916	20.773	0.996	0.5479	0.9974
F8	3.7417	0.9668	-0.0564	0.8333	19.956	0.9893	0.5776	0.9922
F9	3.4181	0.9763	-0.0365	0.9334	17.947	0.9682	0.5817	0.9598

Fig 1. Swelling study of selected polymeric matrix tablets of Itopride Hydrochloride

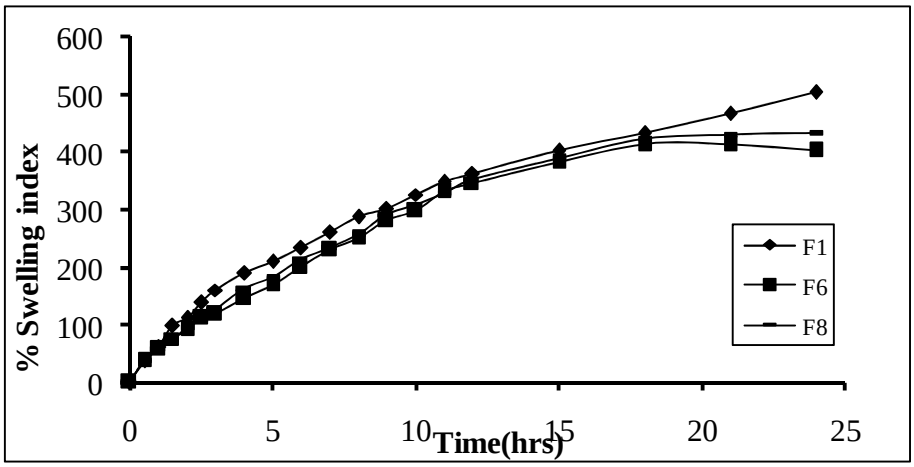


Fig 2. Effect of polymer level on *in-vitro* release of Itopride Hydrochloride from HPMC K100M matrix tablets.

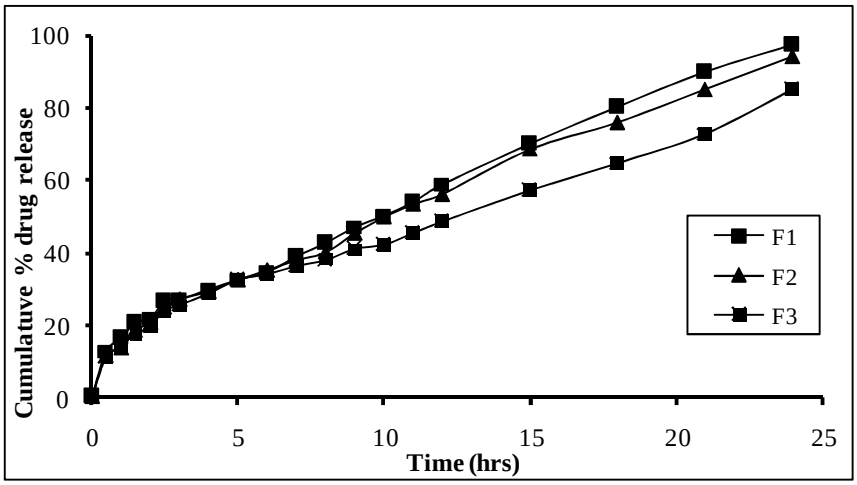


Fig 3. Effect of polymer level on *in-vitro* release of Itopride Hydrochloride from gum karaya matrix tablets.

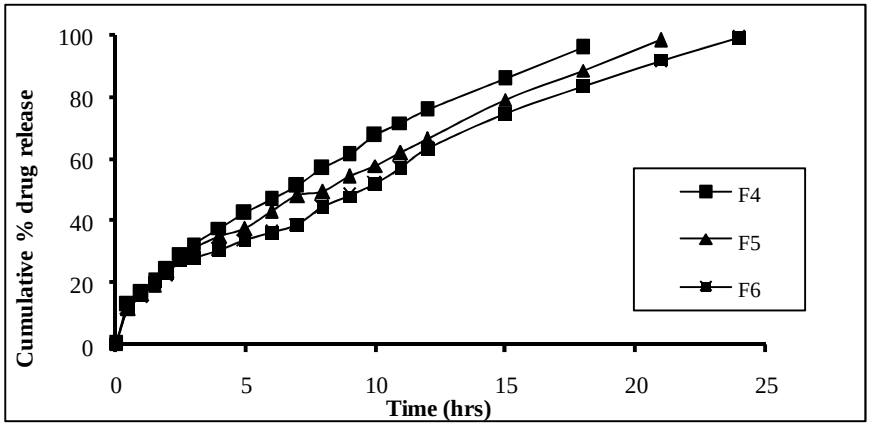


Fig 4. Effect of polymer level on *in-vitro* release of Itopride Hydrochloride from combined HPMC K100M and gum karaya matrix tablets

