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RESEARCH PAPER

Preparation and Evaluation of a Sustained Release Formulation of Metoclopramide Hydrochloride HPMC Tablets

Ramesh Narayanasamy and Ramakrishna Shabaraya

ABSTRACT

The objective of the present study was to develop "once daily" sustained release tablets of metoclopramide hydrochloride by direct compression using hydroxypropyl methylcellulose (HPMC). No significant changes in terms of peak shifting, appearance or disappearance of peaks were noted with pure drug, polymers and mixtures. The developed sustained release and marketed immediate release of metoclopramide hydrochloride were appraised for physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability and *in vitro* release study. Developed sustained release tablets of metoclopramide hydrochloride with respect to its physicochemical parameters and drug content are stable at long term storage conditions at 25°C and 60% RH, and accelerated conditions at 40°C and 75% RH for a period of six months. The *in vitro* drug release of Metoclopramide hydrochloride sustained release was compared with the marketed immediate release. The sustained release tablets of metoclopramide hydrochloride were well absorbed and the extent of absorption was higher than that of the marketed tablet. The Cmax and tmax data showed higher for immediate release compared to sustain release formulation. Developed Metoclopramide hydrochloride sustained release tablets demonstrated higher AUC, half-life and lower elimination rate constant values is indicative, that drug leftover in the body for extended period of time and showed signs of prolonged effect. The sustained and efficient drug delivery system developed in the present study will maintain plasma Metoclopramide hydrochloride levels better, which resolve the drawbacks related with the conventional therapy.

Keywords: Metoclopramide Hydrochloride; Sustained release; Once daily, Hydroxypropylmethyl cellulose; Dissolution study; Pharmacokinetic study.

1. INTRODUCTION

Metoclopramide hydrochloride is normally used for the gastrointestinal disorders. Metoclopramide hydrochloride has dopamine antagonist activity. Metoclopramide hydrochloride inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels. Metoclopramide hydrochloride enhances the motility of the stomach, pylorus and small intestine without stimulating gastric, biliary or pancreatic secretions. The gastrointestinal stimulant action is exerted peripherally, not by central stimulation of the vagus nerve, and it is blocked by anticholinergic drugs such as atropine [1-2].

Metoclopramide hydrochloride is commonly used for the treatment of nausea and vomiting. This drug is highly water soluble and is rapidly absorbed after oral administration. It has a short biological half life about 5 hours and is usually administered in a dose of 10 to 15 mg four times daily in order to maintain effective concentrations throughout the day [2]. Hydrophilic polymers are most commonly used in the formulation of

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modified release dosage forms because of their elasticity to obtain enviable drug release profile, cost-effectiveness. HPMC is the foremost choice for formulation of hydrophilic matrix system, providing a robust mechanism, choice of viscosity grades, steady and reproducible release profiles, cost-effectiveness, and utilization of conservative equipments. Various polymers like hydroxypropylmethylcellulose (HPMC), Carbopol, ethylcellulose, carboxymethylcellulose, etc. were tried. Individual grades of HPMC studied consist of methocel K15M and K100M.

Direct compression is a preferred because it offers the simple, most effective and less complex technique to manufacture tablets. The producer can be able to mix together an API with the excipient and the lubricant, followed by compression, which makes the product simple to process. No additional processing steps are required. Rationale in development of sustained release is to control of drug therapy is achieved, rate and extent of drug absorption can be tailored,frequency of dose can be reduced, to improve patient compliance, convenient, maximize the availability of drug with minimum dose and potency drug can be increased.

The developed sustained release and marketed immediate release were appraised for physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability and *in vitro* release study. The *in vitro* drug release of Metoclopramide hydrochloride sustained release tablets was compared with the marketed immediate release tablet. The accelerated and intermediate stability study carried out for optimized formulations as per ICH guidelines]. The bioavailability study performed for marketed immediate release tablets containing 10 mg Metoclopramide hydrochloride and the developed sustained release tablets containing 5 mg Metoclopramide hydrochloride, and compared in terms of rate and extent of absorption.

Peak plasma concentration of Metoclopramide hydrochloride was 1 to 2 hours. And elimination half life was 2.5 to 5 hours. Due to short Cmax and half life drug is suitable for modified release formualtion. The purpose of this study was to develop an Metoclopramide hydrochloride (i.e. slow, medium & fast) sustained release (SR) tablets and to compare bioavailability with commercially available immediate release tablets (IR). *In vitro and in vivo correlation* study will be performed by using data of the in vitro and in vivo drug release.

2. MATERIALS AND METHODS

2.1 Materials

Metoclopramide hydrochloride and cisapride was a gift sample supplied from Adcock Ingram Healthcare Pvt. Ltd. (Bangalore, India). The HPMCK100M offered as a gift sample by Coloron Asia Pvt Ltd. (Goa, India). Avicel, Ethyl cellulose, Meagnesium sterate and talc were procured from local retailer.

2.2 Drug Excipient Compatibility Study

Compatibility between Metoclopramide hydrochloride and excipients were assessed by using differential scanning calorimetric and FTIR spectroscopy. The DSC thermo grams and FTIR spectra of pure drug, individual excipient and drug excipient mixtures were documented [3].

