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FORMULATION DEVELOPMENT AND EVALUATION OF HIGHLY WATER-SOLUBLE DRUG-LOADED CONTROLLED RELEASE MATRIX TABLETS

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Formulation of controlled release matrix tablets of Itopride hydrochloride (ITP) was done using direct compression method. Different polymers were used to evaluate the influence of different types (HPM, EC, Kollidon® SR), concentration (20-40%) and viscosity grade (HPMC-4000 cps, HPMC-100000 cps, EC-10 cps and Kollidon SR) on drug release. Twelve different tablet formulations were designed with constant amount of ITP in each tablet formulation (150 mg). The dissolution studies of CR matrix formulations were carried out in acidic buffer (pH 1.2) and phosphate buffer (pH 6.8). Drug release kinetics was studied for first order, Zero-order, Higuchi, Korsmeyer-Peppas and Weibull models using DD Solver (an add-in software for MS Excel). Formulation ECF7, ECF8 and ECF9 containing EC (20-40%) greatly controlled the release rate of drug over an extended period of 12 hr. However, drug release from tablets formulations K4F3, K100F5 and ECF8, followed zero-order kinetics with regression coefficient of 0.966-0.999. The release mechanism of tablets formulations K4F2, KK4F3, K4F4, ECF7, KSRF10, KSRF11 and KSRF12 were non-fickian diffusion, whereas the release mechanism from formulations K4F1, K100F5, K100F6, ECF8 and ECF9 were super case-II transport mechanism. It was concluded that HPMC and ethylcellulose (EC-10cps) in the percentage range of 20-30% were excellent release controlling polymers for itopride HCl.

INTRODUCTION

Pharmaceutical scientists are developing different dosage form with better therapeutic profiles and better patient compliance. Development of novel drug delivery system is a continuous process and an integral part of pharmaceutical manufacturing. The development of controlled release matrix systems is one of the approaches to control the rate of drug release for the desirable period of time[1]. Pharmaceutical manufacturers are concentrating on the advancement and development of controlled release dosage forms to enhance patients' compliance, convenience, and personal satisfaction[2-4]. Because of high patient compliance, ease of administration, easy manufacturing and low cost, oral route for drug delivery is most commonly used route of administration[5-7]. There are various methods of formulating controlled release dosage forms such as wet

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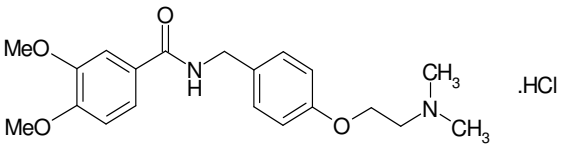
and dry granulation methods, direct compression method, pelletization technique and coating using appropriate polymer for efficiently control the release of drugs which differ in physicochemical properties[7]. A wide variety of controlled release dosage forms have been developed by incorporating water soluble and insoluble polymers. The release of water-soluble drugs can be controlled by using different types of hydrophobic and hydrophilic polymers[8]. In controlled release matrix tablets, releases of drug govern by various mechanisms like dissolution, diffusion, erosion or swelling. The path length for diffusion of drug increases with the elapse of time so the rate of release of drug decrease[9]. Drugs with short half-life are suitable candidate for controlled release formulations long term management of chronically ill patients[10&11].

Hydroxypropyl methylcellulose (HPMC) is a widely used hydrophilic polymer for controlled release of drug. Upon exposure to suitable medium, HPMC formed a gel layer by swelling. This gel layer restrains the release of drug and decides about the accomplishment or failing of the system[7,12&13]. Ethylcellulose (EC) is an extensively used hydrophobic polymer to regulate the release of drug from solid dosage form. EC is pH-independent polymer making them appropriate to be used in controlled drug delivery systems[14-17]. Kollidon® SR (Polyvinyl acetate/Povidone based polymer) is a relatively new controlled release matrix polymer. It consists of 80% polyvinyl acetate and 19% povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica[18].

Itopride hydrochloride was first developed by Hokuriku Seiyaker Co. Ltd., is a novel prokinetic agent, marketed in Japan in September 1995[19&20]. It is a highly water soluble drug[21-24]. Itopride has dual mechanism of action i.e. anti-cholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity[20] and hence, used to enhance gastric motility[19] and to relief GI disorders like gastro-esophageal reflux disease (GERD), epigastric discomfort, dyspepsia, nausea, non-ulcer gastritis and diabetic gastroparesis[25&26]. It is prescribed as 50 mg dose thrice a day for adult in empty stomach, usually an hour before meal. Chemically, Itopride hydrochloride is N-[P-[2-[dimethyl amino]ethoxyl]benzyl]veratramide hydro-chloride as depicted below[24&27].



In the current study, various controlled release formulations of highly soluble drug, Itopride HCl were prepared using different polymers (HPMC K4M and K100M, ethylcellulose EC-10 cps and Kollidon® SR), to study the influence of concentration and viscosity grade on the release profile.

MATERIAL AND METHODS

Materials

Itopride hydrochloride (ITP) was kindly gifted by Abbott Laboratories (Pakistan) Limited. Hydroxypropyl methylcellulose (HPMC-K4M, K100M) and ethylcellulose (EC-10 cps) were purchased from Colorcon Limited (Kent, England). Kollidon® SR was provided by BASF (Ludwigshafen, Germany). Microcrystalline cellulose (MCC, Avicel pH 101) was procured from Dow Chemical Company (USA). Talc was purchased from the BDH Laboratories Suppliers, England. Magnesium stearate was provided by FMC Corporation, USA. All other materials used were analytical grades.

