ISSN 2347-3614

UNIQUE JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL SCIENCES

Available online: www.ujconline.net

Research Article

FORMULATION OF SUSTAINED RELEASE ITOPRIDE HYDROCHLORIDE MATRIX TABLETS USING DIRECT COMPRESSION TECHNIQUE

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Received 13-09-2013; Revised 11-10-2013; Accepted 10-11-2013

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ABSTRACT

Itopride HCl is a novel prokinetic agent. It is used mainly in gastroesophageal reflux disease. The objective of this investigation was to formulate sustained release matrix tablets of Itopride HCl using different polymer and polymer combinations to prolong the drug release over 12 hours hence improve patient compliance and minimize side effects. The tablets of Itopride HCl were prepared using different cellulosic polymers and methacrylate copolymers (Eudragits) in various ratios. The *in-vitro* drug release was carried out using the pH shift method. Optimization of polymer concentration that controls the drug release was performed. Bioavailability study on rabbits was performed to investigate the rate and extent of Itopride HCl absorption from the optimum formulated tablet compared to that of commercial immediate release tablets (Ganaton®).

The drug release was found to depend upon the polymer type and concentration. Sustained release tablets containing either hydroxypropyl methyl cellulose or Eudragit RSPM in 1:3 (drug: polymer, weight ratio) gave the most sustaining effect among the single polymers. The drug release rate from tablets prepared using polymer combinations is slower compared to that from matrices containing single polymers. Tablets containing drug, hydroxypropyl methylcellulose and Eudragit RSPM in weight ratio of 1:1:3 gave the slowest drug release rate.

The time for reaching peak plasma concentration (T_{max}) and the area under the curve from zero to 24 h $AUC_{(0-24)}$ were higher following formulated tablet administration compared to the marketed tablets. The percentage relative bioavailability of Itopride HCl from the selected formula was found to be 129%.

Keywords: Itopride Hydrochloride, sustained release tablets, direct compression, *in-vitro* drug release, bioavailability.

INTRODUCTION

Itopride HCl is a freely water soluble, novel prokinetic agent. It has anticholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity and is used for the symptomatic treatment of various gastrointestinal motility disorders[1,2]. It is the drug of choice in the treatment of Gastroesophageal reflux disease (GERD)[3]. The usual oral dose of Itopride HCl is 50 mg three times daily[4]. On oral administration, Itopride HCl is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 min after oral dosing[5]. It has a relatively short biological half life (6 hours)[4].

Sustained release delivery systems have many advantages over immediate release dosage forms. These include reduction of dosing frequency by administering the drug once or twice a day[6], improved patient compliance and reduced gastrointestinal side effects[7] ,due to less fluctuation of plasma drug levels. Sustaining the drug release leads to more uniform drug effect and decrease total required dose[8]. However, sustained release dosage forms may have some disadvantages which may include; sudden release of large amount of drug i.e. dose dumping which in turn leads to toxicity, reduced potential for accurate dose adjustment, need for additional patient education (as not crush or chew the dosage unit), cost of manufacture, and stability problems[9].

Among the methods used to formulate oral extended release products is retardation of drug release by the use of polymeric materials[10]. Polymers are uniquely suited as materials of construction for oral delivery systems. They offer a wide range of properties such as diffusivity, permeability, and solubility that are important to achieve controlled delivery. These polymers have been broadly grouped into hydrophilic polymers and hydrophobic polymers[11]. Because of the advantages of direct compression technique, it was used to prepare the tablets[12,13]. Hence, Certain cellulosic (Hydroxy Propyl methyl cellulose 15000 (HPMC 1500), sodium carboxy methyl cellulose (NaCMC) and methyl cellulose (MC) and methacrylate copolymers (Eudragits) RLPO, RSPM, RL100, RS100 were used in different proportions either alone or in

combinations to control the release of Itopride HCl. The physical properties of the prepared tablets were investigated. Furthermore, bioavailability study was performed in order to investigate the rate and extent of Itopride HCl absorption from the optimum sustained release tablet formulation compared to that of a commercial immediate release oral tablet (Ganaton®).

MATERIALS AND METHODS

Materials:

Itopride HCl was supplied from Vasuhda Co., India. Eudragit RS100, Eudragit RL100, Eudragit RSPM and Eudragit RLPO were supplied from Röhm Pharma, Darmstadt, Germany. Hydroxy propylmethyl cellulose 15000(HPMC 15000), Sodium carboxymethy cellulose were supplied from Aldrich chemical Company, USA. Microcrystalline cellulose (Avicel pH 101) was supplied from FMCO, Ireland. methyl cellulose(MC) was supplied from Merck Co.,Germany. Magnesium stearate was supplied from EL-Nasr Pharmaceutical Chemicals Co., Egypt. Acetonitrile HPLC grade was obtained from Merck-Schuchardt, Germany. Marketed Itopride HCl tablets (Ganaton®), were obtained from ABBOTT, USA.

Newzeland rabbits (body weight 1.5-2 kg) were obtained from the animal house, Faculty of Medicine, Assiut University.

All other chemicals and solvents were of analytical grade, and were used as received.

Methods:

Drug excipient compatibility study:

Drug excipient compatibility study was done using differential scanning colorimetry (DSC), IR spectroscopy and X-ray diffractometry.