2.3 Preparation of Matrix Tablets[4-8]

Weighed amount of Metoclopramide hydrochloride, polymers (Hydroxypropylmethyl Cellulose [HPMC]/ Ethyl Cellulose [EC]), diluents (Microcrystalline Cellulose (MCC), and mixed by using glass pestle to get uniform mixture. The mixture then blended for 5 minutes with 2% magnesium stearate and 2% talc (E1, E2, E3) and 1% magnesium stearate and 1% talc (E4, E5, E6). Tablets were manufactured by direct compression of such mixtures were done by using Cad mach single punching machine with 10 mm bi-flat round shaped punches. The Metoclopramide hydrochloride sustained release formulation composition are presented in Table 1.

Table 1: Composition of Metoclopramide Hydrochloride Sustained Release Tablets

Formulation	HPMC K100M	Talc (2%)	Magnesium Stearate (2%)	Avicel PH101	Talc (1%)	Magnesium Stearate (1%)	Ethyl cellulose
E1	27.50 mg	1.65 mg	1.65 mg	50 mg	-	-	-
E2	41.25 mg	1.93 mg	1.93 mg	50 mg	-	-	-
E3	55.00 mg	2.20 mg	2.20 mg	50 mg	-	-	-
E4	13.75 mg	-	-	50 mg	0.83 mg	0.83 mg	13.75 mg
E5	20.63 mg	-	-	50 mg	0.96 mg	0.96 mg	20.63 mg
E6	27.50 mg	-	-	50 mg	1.10 mg	1.10 mg	27.50 mg

2.4 Tablet Evaluation

Formulated tablets were assessed for physicochemical properties such as appearance, weight variation, thickness, hardness, friability, drug content [9-10] and *in vitro* studies were carried out by using pH 1.2, 4.5, 5.5, 6.8 and 7.4 (900 ml, 37±0.5 ˚C, 50 & 75 rpm) for 24 h using the USP XXIII basket apparatus (type II, paddle). A minimum of 6 tablets per batch were tested. At predetermined time intervals, 5 ml of samples withdrawn at 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hours, suitably diluted and spectrophotometrically assayed at 309 nm [11-14]. Cumulative percentage of drug release calculated and compared. The percentage of release versus time data was estimated for the drug release kinetics.

2.5 Swelling Index

Optimized sustained release formulations were weighed and placed in a petri plate containing 25 ml of pH 6.4 buffer solution for Metoclopramide hydrochloride. At predetermined time intervals at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 10 hours, the tablets were removed from petri plate and absorbed buffer was removed by using filter paper [15]. The weight of the tablets were recorded after which they were placed in the perti plate for 10 hours. Swelling index calculated by using the following formula.

Swelling Index = (W1 – W2) x 100 (Equation 1)
Where, W1= weight of the polymer (Before swelling)
W2= weight of the polymer (After swelling)

2.6 Stability Study

Optimized Naproxen sodium and Metoclopramide hydrochloride sustained release formulation were packed in HDPE containers and incubated in the stability chamber at 25ºC 60%RH (Long term stability), 40ºC 75%RH (Accelerated stability) for stability studies. Samples were pulled from stability chamber at 1, 2, 3, 6 months intervals and evaluated for their physical properties like appearance, weight variation, thickness, hardness and drug content [16].

2.7 Release Kinetics

To know the mechanism of drug release for optimized formulation, the data were plotted according to zero-order, first-order, Higuchi and Peppas equations to understand the mechanism of drug release and and to compare the differences in the release profile of optimized Metoclopramide hydrochloride sustained release.

2.8 In Vivo Bioavailability Study

The relative bioavailability of the developed Metoclopramide hydrochloride sustained release tablets and the marketed immediate release were assessed in a 6 subjects. The inclusion and exclusion criteria applied to all subjects, before admission, information on the study will be provided to the subjects, subjects are required to give their consent by signing informed consent form prior to participating in the study. All subjects were required to fast overnight for at least 10 hours before dosing and for four hours after dosing. Six subjects were administered the developed Metoclopramide hydrochloride sustained release formulation (i.e. fast, medium & slow) and the marketed formulation with water. Subjects were not permitted to drink any fluids for one hour before dosing and until two hours post dose administration. The subjects were to remain ambulatory or seated upright for the first 2 hours after the study medication administered pre-dose sample will be taken within one hour prior to dosing. After dosing, samples will be taken at the following intervals 0.0, 0.33, 0.67, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 10, 12, 16, 18 and 24 hours post-dose [19]. Total 64 blood samples, so the total volume of blood drawn not exceeded 240 mL. After the 24 hour blood sample, the subjects are allowed to leave the facility. A washout period of at least 07 days, the procedure will be repeated. A high performance liquid chromatography mass spectrometric method for the estimation of Metoclopramide hydrochloride in human plasma was developed and validated by using cisapride as an internal standard. Sample preparation was done by using liquid-liquid extraction method. Chromatographic separation attained on a Eclipse XDB C18 (100 mm x 4.6 mm, 3.5 µm) column by using a mobile phase of methanol and ammonium acetate buffer 5 mM (50:50 v/v). The flow rate was 1 mL/min and injection volume of 10 mL and run time was 3 minutes. The RT of analyte (Metoclopramide Hydrochloride) and internal standard was 1.1 and 2.1 minutes. The method was validated over a concentration range of 0.532 ng/mL to 201.005 ng /mL for Metoclopramide hydrochloride. The plasma samples were analysed by using optimised chromatographic conditions [17-19].