Methods

Preparation of extended release matrix tablet formulations

Matrix tablets formulations of ITP were designed and formulated using hydroxypropyl methylcellulose (HPMC-K4M, K100M), ethylcellulose (EC-10cps) and Kollidon® SR by direct compression technique. The amount of ITP in each tablet formulation was kept constant (150 mg), as available in the market, whereas quantity of different viscosity grades and types of polymers ranges from 20 to 40%. Accurately weighed quantities of drug and excipients were passed through mesh 20 screen for size uniformity. The mixture was transferred in a polybag to mix thoroughly by adding talc (2%) as lubricant and magnesium stearate (2%) as glidant. MCC was used as diluent in all formulations. Final blend was

compressed using single punch machine (TDP-1.5, Sinoped™, China). To investigate the influence of concentration and viscosity grades of polymers on release of Itopride HCl controlled release matrix tablet, all formulations were evaluated for *in-vitro* release. The compositions of Itopride hydrochloride-controlled release formulations are listed in table 1.

Fourier transform infrared spectroscopy (FTIR)

The compatibility between the model drug and polymers was determined in a previous study by Nasiri *et. al.*[28], using Fourier transform infrared spectrophotometer (Nicolet-6700, Thermo Scientific™, USA). Infrared spectra of pure drug and formulations were recorded (OMNICTM Specta Software) over the wave numbers ranging from 4500 to 1000 cm^{-1}.

Characterization of flow properties of powders blends

Flow properties of all powder blends (10 g) were determined. The studied parameters were bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose by using the following formulae[29].

$$\text{Bulk density} = \frac{M}{V_o} \quad (1)$$

$$\text{Tapped density} = \frac{M}{V_f} \quad (2)$$

$$\text{Carr's Index} = \left(\frac{V_o - V_f}{V_o}\right) \times 100 \quad (3)$$

$$\text{Hausner ratio} = \frac{V_o}{V_f} \quad (4)$$

$$\tan(\theta) = \frac{\text{height}}{0.5\,\text{base}} \quad (5)$$

Where, M is the mass of powder samples in gram, V_o is the initial volume of powder in mL, V_f is the final volume of powder samples after tapping in mL and θ is the angle of repose. According to USP, powders show excellent flow properties if Carr's index ≤ 10, Hausner ratio ranges between 1.00-1.11 and angle of repose value lies in between 25-30. Powder blends show good flow properties when the value of Carr's index lies in between 11-15, Hausner ratio 1.12-1.18 and angle of repose values 31-35. Powders with Carr's index in between 16-20, Hausner ratio between 1.19-1.25 and angle of repose value lies between 36-40 shows fair flow. Powder shows poor flow properties if Carr's index 25-31, Hausner ratio ranges between 1.35-1.45 and angle of repose value lies in between 46-56[29].

Evaluation of tablet formulations

Matrix tablets formulations were evaluated using official[29] and un-official methods for quality parameters including weight variation, hardness, thickness, friability and assay. Weight variation of all tablet formulations were assessed by using analytical balance (Sartorius - CP 224S, Germany). Tablets hardness was checked by using Erweka hardness tester (TBH 125, Germany). Normally, to break a tablet, minimum 4 kg of breaking force is required (tablet hardness limit)[30&31]. The degree of compaction was assessed as thickness test and was checked by using digital Vernier Caliper (PT-LT, Pharma Test). The friability test of each tablet formulation was also performed using friabilator (Erweka, Germany), operated for 4 min. at a speed of 25 rotation/min. Friability test was performed by taking initial and final weight of 10 tablets and calculated by using the following formula[32-34].

$$\text{Friability}(\%) = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Initial Weight}} \times 100 \quad (6)$$

The Acceptance criteria specified by UPS for friability test is less than 1% (considered acceptable).

Drug content analysis

Itopride hydrochloride content in each tablet formulation was assessed using UV-Spectrophotometer (UV-1800, Shimadzu, Japan) with the help of reported methods[28,35&36]. Ten compacted ITP tablets of each formulation were randomly selected and crushed into mortar and pestle for their drug content. Take accurately weighed crushed powder equivalent to weight of single tablet (350 mg) and transferred to a 100 mL volumetric flask containing 50 mL of 0.1 N

hydrochloric acid (HCl). Then, the flask was sonicated (Digital Ultrasonic Cleaner-Supersonic X3, Germany) for 10 min and volume was made up with the same solvent. The sample was subjected to analysis after filtration and appropriate dilution to 25 µg/mL and detection was performed at a wavelength of 258 nm using spectrophotometer (Shimadzu UV 1800, Japan)

***In-vitro* drug release studies**

Six (n= 6) tablets from each formulation were transferred to the USP dissolution apparatus – II (Electro Lab ED-2 SAPO). The test was run for up to 12 hrs. The dissolution media used for studies were 900 mL of 0.1 N hydrochloric acid (pH-1.2) and phosphate buffer (pH-6.8), maintained at temperature 37±0.5°C. The paddle speed was kept at 50 rpm. The 5 mL aliquots were drawn at regular time intervals of 1, 2, 4, 6, 8, 10, and 12 hr and were replaced with 5 mL of fresh medium maintained at same temperature. The collected samples were filtered and analyzed after appropriate dilution, using UV spectrophotometer (Shimadzu UV 1800, Japan) at 258 nm. All the release studies were carried out in triplicate and the amount of drug released from the samples was calculated in percentage. Drug release vs time has been shown in figure 1 to figure 4[37&38].