Preparation of Itopride HCl sustained release tablets:

Itopride HCl sustained release tablets were prepared by mixing Itopride HCl 75 mg /tablet with the different studied polymers either single or in combination in different weight ratios and other additives. Single polymers were added in the following weight ratios; 1:1, 1:2, 1:3 drug: polymer. In case of polymer combination, three weight ratios were used 1:1:1, 1:1:2, 1:1:3, drug: polymer 1: polymer 2. Diluent was added and mixing was performed using the serial mixing procedure in a mortar for at least 5 minutes for each step, this is followed by tumble mixing in a stoppered glass bottle for fifteen minutes. Magnesium stearate was finally added to the blend and mixed for five minutes. The produced mixtures were compressed into tablets using single punch tablet machine. The machine is adjusted to produce tablets weighing 450 mg. Table 1 shows the composition of the prepared Itopride HCl sustained release tablets.

Evaluation of the prepared sustained released tablets[14]:

The prepared Itopride HCl sustained release tablets were evaluated for the following parameters: tablet weight, drug content, tablet friability, tablet thickness and tablet hardness.

***In-vitro* release of Itopride HCl from the prepared sustained release tablets:**

The USP dissolution apparatus II (paddle -type) rotating at 100 rpm was utilized. The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2) for the first 2 hours after which the pH of the dissolution medium was elevated to 6.8 by adding tribasic sodium phosphate powder[15]. The dissolution medium was previously degassed and warmed to 37.5± 0.5C. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium using volumetric pipette and replaced immediately with the same volume of the fresh dissolution medium maintained at the same temperature. The amount of Itopride HCl was determined spectrophotometrically at λ max 258ηm, using the same dissolution medium as a blank. All assays were done in triplicate and the mean value and standard deviation (S.D) were calculated.

Kinetic analysis of the drug release from the prepared sustained release tablets:

The release data of Itopride HCl were subjected to kinetic treatment. The diffusion-controlled (Higuchi model), first-order, and zero-order kinetic models were applied to interpret the release rate mechanism of the drug from the prepared tablets. The data were treated on the basis of these kinetic models[16]. In addition, the drug release data were analyzed to show the mechanism of drug release according to Fickian, non Fickian, and Case-II transport using the equation proposed by Korsmeyer: $M_t / M_\infty = Kt^n$ Where M_t / M_∞ is the fractional release of the drug at time t, K is the release rate constant and n is the diffusional exponent that characterizes the type of release mechanism during the dissolution process, The values of *n* and *k* were estimated by linear regression of log (M_t / M_∞) versus log *t*.

For non-Fickian (Anomalous) release, the value of n falls between 0.45 and 0.89; while in case of Fickian diffusion, n= 0.45; for zero order release (case II transport), n= 0.89[17].

Bioavailability study of Itopride HCl from the prepared sustained release tablets:

The study was carried out using 3 groups each of 3 Newzeland rabbits (1.5-2 kg). The first group was used as Control group, the second group was given drug dose 3.75 mg/kg from the tested tablets (Ganaton ®) and the third group was given drug dose 3.75 mg/kg from formulae DCE 9 containing Itopride HCl: HPMC 15000 :Eudragit RSPM 1:1:3. The control group was starved, no drug administered with free access to water. While the second and third groups were starved overnight before drug administration and continued fasting until 4 hours post dose with free access to water. The study was conducted as single dose cross over design, with 7-days washout period. 1 ml blood samples were withdrawn from the marginal ear vein into heparinized tubes at 0, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hours after drug administration. Plasma was directly separated by centrifugation and was stored at -20°C until analysis. For the determination of Itopride HCl in plasma, a sensitive, selective and simple method using precipitation of protein with 10% perchloric acid, followed by high-performance liquid chromatography (HPLC) with fluorescence detection was developed using levofloxacin as the internal standard (IS). Chromatographic separation was obtained within 7.0 min using a reverse phase Hypersil BDS C18 (250 mm×4.6 mm, 5 m) column and an isocratic mobile phase, constituting of a mixture of 0.1 mol/l ammonium acetate–methanol (30:70, v/v) flowing at 1.1 ml/min. The excitation and emission wavelengths were set at 304 and 344 nm[18]. Before drug administration, blood samples were

collected and plain plasma was separated and used for the calibration curve construction. Pharmacokinetic parameters of Itopride HCl following oral administration were determined from plasma concentration-time data.

Statistical analysis:

The data were presented as mean ± SD. Student's t-test was employed to assess the significance of the difference between the tested sustained release formulations and the commercial immediate release tablets Ganaton®, at traditional level ($P<0.05$) using a statistical computer package (SPSS version 13.0).

RESULTS AND DISCUSSION

Drug Excipient Compatibility Study:

DSC thermograms ofthe drug and the investigated excipients showed the absence of any change in the endothermic peaks corresponding to the melting point of Itopride HCl. In addition, there was no change in the characteristic IR bands of Itopride HCl when present in physical mixture with the investigated excipients. Hence the DSC Study and IR spectroscopy showed that there was no significant drug-excipient interaction. Also X-ray studies revealed that there was no change in diffraction peaks of Itopride HCl indicating that there was no change of crystallinity of Itopride HCl. The previous results indicated that Itopride HCl was compatible with HPMC 15000, methyl cellulose, sodium carboxymethyl cellulose, Eudragits RL 100, RS 100, RLPO and RSPM, starch RX , Avicel pH 101, and magnesium stearate.

Physical evaluation of Itopride HCl sustained release tablets prepared by direct compression:

All prepared Itopride HCl tablets were of uniform weight, uniform thickness, and uniform drug content. The weight of the formulated tablets ranged from the 447 to 454 mg which was considered acceptable values. The mean of drug content in the prepared Itopride HCl tablets was found to be within the range of 99.5 to 102.5%. The % friability was also in the acceptable range 0.35-0.95 % w/w. All the previous results complied with USP XXXI requirments. Itopride HCl formulated tablets showed hardness values ranged from 4.1 to 7.6 Kg.