3. RESULTS

Precompression parameter plays a vital role in the preparation and optimization of tablets. The sustained release tablets were prepared by direct compression method. Pre-compression studies such as determinations of density, angle of repose, Carr's index, Hausner's ratio and effect of different concentrations of talc and magnesium stearate on the flow properties were performed. Carr's Index (%) was found in the range of 13.31 to 14.91, Hausner's Ratio was in the range of 1.15 to 1.17 for the all the formulation indicates the good flow property (C.I (%) 11 – 15 and Hausner's Ratio 1.12 – 1.18) and (angle of repose < 25). This indicates flow properties of the powder blend was within the acceptable limits. The granules of different formulations were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), and Carr`s index tabulated as shown in Table 2.

No significant changes in terms of peak shifting, appearance or disappearance of peaks were noted with pure drug, polymers and mixtures. The result revealed that there was no appreciable change in the melting endothermic peak of Metoclopramide hydrochloride in the presence of all the ingredients of sustained release formulation (185.53 ^{o}C). The results indicate the absence of any chemical interactions between Metoclopramide hydrochloride and the excipients used. DSC thermo grams are presented as in Fig 1 A & B.

Table 2: Precompression Powder Properties of the Different Formulations of Metoclopramide Hydrochloride

Formulation	LBD (g/ml)	TBD (g/ml)	Angle of Repose	Carr's Index (%)	Hausner's Ratio
Metoclopramide hydrochloride	0.52	0.71	35.97	26.77	1.36
E1	0.35	0.41	24.01	13.31	1.15
E2	0.37	0.43	22.16	14.91	1.17
E3	0.36	0.43	22.56	14.52	1.17
E4	0.37	0.43	23.23	14.14	1.16
E5	0.37	0.43	22.56	14.76	1.17
E6	0.36	0.42	23.46	14.12	1.16