Drug release kinetics studies

Different kinetic models have been proposed for drug release mechanism from immediate and controlled-release dosage forms[39]. The *in-vitro* release data were fitted to various kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas, for interpretation of drug release rate from matrix tablets formulations using DDSolver (an add-in software of MS Excel).

RESULTS AND DISCUSSIONS

Formulation development

In the current study, direct compression technique was employed to formulate itopride hydrochloride matrix tablets by using HPMC (K4M and K100M), ethylcellulose and Kollidon® SR, as illustrated in table 1. All the formulations contained 20-40% of HPMC, EC and Kollidon® SR. The influence of different concentrations and viscosity grades of polymers on to the release of highly water-soluble drug (ITP) was investigated. Use of different grades of hydrophilic and hydrophobic polymer is very common for preparation of controlled release system[35&40]. A non-toxic inert hydrophobic polymer, ethyl cellulose is also extensively used as matrix agent[41]. The main purpose of the controlled release system is to obtain a cost-effective and efficient extended release system to deliver drugs at a constant rate in order to obtain zero order release[42].

Characterization of powder blends

The powder blends were evaluated by calculating the bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose of all formulations (Table 2)[35&43]. These parameters were found within the prescribed limits[29] and no considerable difference was observed between HPMC of different viscosity grade (4000-cps, 100000-cps), EC (10-cps) and Kollidon® SR matrix tablets. The powder blends which comply with USP specification are categorized as Fair to Excellent, were chosen for compression and further studies.

Fourier transform infrared spectroscopy (FTIR)

The drug polymers compatibility studies were carried out in a previous study by Nasiri *et. al.*[28], using FTIR spectroscopy to detect any possible interaction between pure drug with polymers used in the formulations. The recorded infrared spectra of pure drug (ITP) and formulations indicated that no drug-excipients interaction occurred between drug and polymers used in formulations (Fig. 5).

Characterization of tablet formulations

Weight variation test of all formulations of ITP tablets were performed and results were found within the described USP specification of ±5%[29]. Previously, the effects of weight variation on matrix tablet was also explained by Reddy *et al.*, during the development of nicorandil SR matrix tablets[6]. Hardness of all formulations was found satisfactory and the values were observed in the range of 6.23±0.67 – 7.21±0.72 kg (Table 3). The average thickness of all formulations was observed in the ranges of 4.95±0.02 – 5.25±0.01 mm.

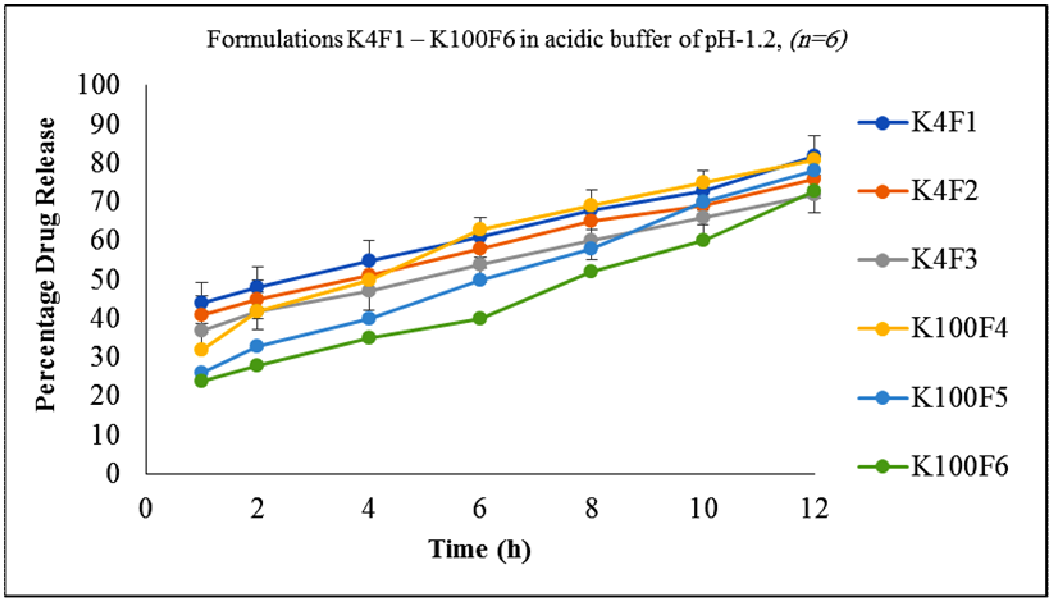


Fig. 1: *In-vitro* drug release profile of formulations K4F1 - K100F6 in acidic buffer of pH-1.2.