***In-vitro* release of Itopride HCl from the prepared sustained release tablets:**

The cumulative percent release of Itopride HCl from tablets containing drug alone (DP), certain ratios of HPMC 15000 (DCE 1-DCE 3), NaCMC (DCE 4-DCE 6) and methylcellulose (DCE 7-DCE9) is shown in Table 2. The release of Itopride HCl from tablets containing the drug alone (Formula DP) was rapid and complete drug release was obtained after 60 min. The release of Itopride HCl was markedly decreased with increasing the ratio of the cellulosic polymer. When cellulose polymers in their matrices are exposed to an aqueous medium, they undergo rapid hydration and chain relaxation[19] to form a viscous gelatinous layer which is commonly termed the 'gel layer', at the surface of the tablet[20] through which the drug diffuse during the dissolution process. Increasing the polymer concentration resulted in increasing the viscosity of this gel layer with a longer diffusional path which decreases the drug release rate[21,22]. The release profiles of Itopride HCl from tablets containing drug: cellulosic polymer; 1:3 is shown in fig.1. Generally it is observed that the release of Itopride HCl from all the formulations in acidic medium was pronouncedly more rapid than in phosphate buffer (pH 6.8). This initial rapid release of Itopride HCl from the sustained release tablets in pH 1.2 may be attributed to the presence of the drug in higher concentration in the ionized form (salt form), which has higher solubility than the base, hence the drug particles close to the tablet surface might be released first giving this initial higher release of the drug[23]. Moreover, the viscosity of the gel layer around the drug may decrease in acidic medium. By increasing the pH of the dissolution medium, more sustaining drug release was obtained and this may be due to the increase in the viscosity of the gel layer [24].

Formula DC3 containing HPMC 15000 shows the highest sustaining effect as complete drug release is obtained after 11 hours, this may be attributed to its nature as a highly swellable non-ionic hydrophilic polymer[25].The faster drug release from matrix tablets containing NaCMC may be due to the presence of the ionized carboxylic acid groups in this polymer leading to rapid dissolution and erosion of NaCMC matrix[26]. Matrix tablets containing methyl cellulose showed the fastest release of the drug compared to other investigated cellulosic polymers which can be attributed to the absence of hydroxypropoxyl groups in its structure which is responsible for a lower hydrophilicity and lower water uptake[27]. Moreover, matrices containing only methylcellulose swell and collapsed rapidly resulted in rapid release of drug[28].

The sustaining effect of the three tested hydrophilic polymers on drug release was found to be in the following descending order: HPMC 15000 > NaCMC > MC[29].

Table 3 shows the cumulative release of Itopride HCl from tablets containing Eudragits. The data shows that drug release is markedly decreased due to the presence of Eudragits. This may be attributed to formation of water-insoluble coat through which diffusion of the drug occurs[30]. The drug release was markedly decreased when the percentage of Eudragits increased in the tablet formulae as previously reported[31].

Fig.2 shows the drug release of Itopride HCl from tablets containing 50% (w/w) of certain Eudragits. The sustaining effect of the investigated Eudragits on the drug release can be arranged in the following descending order: Eudragit RSPM > Eudragit RLPO > Eudragit RS100 > Eudragit RL100.

The Eudragits are methacrylate copolymers. Eudragits(RS 100,RL100,RLPO and RSPM) are polycationic water insoluble pH independent.

The permeability of the polycationic Eudragits depend on the content of the ammonium group. Eudragit RS and RL contain 5 and 10%, respectively, of quaternary (quaternized Zwitter-ionic) groups. Hence Eudragits RS have lower water permeability than that of RL . Eudragit RL 100 and RS100 are granular while RSPM and RLPO are powder [32]. The maximum retardation effect on the drug release was obtained with Eudragit RSPM which may be attributed to its pH-independent solubility properties and the low permeability to water-soluble drugs[33]. Similar results were obtained with sustained-release matrix tablets of Verapamil HCl using Eudragits[34].

Figures 3-5 show the release profiles of Itopride HCl from the prepared matrix tablets containing certain polymer blends. Fig. 3 shows the effect of certain ratios of NaCMC on Itopride HCl release from tablets containing drug:HPMC 15000 in weigh ratio 1:1. Itopride HCl matrix tablets containing a combination of NaCMC (ionic hydrophilic polymer) and HPMC 15000 (non ionic hydrophilic polymer) gave slower release rate than tablets prepared using HPMC 15000 alone, formula DC3. Increasing the amount of NaCMC in the polymer blend led to more retardation in the release of the drug. The maximum retardation was obtained with formula DCE3 which contains polymer blend of HPMC 15000: NaCMC (1:3 w/w) and drug release continued for 10 hours. This may be due to the assumption that addition of NaCMC to a non-ionic cellulose polymer like HPMC will form strong hydrogen bonding between the carboxyl groups of NaCMC and the hydroxyl groups of HPMC, leading to strong cross-linking between the two polymers so the blends of HPMC and NaCMC increase the viscosity of the gel layer, which retards drug diffusion from the tablet and as the percentage of NaCMC increased in the polymer blend. The synergistic retardation effect of the polymer blend increased and a marked decrease of drug release rate could be achieved[35]. Similar results were obtained with propanolol HCl matrix[36].