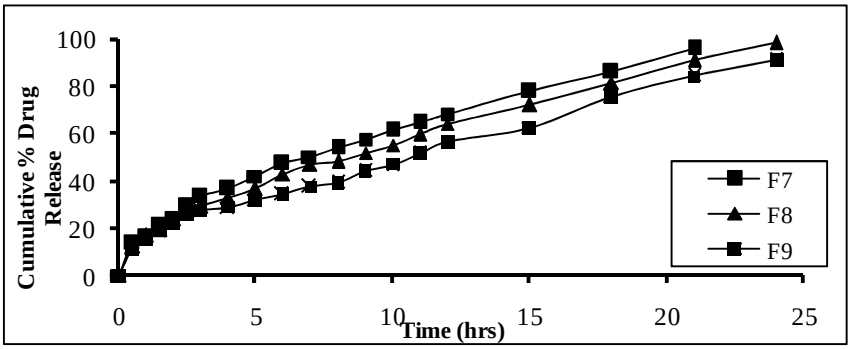
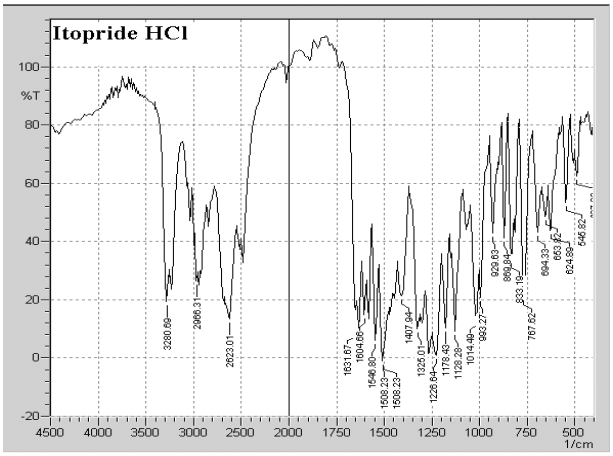
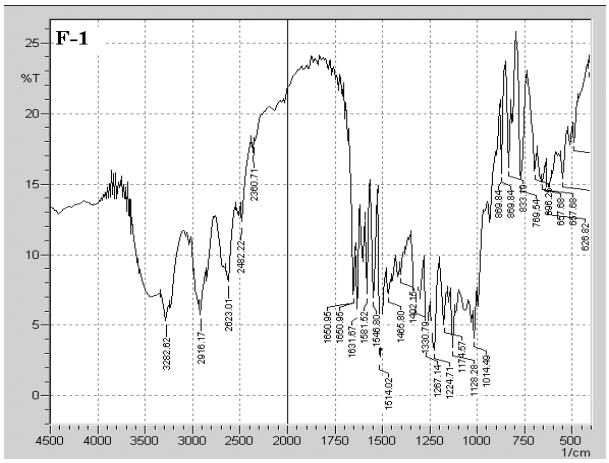
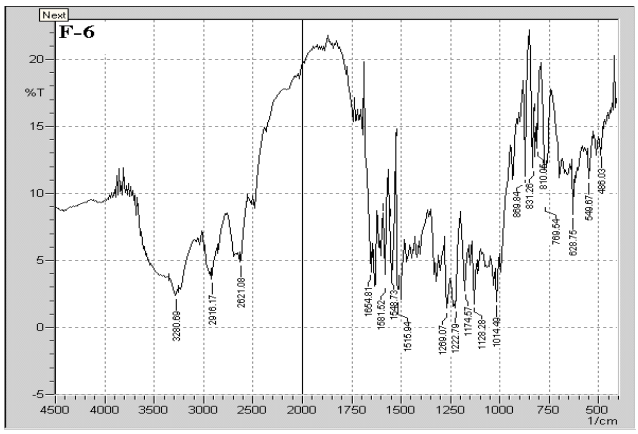


Fig 5. IR spectra of Itopride Hydrochloride and selected formulations.