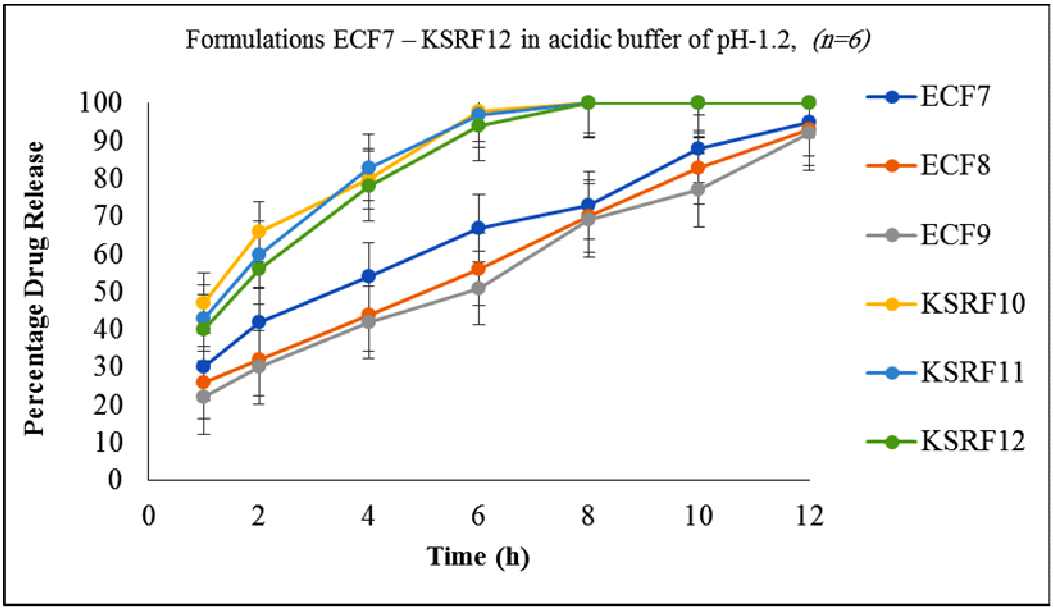


Fig. 2: *In-vitro* drug release profile of formulations ECF7 - KSRF12 in acidic buffer of pH-1.2.

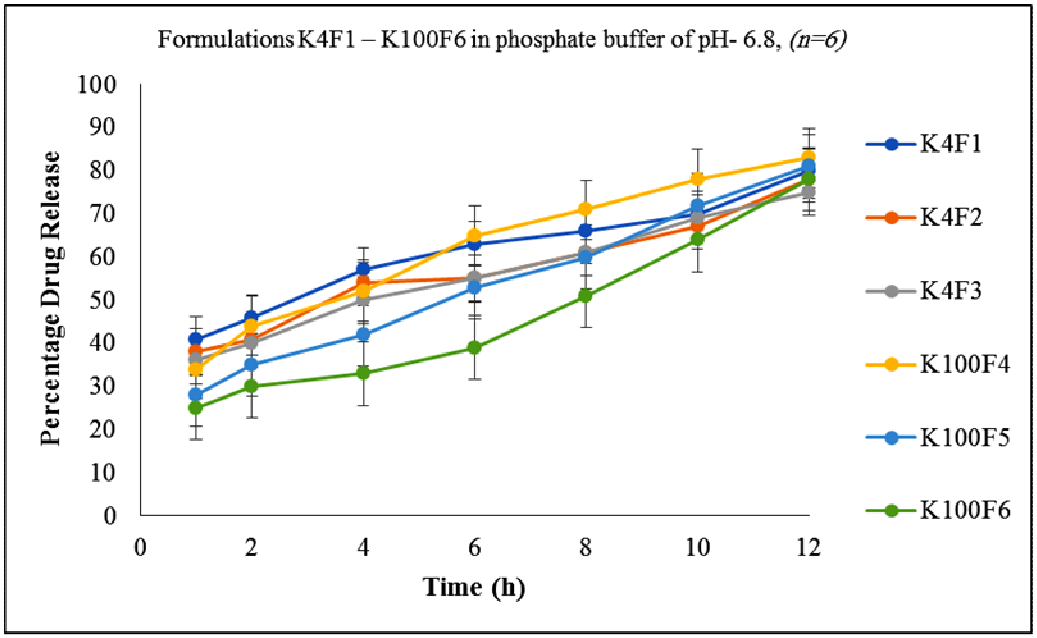


Fig. 3: *In-vitro* drug release profile of formulations K4F1 - K100F6 in phosphate buffer of pH- 6.8.