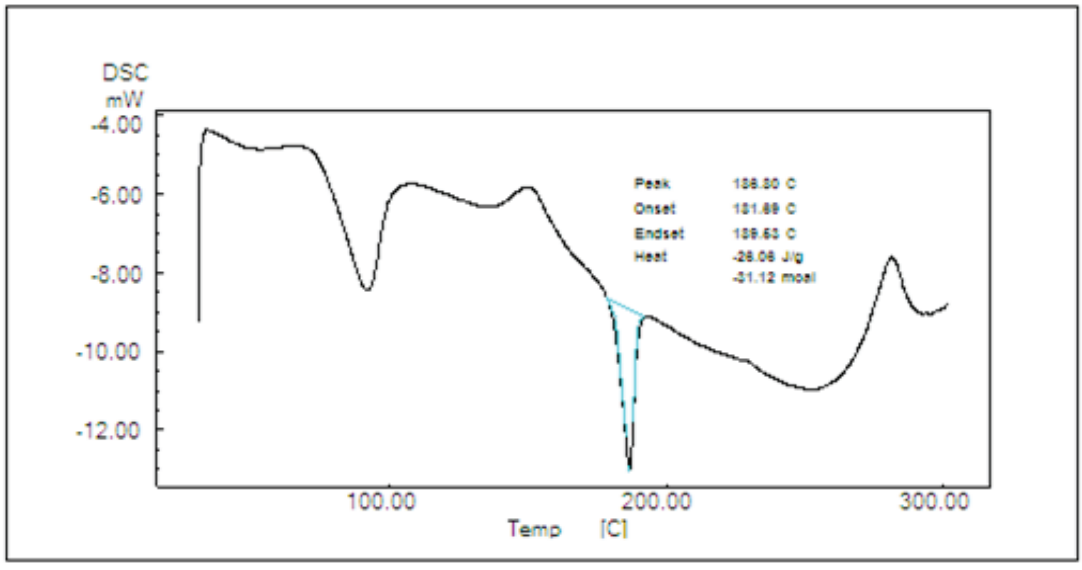

Fig. 1 A. DSC Thermogram of Pure Metoclopramide Hydrochloride

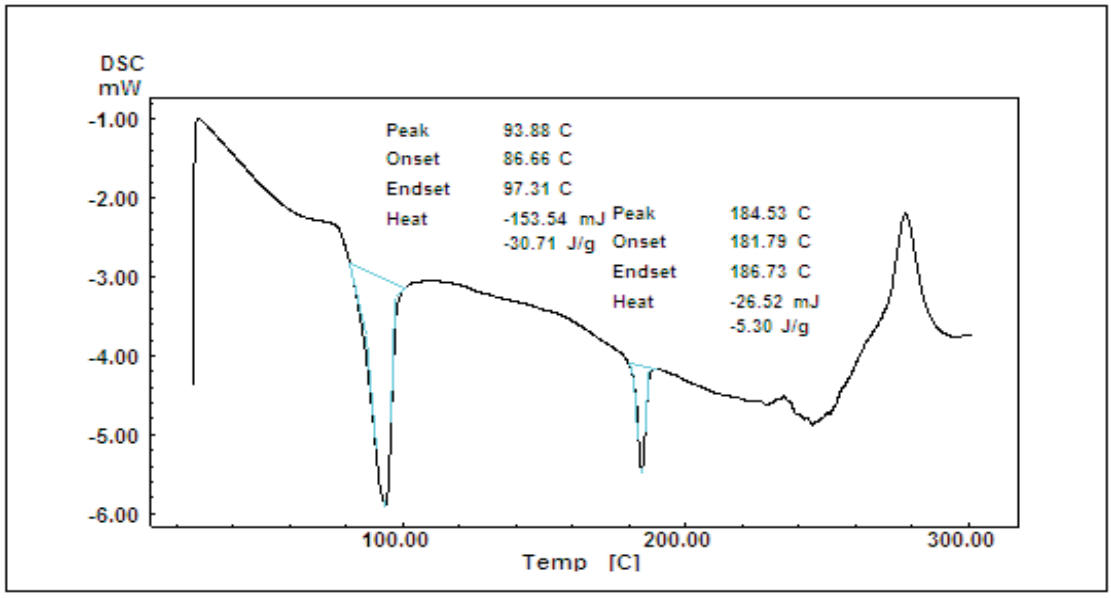

Fig. 1 B. DSC Thermogram of Metoclopramide Hydrochloride and Excipients

The characteristic bands of Metoclopramide hydrochloride were appeared in FTIR spectrum without any changes. The spectrum indicated as there is no chemical interaction between Metoclopramide hydrochloride and excipients. The spectrum clearly showed the functional groups bands which are related to Metoclopramide hydrochloride. The major band observed in 3396 cm-1 (N-H stretching), 2941 cm-1 (C-H stretching),1632 cm-1 (C=O stretching),1539 cm-1 (N-H bending).679 C-Cl. No significant changes in terms of peak shifting, appearance or disappearance of peaks were noted with the drug and excipients. The IR spectra as in (Fig 2 A& 2B).