Fig.4 illustrates the effect of certain ratios of Eudragit RLPO on Itopride HCl release from tablets containing drug:HPMC 15000 in weigh ratio 1:1. There was a marked decrease in the release rate of Itopride HCl from the prepared sustained release tablets containing the blend of HPMC and Eudragit RLPO than those containing HPMC 15000 alone. Eudragit RLPO is a pH independent polymer with low water permeability[37]. Therefore, its combination with HPMC 15000 resulted in pronounced sustaining of drug release. As the percentage of Eudragit RLPO increased, the drug release was decreased.

Fig.5 illustrates the effect of certain ratios of Eudragit RSPM on Itopride HCl release from tablets containing drug:HPMC 15000 in weigh ratio 1:1. A marked decrease in the release rate of Itopride HCl from the prepared sustained release tablets containing the blend of HPMC and Eudragit RSPM was observed. Eudragit RSPM is a pH independent water insoluble polymer with poor surface wettability and low swelling properties, being a hydrophobic polymer should lower water penetration and provide effective release retardation when used in combination with a hydrophilic polymer such as HPMC in matrix tablet[38]. Similar results were obtained with the sustained release tablets of venlafaxine in which polymer blend of Eudragit RSPM and HPMC has given sustained release more than HPMC alone[39].

Fig. 6 shows that the polymer blends gave more sustaining release for the drug than HPMC 15000 alone. Formula DCE 9,Itopride HCl: HPMC 15000:Eudragit RSPM 1:1:3, gave the most sustaining effect.

Kinetic analysis of the release data:

It was found that the release of Itopride HCl from all prepared tablets containing single polymers are best fitted to simplified Higuchi model as indicated from the highest correlation coefficient (r^2) indicating that the release rate of Itopride HCl is dependent on diffusion mechanism. The release of Itopride HCl from the tablets containing HPMC 15000 with either NaCMC, Eudragit RLPO or Eudragit RSPM followed zero-order release mechanism. This may be attributed to the maximum sustaining of the drug release due to the presence of polymer blend that lead to increase in the total polymer content which resulted in formation of highly viscous gel layer leading to zero- order drug release.

Upon application of Korsmeyer–peppas equation it was found that the obtained values of *n* (release exponent) of cellulosic polymers lied between 0.45 and 0.89 in all the formulations exhibiting a non-fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism. The presented results are in a good agreement with earlier workers[29,40]. In case of formulation containing Eudragits, the obtained values of n <0.45 thus the drug release from all the formulations exhibiting a fickian release behavior controlled by diffusion mechanism. The obtained values of *n* lied between 0.45 and 0.89 in all the formulations containing polymer blends exhibiting a non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism. The same results have been obtained with J. Siepmann et *al*. in modeling of drug release from delivery systems based on hydroxypropyl methylcellulose[16].

Bioavailability study of Itopride HCl from the prepared sustained release tablets:

The HPLC method used in the assay of Itopride HCl is accurate, precise, specific and practical tool for the analysis of Itopride HCl in plasma samples. The average recovery of the drug from plasma was found to be from (95.80 to 97.53%). The percent relative standard deviation (RSD) for six replicates of the standard injection ranged from 1.243 to 2.296 indicating that HPLC method was highly accurate[41]. Fig. 7 shows typical HPLC chromatograms of blank plasma spiked with 1.875 µg/ml internal standard(IS) levofloaxacin and Itopride HCl at concentrations of 200 ng /ml (trace A), 400 ng /ml (trace B) and 800 ng /ml (trace C). The chromatograms show sharp peak, clearly identifiable and separated from the internal standard peak. The retention times of levofloxacin and Itopride HCl were 4.7 and 3.2 min,respectively.A good resolution was obtained without interference with the endogenous plasma components, indicating efficient extraction of both the drug and the internal standard by the adopted assay procedure.

Fig. 8 shows the mean plasma concentration-time profiles of Itopride HCl after oral administration of the commercial tablets to rabbits Ganaton® and the optimal formula DCE 9. These curves reflect the sustaining of drug absorption from the tablet formula DCE9 compared with the immediate release tablets Ganaton®.

A summary of the pharmacokinetic parameters were listed in Table 4. Following oral administration of Ganaton®, the C_{max} was 812.5651 ng/ ml and t_{max} was 1.0 hr after oral dosing. After oral administration of (DCE 9), C_{max} was 563.064 ng/ ml and t_{max} was 6.0 hr after oral dosing. The value of C_{max}, K_{ab}, $t_{(1/2)ab}$, K_{el}, $t_{(1/2)el}$, AUC_{0-24} and $AUC_{0-\infty}$, were statistically significant ($p < 0.05$) for drug administered from oral (DCE 9) than reference (Ganaton®) demonstrating improved and longer bioavailability of Itopride HCl from formulae DCE9.

CONCLUSION

Sustained release matrix tablets of Itopride hydrochloride were prepared using different ratios of cellulosic and Eudragits using direct compression technique. Formulated tablets were with satisfactory physical properties. The comparative Itopride HCl release studies revealed that the release rate was dependent on the polymer relative amount either alone or in combination. The bioavailability study of optimum formula DCE 9 containing Itopride HCl:HPMC 15000:Eudragit RSPM 1:1:3, revealed delayed drug absorption , lower peak plasma concentration and maintained higher plasma concentration for longer time compared to those of immediate release tablets Gananton®. Therefore, Itopride HCl sustained release dosage forms with the desired *in-vivo* performance is believed to be successfully designed in this work.