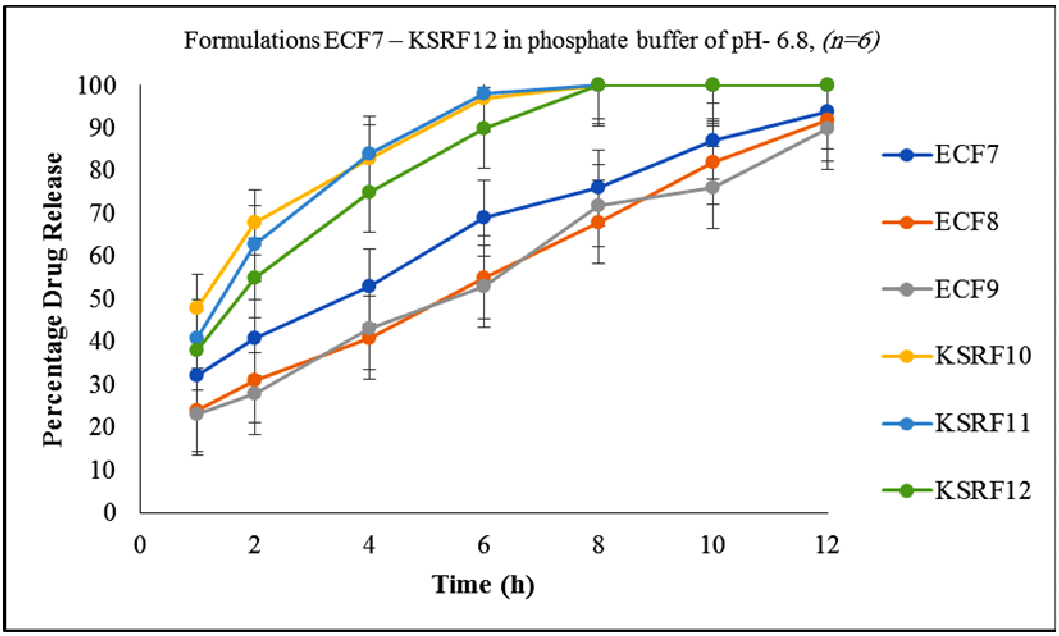


Fig. 4: *In-vitro* drug release profile of formulations ECF7- KSRF12 in phosphate buffer of pH- 6.8.

Table 1: Composition of Itopride HCl controlled release formulations.

Compositions	Formulation codes											
	K4F 1	K4F 2	K4F 3	K100F 4	K100F 5	K100F 6	ECF 7	ECF 8	ECF 9	KSRF 10	KSRF 11	KSRF 12
Drug, ITP (mg)	150	150	150	150	150	150	150	150	150	150	150	150
MCC (mg)	116	81	46	116	81	46	116	81	46	116	81	46
Magnesium stearate (mg)	7	7	7	7	7	7	7	7	7	7	7	7
Talc, (mg)	7	7	7	7	7	7	7	7	7	7	7	7
HPMC - K4M (mg)	70	105	140									
HPMC - K100M (mg)				70	105	140						
EC - 10 cps (mg)							70	105	140			
Kollidon® SR (mg)										70	105	140
Total weight (mg/tablet)	350	350	350	350	350	350	350	350	350	350	350	350

Table 2: Micromeritic characterization of powder blends.

Formulation codes	Angle of Repose (θ^0)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Flow properties according to USP 35
K4F1	32.46	0.55	0.69	20.29	1.25	Good
K4F2	26.43	0.60	0.72	16.17	1.20	Excellent
K4F3	34.56	0.59	0.67	11.94	1.14	Good
K100F4	31.82	0.72	0.87	17.24	1.21	Good
K100F5	28.70	0.52	0.66	21.21	1.27	Excellent
K100F6	34.47	0.57	0.67	14.93	1.18	Good
ECF7	25.54	0.65	0.76	14.47	1.17	Excellent
ECF8	27.45	0.59	0.68	13.24	1.15	Excellent
ECF9	29.43	0.61	0.76	19.74	1.25	Excellent
KSRF10	33.11	0.59	0.73	19.18	1.24	Good
KSRF11	30.65	0.64	0.78	17.95	1.22	Good
KSRF12	29.91	0.71	0.82	13.41	1.15	Excellent