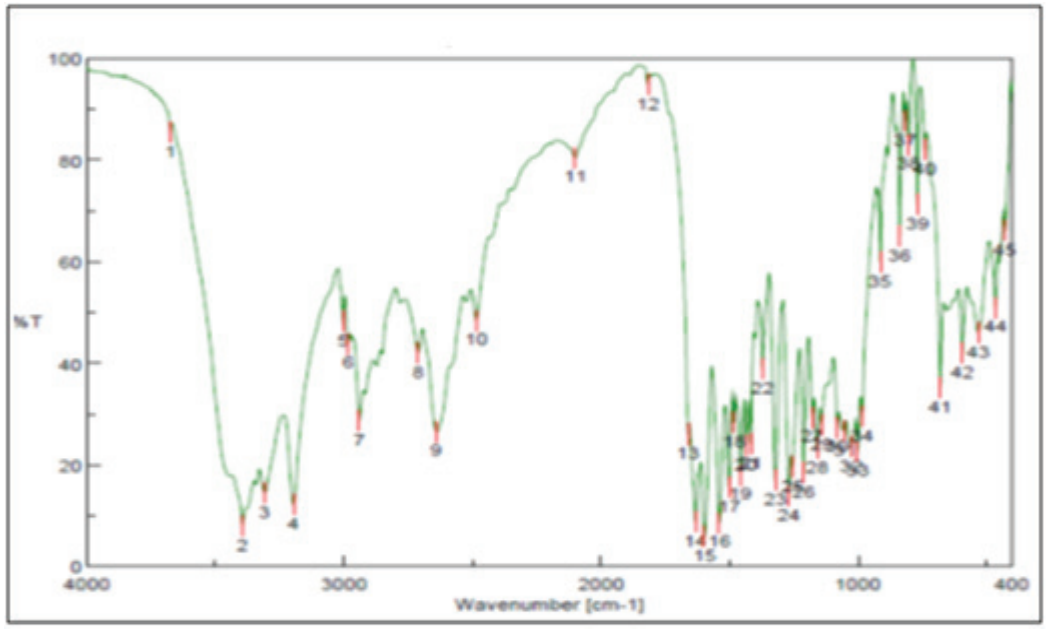

Fig. 2 A. FTIR Spectrum of Pure Metoclopramide Hydrochloride

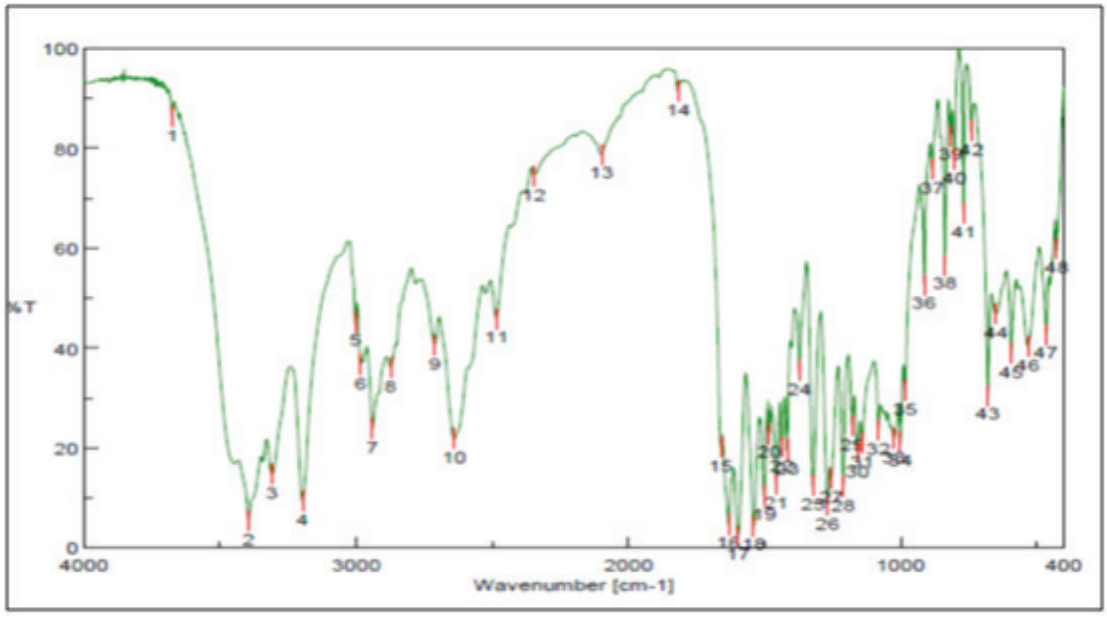

Fig. 2 B. FTIR Spectrum of Metoclopramide Hydrochloride and Excipients

3.1 Evaluation of Physicochemical Properties of Metoclopramide Hydrochloride Tablets

Twenty (20) tablets were individually weighed in grams (gm) by using analytical balance. The average weight deviation of 20 tablet of each formula for Metoclorpamide hydrochloride was ± 1.054% which falls within the acceptable weight variation range of ± 5%. and and none deviated more than ±10%[11]. Hence all the tablets were with in the limit for weight variation test. The thickness in millimeters (mm) was measured individually by using a vernier caliper and Thickness for the tablets was in the range of 3.15 to 4.23 and showed little variation between the formulations manufactured. Tablet hardness was measured by using a Dr. Schridnger (model 8M) hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded and reported. Hardness for tablets was in the range of 4.03-5.20 which falls above the limit of not less than 3.0 kg/cm2. Twenty (20) tablets were selected from each batch and weighed and tablets were rotated at 25 rpm for 4 minutes (100 rotations) in the friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets. Friability values of all the batches are less than 1%. The drug content for all the formulations were found in the range of 96-102.45% found to be more than 90%.

3.2 In Vitro Drug Release Study

In vitro drug release study performed in multimedia dissolution to mimic the in-vivo condition. pH/buffer selection based on the exposure of drug from stomach to intestine/colon and to ensure the impact of pH changes on dissolution and release of drug substance for absorption (14-16). The *in vitro* drug release studies were conducted at different pH conditions (namely pH 1.2, 4.5, 5.5, 6.8, 7.4) at two different rpm i.e. 50 & 75 rpm to check the release and to select the optimize pH condition for the drug ().

Table 3: Physicochemical Evaluation of Compressed Tablets Containing Metoclopramide Hydrochloride

Formulations	Hardness (kg/cm^2)	Weight Variation (gm)	Thickness (mm)	Friability (%)
E1	4.03	105.23 ± 2.36	3.15	<1%
E2	4.23	107.66 ± 1.16	3.46	<1%
E3	4.63	82.04 ± 4.57	3.89	<1%
E4	5.07	98.88 ± 1.80	3.17	<1%
E5	5.20	113.90 ± 1.05	3.56	<1%
E6	4.97	85.11 ± 0.671	4.23	<1%

At pH 1.2 and 50 rpm, drug release was partial and a highest of about 31.98% was released within 24 hours for all the formulation. At pH 4.5, the drug release was very sluggish and 85.64% was released over the period of 24 hours. At pH 5.5, about 94.50-99.23% of drug release observed and it was identical and slow within 24 hours. At pH 6.8 and 7.4 with 50 rpm, although about 91.08-95.21% and 89.57-90.47% release of drug was observed. Hence pH 5.5 was optimized for all the developed formulations. The *in vitro* drug release profiles were not much changed when the rpm was increased to 50 from 75. Based on the in vitro dissolution studies of E1 to E6 sustained release formulations in pH 5.5 and 50 rpm E2, E4 and E5 were considered as slow, medium and fast rate releasing formulations. The cumulative percentage of drug release are presented in Table. 4 and Fig. 3.

Table 4: Cumulative Percentage of Metoclopramide Hydrochloride Sustained Release and Marketed Release Tablet

	Slow (E2)		Medium (E4)		Fast (E5)		Marketed (Drug Reference)	
Time	% Release	% Cumulative Release	% Release	% Cumulative Release	% Release	% Cumulative Release	% Release	% Cumulative Release
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	12.60	12.60	15.40	15.40	19.20	19.20	75.69	75.69
1.00	17.70	17.77	20.50	20.59	24.20	24.31	82.96	83.38
1.50	26.10	26.20	31.70	31.81	34.30	34.43	92.98	93.44
2.00	32.90	33.05	38.50	38.68	42.60	42.79	97.78	98.30
2.50	39.60	39.78	49.70	49.91	53.50	53.74	98.76	99.30
3.00	48.00	48.22	57.40	57.68	61.00	61.30	99.65	100.20
4.00	53.90	54.17	63.40	63.72	67.70	68.04	99.82	100.37
6.00	58.10	58.40	69.30	69.65	76.10	76.48	99.90	100.45
8.00	66.50	66.82	76.20	76.59	79.40	79.82	100.01	100.57
10.00	73.30	73.67	80.50	80.92	85.20	85.64	100.05	100.61
12.00	78.30	78.71	86.50	86.95	89.40	89.87	100.06	100.62
18.00	85.10	85.54	92.50	92.98	95.30	95.80	100.18	100.74
24.00	91.80	92.27	95.00	95.51	98.60	99.13	100.21	100.77