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Table 1: Composition of 75 mg Itopride HCl tablets prepared by direct compression using certain cellulosic polymers and Eudragits

Tablet formula No.	Ingredients in each tablet (mg)								
	HPMC 15000	NaCMC	Methyl cellulose	Eudragit RS 100	Eudragit RL 100	Eudragit RLPO	Eudragit RSPM	Avicel PH 101	Starch Rx
Dp	-	-	-	-	-	-	-	185.25	185.25
DC1	75	-	-	-	-	-	-	147.75	147.75
DC 2	150	-	-	-	-	-	-	110.25	110.25
DC 3	225	-	-	-	-	-	-	72.75	72.75
DC 4	-	75	-	-	-	-	-	147.75	147.75
DC 5	-	150	-	-	-	-	-	110.25	110.25
DC 6	-	225	-	-	-	-	-	72.75	72.75
DC 7	-	-	75	-	-	-	-	147.75	147.75
DC 8	-	-	150	-	-	-	-	110.25	110.25
DC 9	-	-	225	-	-	-	-	72.75	72.75
DE 1	-	-	-	75	-	-	-	147.75	147.75
DE 2	-	-	-	150	-	-	-	110.25	110.25
DE 3	-	-	-	225	-	-	-	72.75	72.75
DE 4	-	-	-	-	75	-	-	147.75	147.75
DE 5	-	-	-	-	150	-	--	110.25	110.25
DE 6	-	-	-	-	225	-	-	72.75	72.75
DE 7	-	-	-	-	-	75	-	147.75	147.75
DE 8	-	-	-	-	-	150	-	110.25	110.25
DE 9	-	-	-	-	-	225	-	72.75	72.75
DE 10	-	-	-	-	-	-	75	147.75	147.75
DE 11	-	-	-	-	-	-	150	110.25	110.25
DE 12	-	-	-	-	-	-	225	72.75	72.75
DCE 1	75	75		75	-	-	-	110	110
DCE 2	75	150		150	-	-	-	72	72
DCE 3	75	225		225	-	-	-	35	35
DCE 4	75	-		-		75	-	110	110
DCE 5	75	-		-		150	-	72	72
DCE 6	75	-		-		225	-	35	35
DCE 7	75	-		-	-	-	75	110	110
DCE 8	75	-		-	-	-	150	72	72
DCE 9	75	-		-	-	-	225	35	35

The total tablet weight was 450 mg.
Avicel PH 101 and Starch Rx were used as directly compressible vehicles. Magnesium stearate 1% was added as lubricant.

Table 1: Cumulative percent released of Itopride HCl from tabets containing cellulosic polymers

Time(h)	Mean % of Itopride HCl released from different formulae (± SD)									
	DP	DC 1	DC 2	DC 3	DC 4	DC 5	DC 6	DC 7	DC 8	DC 9
0	0	0	0	0	0	0	0	0	0	0
0.25	68.0(±3.55)	14.0(±0.60)	10.2(±1.41)	8.1 (±1.01)	45.3(±1.53)	30.8(±1.53)	20.5(±1.53)	48.9(±1.52)	45.2(±1.21)	40(±1.24)
0.5	80.0(±3.05)	20.2(±1.53)	14.3(±1.53)	12.5(±1.64)	55.2(±2.64)	42.4(±1.80)	35.6 (±1.26)	70.8(±2.11)	65.3(±2.50)	60(±1.73)
1	98.0(±2.50)	29.2(±1.69)	19.2(±1.08)	18.7(±0.95)	69.4(±1.67)	50.6(±1.68)	45.6(±1.34)	97.8(±3.12)	90.4(±2.16)	85(±2.56)
1.5		35.7(±2.55)	25.3(±1.69)	20.9(±1.40)	80.4(±2.08)	60.5(±2.98)	53.4(±1.79)		98.3(±3.23)	90(±2.53)
2		43.0(±1.57)	30.2(±2.53)	25.2(±1.52)	90.3(±2.87)	71.7(±1.75)	63.2(±1.90)			98(±2.19)
3		57.0(±1.75)	40.3(±2.52)	34.4(±1.27)	98.8(±2.09)	85.8(±1.51)	75.5(±1.15)			
4		66.5(±2.28)	48.5(±2.56)	40.5(±1.53)		98.7(±1.95)	82.7(±1.42)			
5		78.9(±2.08)	55.4(±2.76)	50.7(±2.42)			92.6(±1.19)			
6		89.0(±2.88)	63.4(±1.73)	58.9(±3.07)			98.5(±1.43)			
7		97.8(±2.10)	74.5(±2.08)	67.6(±1.07)						
8			85.6(±1.90)	77.3(±2.25)						
10			98.7(±2.07)	87.7(±3.12)						
11				97(1.80)						

Table 2: Cumulative percent release of Itopride HCl from tablets containing Eudragits

Time(h)	Mean % Itopride HCl released from different formulae (± SD)					
	DE 7	DE 8	DE 9	DE 10	DE 11	DE 12
0	0	0	0	0	0	0
0.25	60.3(±1.3)	55.2(±1.92)	40.0(±2.45)	55..2(±1.21)	45.2(±1.81)	39(±1.62)
0.5	70.5(±2.3)	65.3(±2.03)	55.2(±2.31)	66.2(±1.92)	56.3(±2.12)	48(±1.23)
1	80.6(±2.2)	78.2(±2.60)	68.3(±1.72)	80.7(±2.19)	64.2(±2.03)	56(±1.455)
1.5	90.7(±3.1)	85.1(±2.20)	78.2(±2.23)	91.8(±2.32)	78.3(±1.34)	68(±1.65)
2	98.5(±2.9)	95.2(±3.13)	85.4(±2.01)	98.7(±1.82)	85.2(±2.13)	76(±2.16)
3		97.9(±2.33)	90.3(±2.88)		90.4(±1.72)	88(±2.37)
4			98.2(±2.99)		99.1(±2.20)	92(±2.56)
5						98(±1.53)