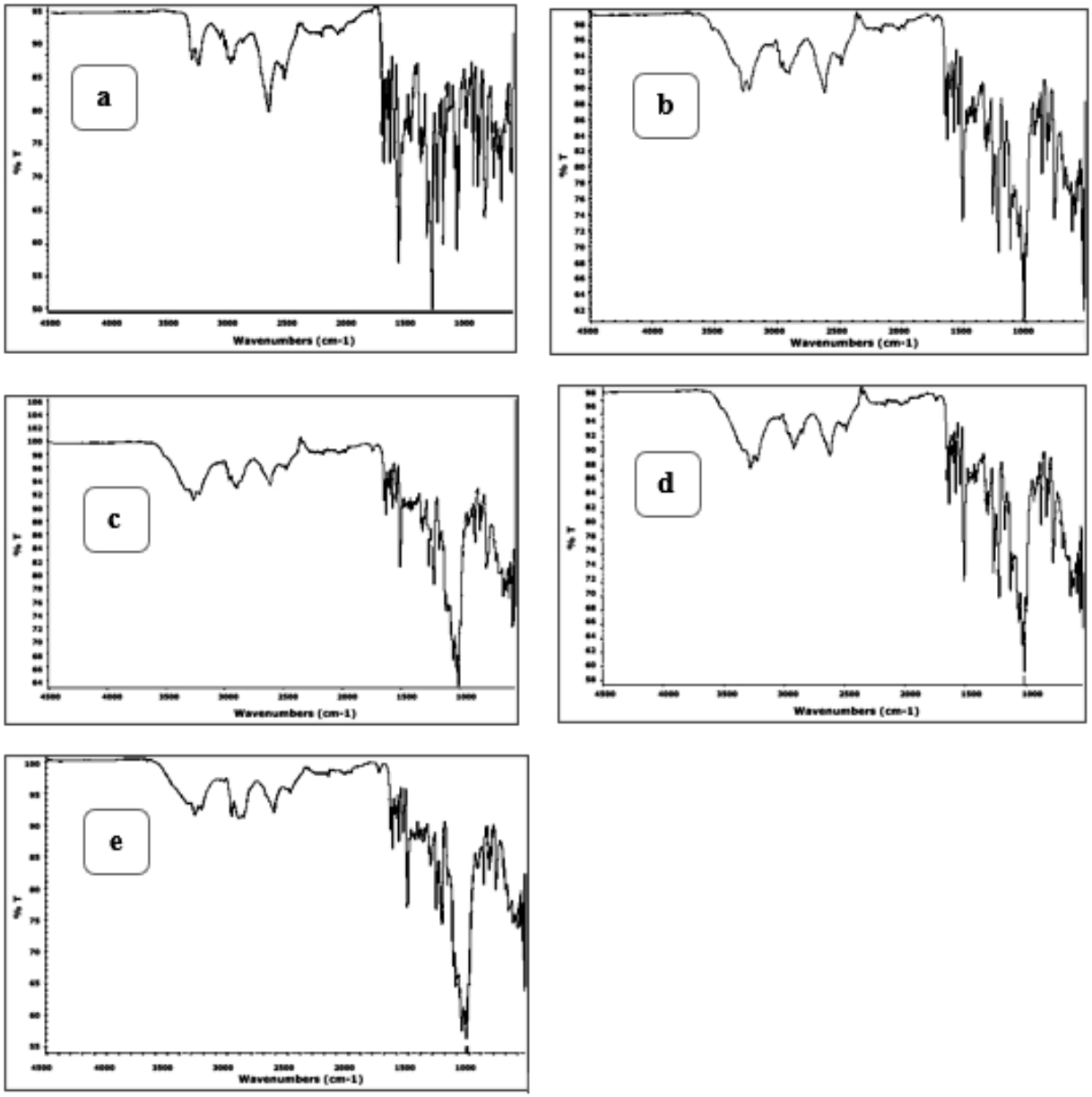


Fig. 5: FTIR spectra of (a) Pure ITP (drug), (b) ITP + HPMC (K4M), (c) ITP + HPMC (K100M), (d) ITP + EC, and (e) ITP + KSR.

Table 3: Physicochemical evaluation of tablet formulations.

Formulation Codes	Physical evaluation				Chemical evaluation
	Weight variation* (mg)	Hardness** (Kg)	Thickness** (mm)	Friability** (%)	Assay (%)
K4F1	334.30 ± 8.51	6.73 ± 0.43	5.22 ± 0.01	0.23	98.06 ± 0.72
K4F2	336.10 ± 7.76	6.81 ± 0.27	4.98 ± 0.01	1.07	98.53 ± 0.73
K4F3	342.05 ± 7.45	6.92 ± 0.32	5.20 ± 0.02	0.81	97.11 ± 0.61
K100F4	343.05 ± 10.1	7.00 ± 0.29	5.15 ± 0.29	0.92	98.21 ± 0.55
K100F5	347.50 ± 8.72	7.20 ± 0.32	4.96 ± 0.09	0.20	97.74 ± 0.62
K100F6	349.40 ± 6.96	6.90 ± 0.47	5.06 ± 0.01	0.11	98.53 ± 0.80
ECF7	348.45 ± 1.35	7.11 ± 0.51	5.12 ± 0.01	0.38	99.01 ± 0.69
ECF8	348.30 ± 1.03	7.00 ± 0.60	5.09 ± 0.01	0.20	99.16 ± 0.45
ECF9	343.65 ± 2.75	7.21± 0.72	5.11 ± 0.04	0.38	99.32 ± 0.54
KSRF10	352.50 ± 9.88	6.23 ± 0.67	4.99 ± 0.04	1.02	99.48 ± 0.83
KSRF11	350.50 ± 11.3	6.55 ± 0.64	5.25 ± 0.01	0.42	99.16 ± 0.48
KSRF12	357.40 ± 15.4	6.44 ± 0.38	4.95 ± 0.02	0.14	99.01 ± 0.68

*n= 20, ** n= 10

Davis explained the effect and co-relation of powder flowability and thickness of tablet[44]. Friability of all formulations were found within the limit of NMT 1%, except formulations K4F2 and KSRF10, which were found out of the limits (> 1%) as mentioned in table 3. Previously, different researchers reported friability results of NMT 1% for itopride matrix tablets[7&21]. Table 3 shows that the percent content of ITP in each formulation was found within the prescribed limit of 97.11±0.61 – 99.48±0.83%, showing uniformity of drug content[21&45].

***In-vitro* drug release studies**

All the matrix tablets formulations of ITP containing HPMC (K4F1-K4F6) and Kollidon SR (KSRF10-KSRF12) exhibited swelling except formulations containing EC (ECF7-ECF9), however, none of the formulation disintegrated during the entire dissolution time period of 12 hr.

Influence of viscosity grade and concentration of HPMC on drug release

The influence of two viscosity grades of HPMC polymers, including K4M (4000cps) and K100M (100000cps) on release of ITP were studied. Figure 1 shows that at 1 hr, 44% drug released by K4F1 (20%K4M), 41% by K4F2 (30% K4M), 37% by K4F3 (40% K4M). The comparison of drug release of K100F4, K100F5, and K100F6 is also shown in figure 1, indicating 32% drug released at 1 hr for K100F4, 26% for K100F5 and 24% for K100F6 containing 20%, 30% and 40% K100M, respectively. Similarly, at 6 hr, 61% drug released by K4F1, 58% by K4F2 and 54% by K4F3, whereas, 82%, 76% and 72% at 12 hr, accordingly. The formulations K100F4, K100F5, and K100F6 released 63%, 50% and 40% drug at 6 hr, while, 81%, 78% and 73% drug released at 12 hr, sequentially. HPMC was used in viscosity range of 4000-100,000 cps in formulations K4F1 to K100F6 (Table 1). There was an inverse relationship between formulations K4F1 to K100F6 in term of cumulative % drug release *vs* time up to 12 hrs. Qazi *et al.*, also observed a similar trend for HPMC concentration and viscosity grade and reported that the viscous gel layer of HPMC increases both the diffusion path length as well as resistance to diffusion[46]. Nevertheless, both the viscosity grades (K4M: 4000 cps & K100M; 100,000-cps) and concentrations (20-40%) retarded the drug release significantly and released up to 80% at 12 hr. This slow release of highly water- soluble drug was due to the slow diffusion of dissolved drug through the hydrophilic gel network.