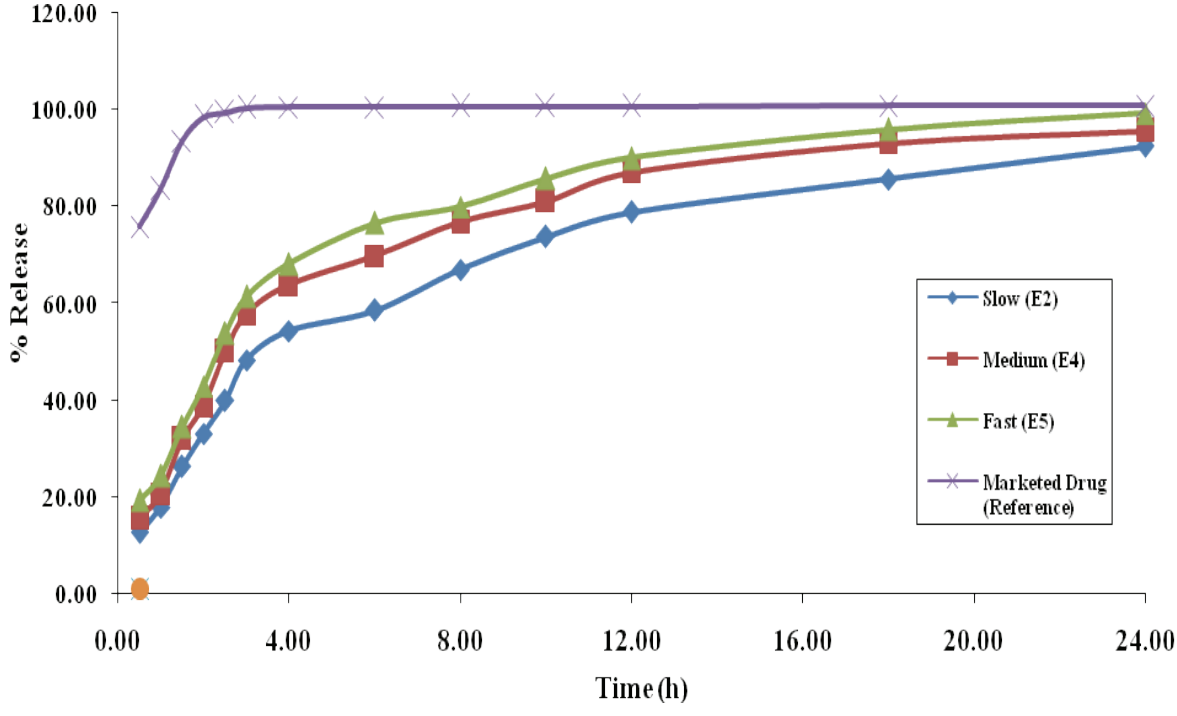

Fig. 3. Cumulative Percentage of Metoclopramide Hydrochloride Sustained Release and Marketed Release Tablet

3.3 Release Kinetics

The release kinetics of optimized Metoclopramide hydrochloride sustained release tablets are presented in the Table. 5 and graphical representation as mentioned in the Fig. 4 A, 4 B, 4 C & 4D.

Table 5: Release Kinetics of Optimized Metoclopramide Hydrochloride Sustained Release tablets (slow, medium & fast)

	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
Formulation	r^2	Ko (h^{-1})	r^2	K1 (h^{-1})	r^2	KH ($h^{-1/2}$)	r^2	Slope (n)
E2 (Slow)	0.8075	3.2357	0.6026	0.0669	0.9391	19.511	0.9463	0.5212
E4 (Medium)	0.7301	3.2061	0.5465	0.0601	0.8877	19.694	0.9159	0.4837
E5 (Fast)	0.7168	3.1824	0.5545	0.0552	0.878	19.768	0.9200	0.4426