Table 3: Pharmacokinetic parameters of Itopride HCl following oral administration of the prepared Itopride HCl sustained release tablets formula (DCE 9) in comparison with the commercial immediate release tablets Ganaton®

Pharmacokinetic Parameters	Ganaton ®	Formulae DCE9	Significance
Dose (mg/kg)	3.75	3.75	---------
T_{max} (hr)	1	6	S
C_{max} (ng/ml)	812.5651	563.064	S
K_{ab} (hr^{-1})	0.825874	0.214589	S
$t_{(1/2)}$ ab (hr)	0.839111	3.22943	S
K_{el} (hr^{-1})	0.36607	0.117054	S
$t_{(1/2)}$el (hr)	1.893078	5.920354	S
Volume of distribution (Vd) (Liters)	0.078503	0.101751	S
AUC $_{(0-24)}$ (ng.hr/ml)	4450.094	5740.95	S
AUC $_{(0-\infty)}$ (ng.hr/ml)	6669.79	10551.25	S

***S. = statistically significant ($p < 0.05$). T_{max}: the time at which the C_{max} occurs., C_{max}: is the peak concentration in the plasma.**
K_{abs}: absorption rate constant.
K_{el}: elimination rate constant.

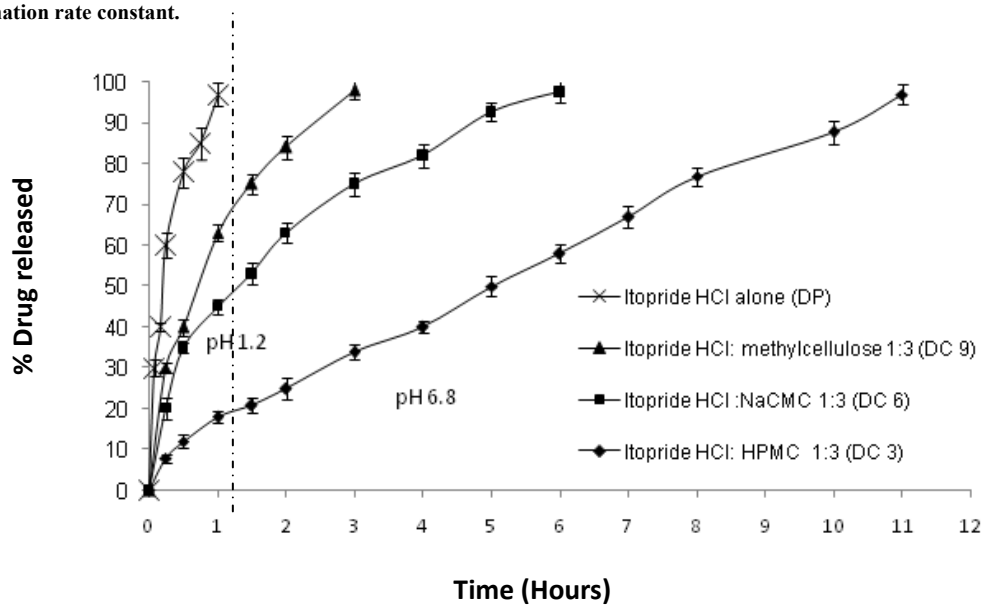

Figure 1: Release profiles of Itopride HCl from tablets containing certain hydrophilic polymers.

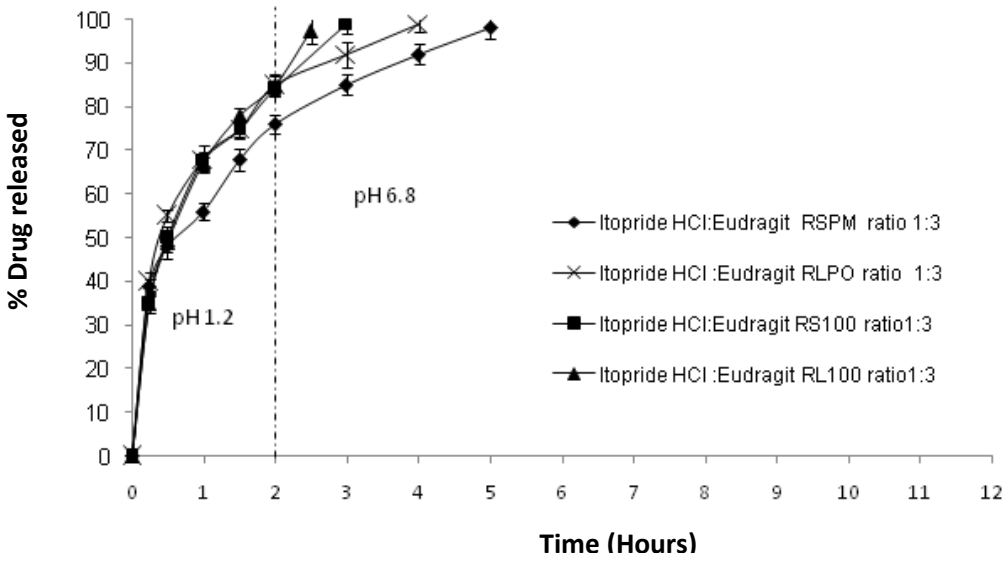

Figure 2: Release profiles of Itopride HCl from tablets containing drug: Eudragit in 1:3 w/w.