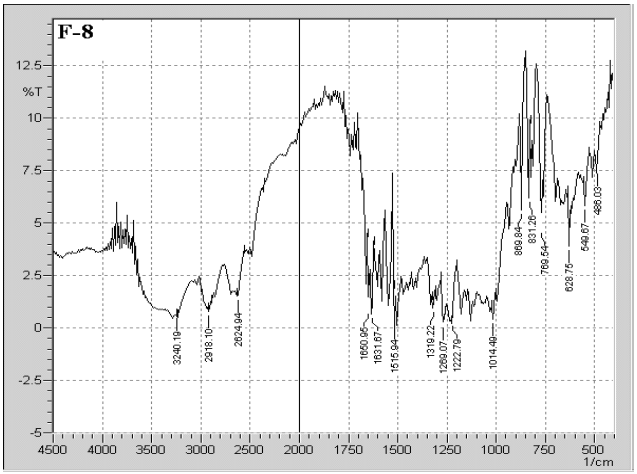
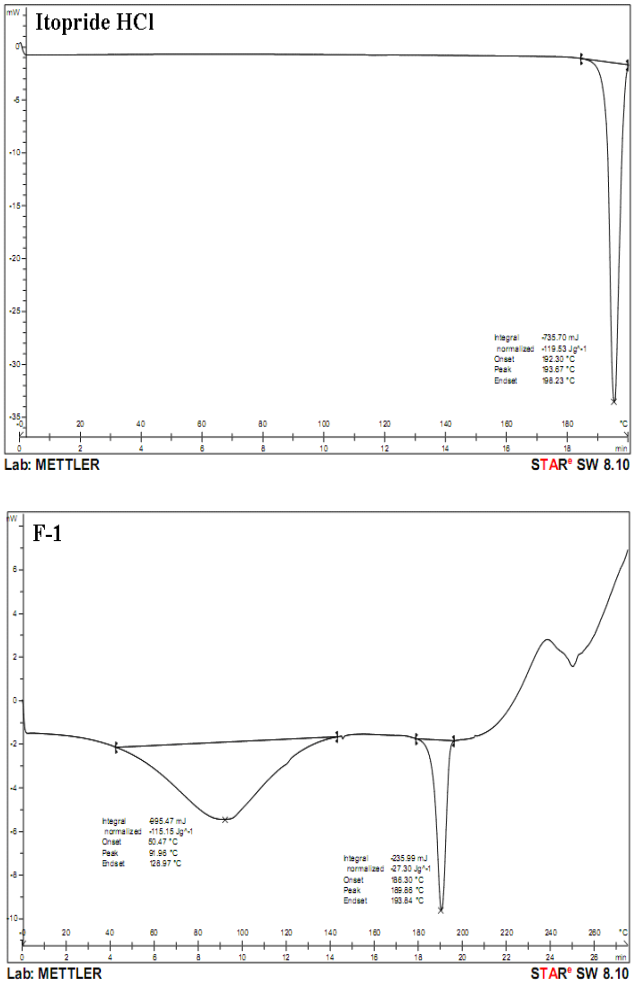
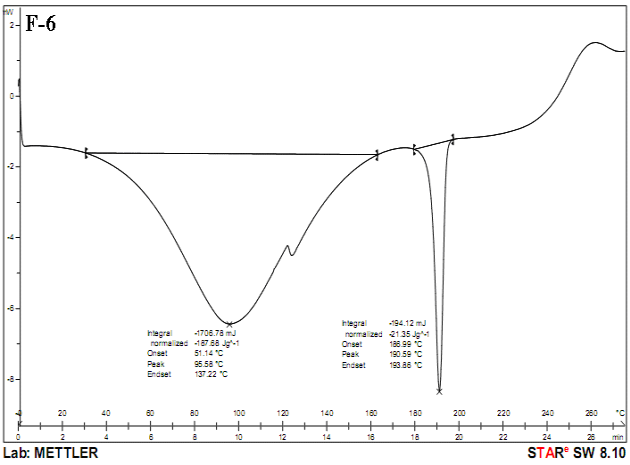
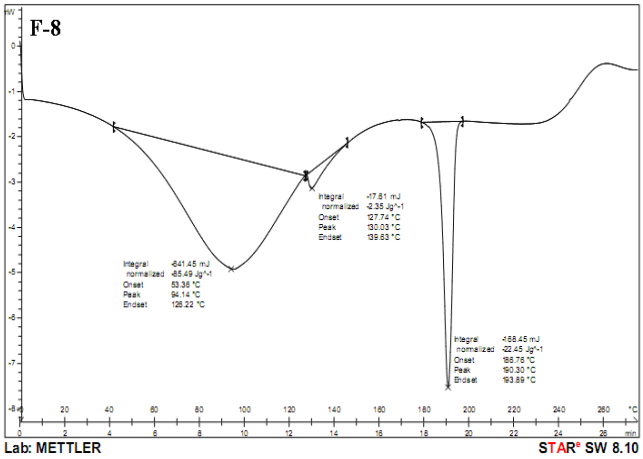


Fig 6. Differential scanning thermograms of Itopride Hydrochloride and selected formulations.







CONCLUSION

The drug release from all matrix tablets showed a polymer concentration dependent retardation effect and non-fickian (anomalous) release. Matrix tablets containing HPMC K100M (35%) and gum karaya (45%) alone showed controlled release upto 24 hrs. When gum karaya combines with HPMC K100M, concentration of gum was reduced up to 20 %.

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