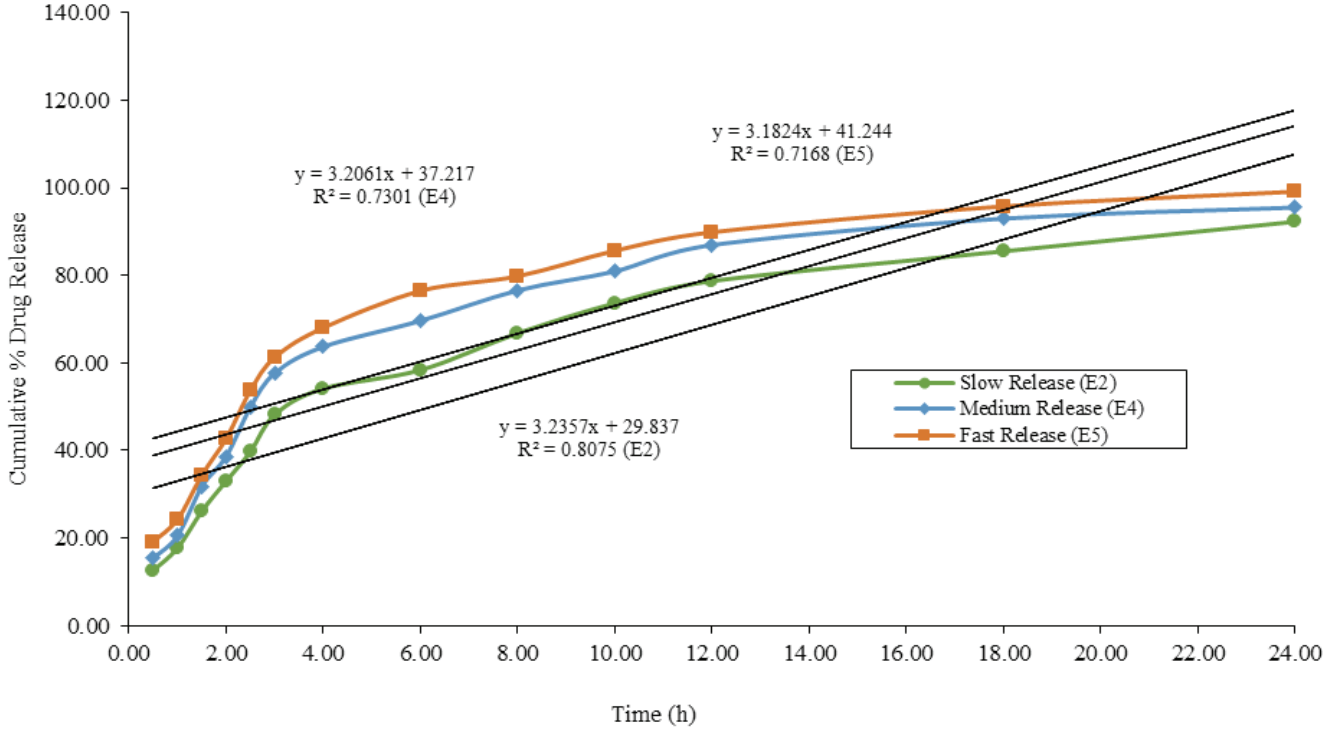

Fig. 4 A. Zero Order Release Profile of Metoclopramide Hydrochloride Sustained Release Tablets (slow, medium & fast)

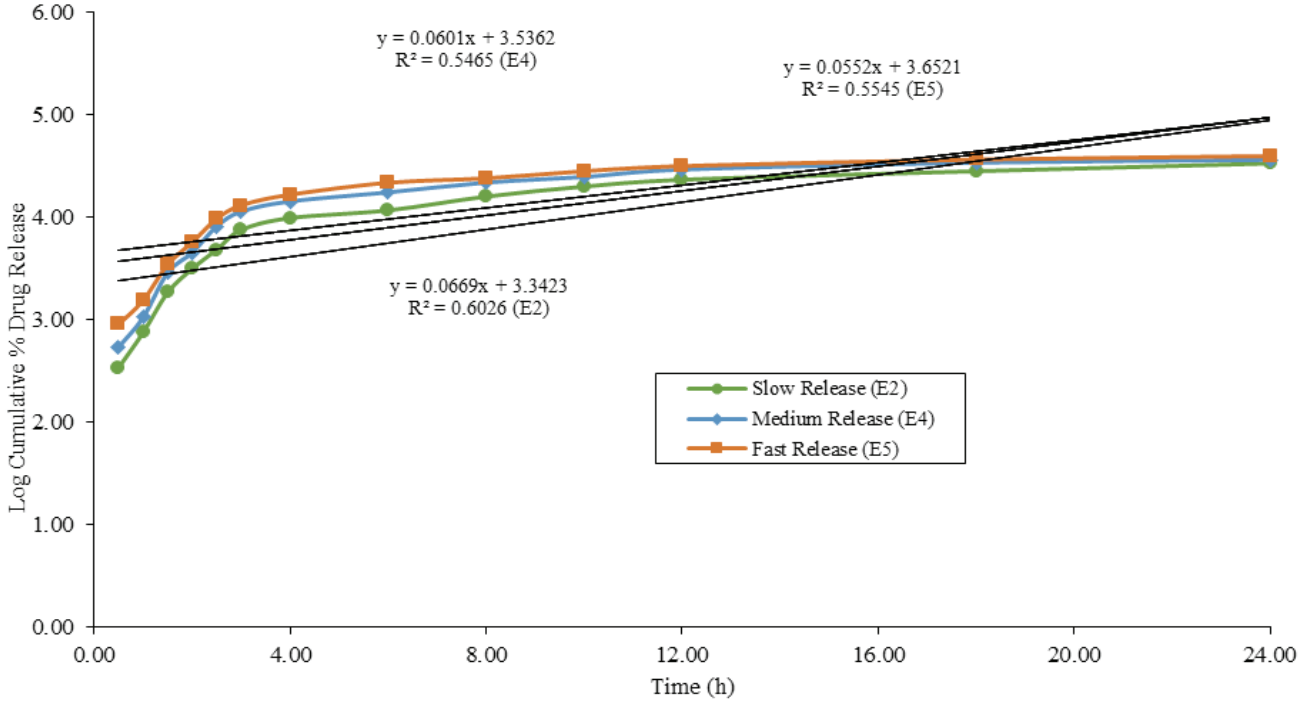

Fig. 4 B. First Order Release Profile of Metoclopramide hydrochloride Sustained Release Tablets (slow, medium & fast)