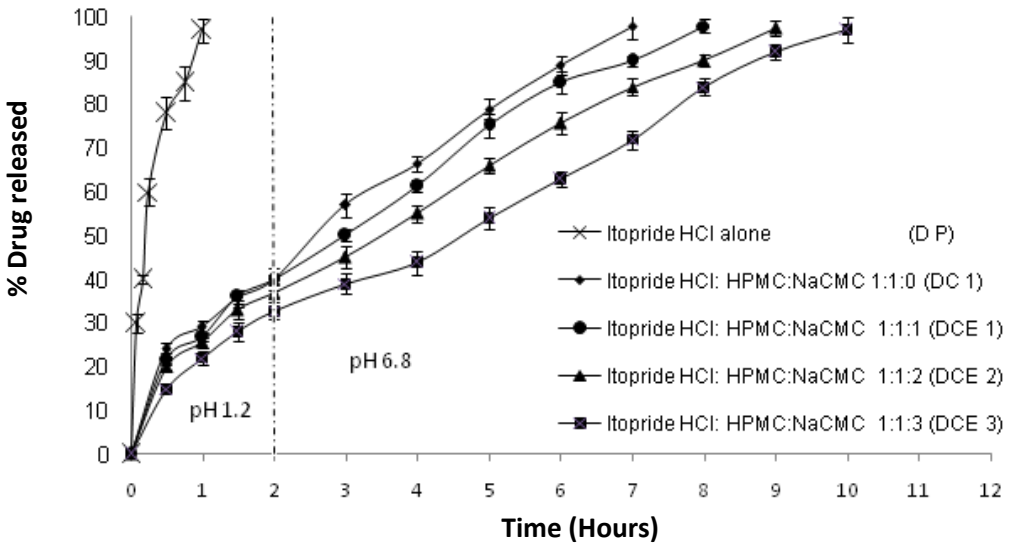

Figure 3: Release profiles of Itopride HCl from tablets containing drug: HPMC 15000: NaCMC in different weight ratio .

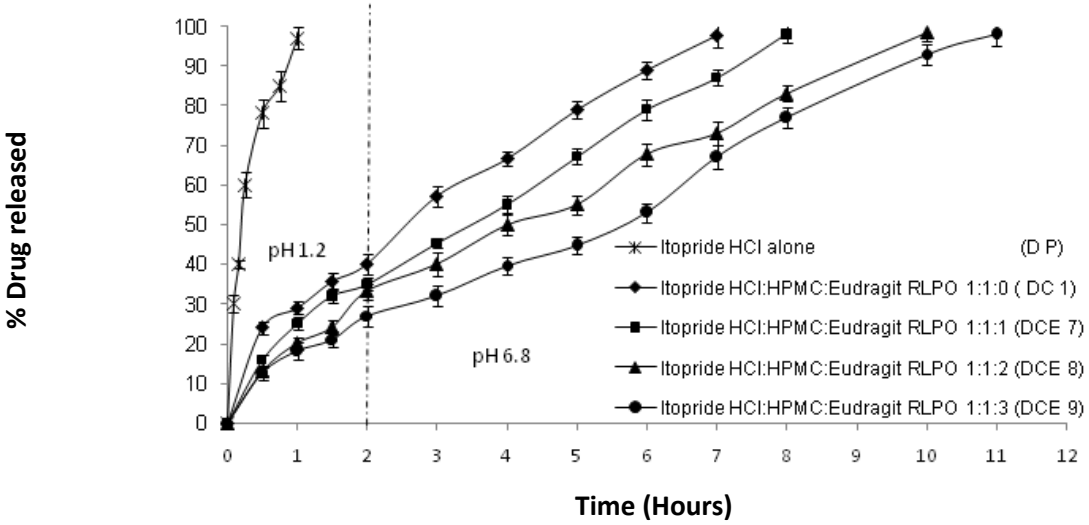

Figure 4: Release profiles of Itopride HCl from tablets containing drug: HPMC 15000: Eudragit RLPO in different weight ratio.

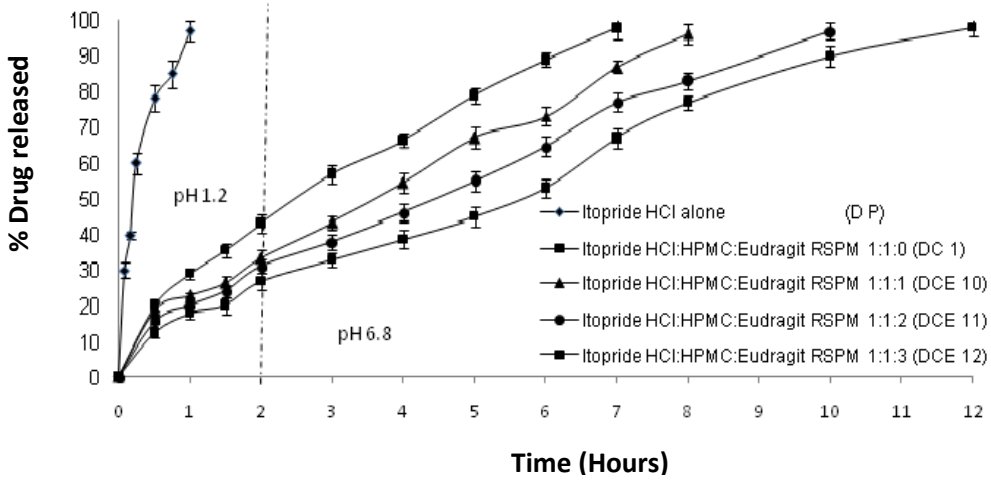

Figure 5 : Release profiles of Itopride HCl from tablets containing drug: HPMC 15000: Eudragit RSPM in different weight ratio.