Influence of ethyl cellulose concentration on drug release

Formulations ECF7-ECF9 were composed of EC (10-cps) in the concentration range of 20-40%. ECF7 (EC-20%), ECF8 (EC-30%) and ECF9 (EC-40%) showed 30%, 26% and 22% drug release at 1 hr, respectively. ECF7 (EC-20%), ECF8 (EC-30%) and ECF9 (EC-40%) released 67%, 56% and 51% drug at 6 hr, whereas, 95%, 93% and 92% drug released at 12 hr, respectively, as shown in figure 2. EC retarded the ITP release up to the desired time period of 12 hrs.

Influence of Kollidon® SR concentration on drug release

Kollidon® SR containing formulations (KSRF10-KSRF12) as polymer in the concentration range of 20-40%, were dissolved completely before the specified time period and thus, the release of drugs up to the desired period of time was not controlled. Formulations KSRF10 (KSR; 20%), KSRF11 (KSR; 30%) and KSRF12 (KSR; 40%) released 47%, 43% and 40% drugs at 1 hr, whereas, maximum drugs (>80%) released at 4 hr (Fig. 2). However, using this polymer in higher percentage ranges might be more effective in retarding the drug release for a longer time. Draganoiu *et. al.,* explained that Kollidon® SR is appropriate polymer for pH-independent extended release matrix tablets[47].

Effect of dissolution medium on drug release

The *in-vitro* drug release profiles of all formulations in acidic buffer (pH 1.2) and phosphate buffer (pH 6.8) are shown in figures 1-4. The drug release profile of all formulations indicated that the release of ITP from matrix tablets containing different polymers was independent of the dissolution media pH. Previously, different literatures also reported pH-independent release profile from HPMC, ethyl cellulose and Kollidon SR containing formulations[28,37&46].

Drug release kinetics

Various kinetic models including, Firs-order, Zero-order, Higuchi, Korsmeyer-Peppas and Weibull model were used to explain the release kinetics from the matrix tablets using MS Excel (DD Solver). Table 4 shows the release kinetic data of all matrix formulations (K4F1-KSRF12). Matrix formulations K4F2 and K100F4 showed linear relationship when applied to First order model (R^2 = 0.990 and

Table 4: Drug release kinetics of formulations in acidic buffer (pH-1.2).

Formula-tions code	First Order		Zero Order		Higuchi		Korsmeyer-peppas			Weibull model		
	r^2	k_1 (hr^{-1})	r^2	k_o (hr^{-1})	r^2	k_H ($hr^{-1/2}$)	r^2	*n*	K_{kp} (hr^{-n})	r^2	A	β
K4F1	0.975	0.087	0.996	3.336	0.988	20.130	0.995	1.048	2.762	0.894	1.984	0.411
K4F2	0.990	0.076	0.996	3.144	0.995	18.994	0.997	0.694	9.864	0.920	2.162	0.399
K4F3	0.989	0.069	0.997	3.123	0.993	18.247	0.997	0.801	6.588	0.922	2.457	0.409
K100F4	0.993	0.112	0.963	4.334	0.991	22.604	0.992	0.421	28.10	0.976	2.853	0.589
K100F5	0.968	0.095	0.996	4.763	0.969	21.145	0.995	1.092	3.409	0.926	4.318	0.684
K100F6	0.934	0.076	0.980	4.317	0.920	18.769	0.993	2.544	0.011	0.877	5.288	0.685
ECF7	0.965	0.166	0.980	5.729	0.990	26.748	0.990	0.572	22.01	0.945	3.330	0.780
ECF8	0.944	0.145	0.999	6.210	0.964	25.655	0.998	0.984	6.528	0.925	5.174	0.912
ECF9	0.941	0.137	0.994	6.239	0.954	24.894	0.992	1.035	5.579	0.930	6.131	0.954
KSRF10	0.952	0.408	0.728	4.527	0.908	28.665	0.942	0.186	66.970	0.970	1.651	0.844
KSRF11	0.982	0.430	0.958	10.661	0.994	39.466	0.998	0.394	49.071	0.975	1.911	0.913
KSRF12	0.982	0.369	0.975	10.644	0.999	38.215	0.999	0.457	41.737	0.973	2.113	0.887

0.993, respectively) indicating concentration-dependent drug release. Nevertheless, formulations K4F3, K100F5 and ECF8 showed concentration-independent drug release as indicated linearity to Zero order kinetics (R^2= 0.997, 0.996 and 0.999, respectively). The *in-vitro* release of all formulations was also best explained by the Higuchi kinetic model with linearity (R^2= 0.908-0.999) indicating drug diffuses at slower rate comparatively as the distance for diffusion increases. When Weibull model was used, all formulations (K4F1-KSRF12) presented linearity (R^2= 0.877-0.976), indicating the amount of drug dissolved from matrix decreases as a function of time, with the progressive dissolution time. A linear relationship was also achieved when the Korsmeyer-peppas model was plotted (R^2= 0.942-0.999). Qazi *et al.*, formulated diltiazem HCl sustained release matrix tablets using HPMC K4M and K100M and reported a highest linearity values (R^2= 0.975-0.997) with Korsmeyer-peppas, followed by Higuchi model (R^2 = 0.918-0.996)[46]. Another study of sustained release tablets of itopride hydrochloride was also analyzed according to kinetic models, and the correlation coefficient (R^2) values in the Korsmeyer-peppas model were higher when compared to the first and zero-order models in all the formulations[45].