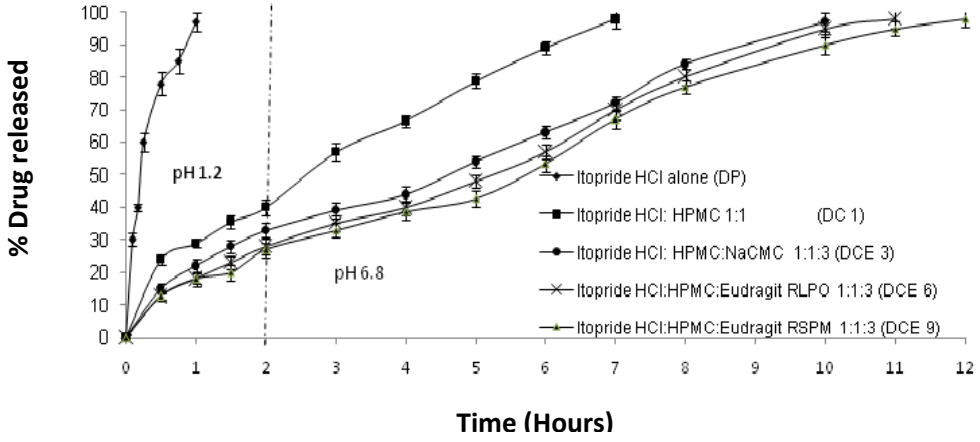

Figure 6: Release profiles of Itopride HCl from tablets containing HPMC 15000 blended with other polymers in comparsion with HPMC alone.

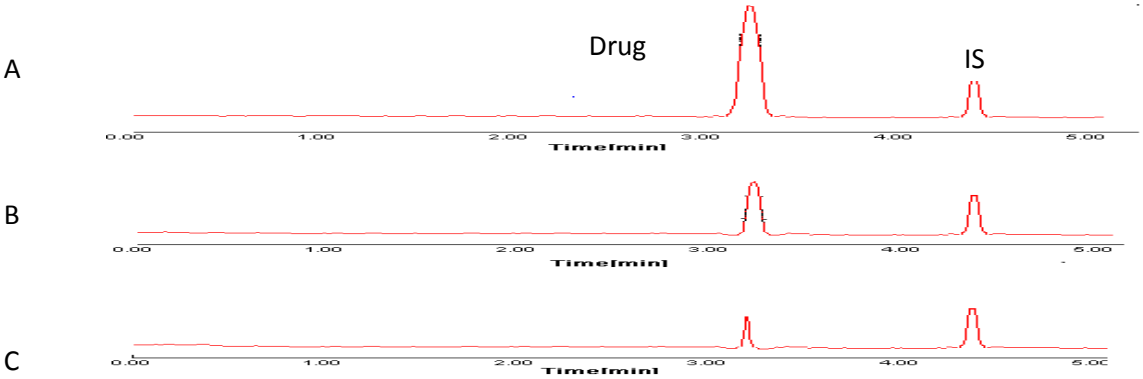

Figure 7: HPLC chromatograms of blank plasma spiked with the internal standard at 1.875 µg/ml levofloxacin (internal standard) and Itopride HCl at concentrations of 800 ng/ml (A), 400 ng/ml (B), and 200 ng/ml (C).

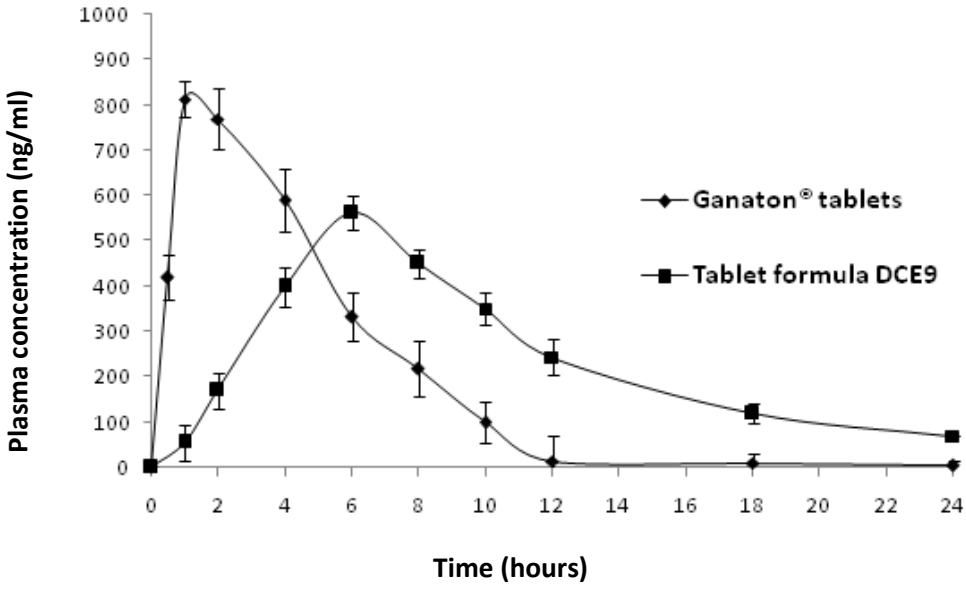

Figure 8: Plasma concentrations of Itopride HCl after oral administration of the commercial tablets Ganaton® and the prepared Itopride HCl sustained release tablet formula DCE 9.

Source of support: Nil, Conflict of interest: None Declared