Drug release mechanism

The first 60% *in-vitro* release data was plotted in the Korsmeyer-Peppas model, to determine the drug release mechanism[48]. The correlation co-efficient for all formulations were high (R^2= 0.942-0.999) enough to assess the drug release behaviour. The release exponent *(n)* and kinetic rate constant *(k)* are presented in table 4. The release exponent *n* for formulations K4F2, KK4F3, K4F4, ECF7, KSRF10, KSRF11 and KSRF12, were observed in the range of $0.45<n<0.89$, indicating non-Fickian diffusion mechanism, also termed as anomalous transport. Non-fickian diffusion refers to the combination of both diffusion and erosion-controlled rate release. The values of release exponent *(n)* for different formulations (0.513-0.589) reported by Rao *et al.,* showing non-Fickian diffusion[35]. Liu *et al.* also reported a similar type of release mechanism with value of *n* between 0.45 and 0.89 for ethyl cellulose coated pellets[49]. Similarly, for formulations K4F1, K100F5, K100F6, ECF8 and ECF9, the value of release exponent *n* was noted as $n> 0.89$ showing super case -II transport mechanism, which refers to the erosion of the polymeric chain. The release exponent *(n)* was a function of polymer used and the physicochemical property of the drug molecule itself[3]. This finding was also in close agreement with the previous research study for diltiazem HCl SR using HPMC[50].

Conclusion

Based on the findings of the current study, it can be concluded that controlled release matrix formulations of itopride HCl were prepared by direct compression technique. Different polymers were used with varies concentration and viscosity grade. *In-vitro* dissolution profiles of all formulations were evaluated. Drug release kinetics were studied using different kinetic models such as zero order, first order, Higuchi, Korsmeyer-Peppas, and Weibull model, using DD Solver. Formulation K4F3, K100F5 and ECF8 were followed Zero order kinetics and these are considered as best formulations, after application of quality attributes parameters. It became evident from the current studies that directly compressible controlled release ITP tablets can be formulated using hydrophilic and hydrophobic polymers. Thus, HPMC and ethylcellulose were found to be an excellent rate controlling agent for highly water-soluble drug ITP. This study has established that controlled release tablets formulation of ITP can be a good oral alternative formulation for the treatment of gastrointestinal disorders.

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تطوير الصياغة وتقييم أقراص المصفوفة محملة بالعقار منضبطة الانطلاق وعالية الذوبان في الماء

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تم صياغة وتقييم أقراص مصفوفة منضبطةالإنطلاق من عقار هيدروكلوريدايتوبريد باستخدام طريقة الضغط المباشر. تم استخدام بوليمرات مختلفة لتقييم تأثير الأنواع المختلفة (هيدروكسى بروبيل ميثيل سيليلوز وايثيل سيليلوز و Kollidon® SR) والتركيز (٢٠-٤٠٪) ودرجة اللزوجة (هيدروكسى بروبيل ميثيل سيليلوز-٤٠٠٠ سنتى بواز وهيدروكسى بروبيل ميثيل سيليلوز -١٠٠٠٠ سنتى بواز وايثيل سيلولوز-١٠ سنتى بواز و Kollidon SR) على إنطلاق العقار.

تم تصميم اثني عشر صياغة مختلفة للأقراص بكمية ثابتة من العقار في كل صياغة (١٥٠ مجم/ قرص). أجريت دراسات الذوبانية للصياغات في محلول حمضي (ذو أس هيدروجيني ١,٢) ومحلول فوسفات (ذو أس هيدروجيني ٦,٨). تمت دراسة حركيات إنطلاق الدواء من الدرجة الأولى ، والدرة الصفرية ، ونماذج Higuchi و Korsmeyer-Peppas و Weibull باستخدام DD Solver (برنامج إضافي لبرنامج MS Excel). وأن صياغات ECF7 و ECF8 و ECF9 المحتوية على ايثيل السيليلوز (٢٠-٤٠٪) تتحكم بشكل كبير في معدل إطلاق الدواء على مدى فترة ممتدة ل ١٢ ساعة. ومع ذلك ، فإن إنطلاق الدواء من صياغات الأقراص K4F3 و K100F5 و ECF8 ، يتبع الحركية الصفرية مع معامل الانحدار ٠,٩٦٦-٠,٩٩٩. كانت حركية إنطلاق صياغات الأقراص K4F2 و KK4F3 و K4F4 و ECF7 و KSRF10 و KSRF11 و KSRF12 عبارة عن انتشار غير فيكي ، في حين أن حركية الإنطلاق من الصيغ K4F1 و K100F5 و K100F6 و ECF8 و ECF9 كانت حركية نقل فائقة للحالة II. تم استنتاج أن هيدروكسى بروبيل ميثيل سيليلوز وايثيل سيليلوز في نطاق التركيز من ٢٠-٣٠٪ كانا بوليمرات ممتازة للتحكم في انطلاق عقار هيدروكلوريد ايتوبريد.