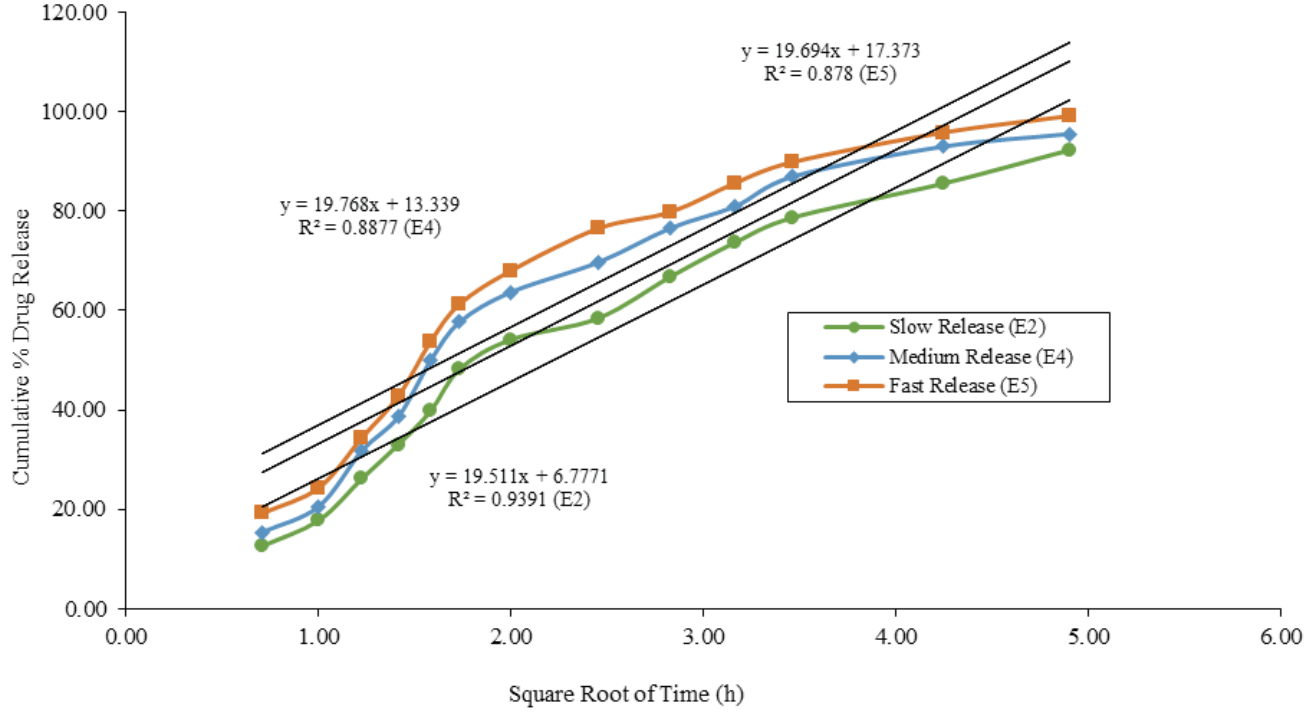

Fig. 4 C. Higuchi Kinetics Release Profile of Metoclopramide Hydrochloride Sustained Release Tablets (slow, medium & fast)

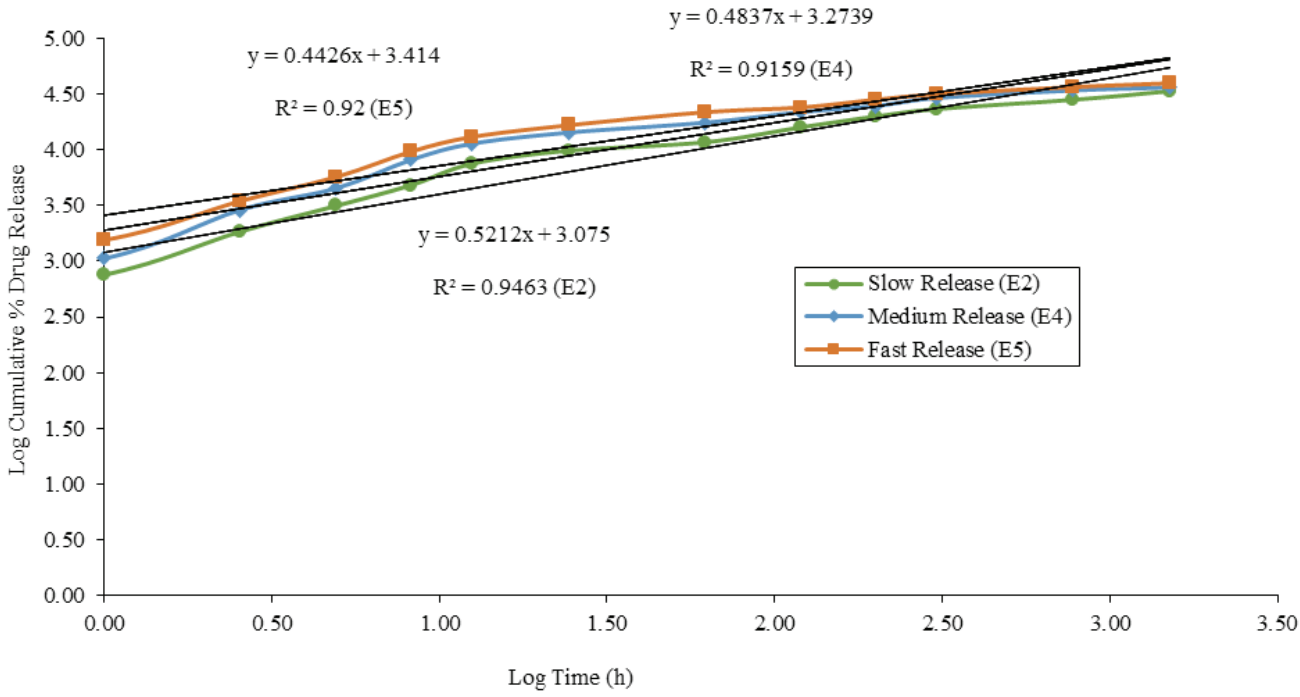

Fig. 4 D. Korsmeyer-Peppas Kinetics Release Profile of Metoclopramide Hydrochloride Sustained Release Tablets (slow, medium & fast)

3.4 Stability Study

No significant change were observed for the developed sustained release tablets of Metoclopramide hydrochloride with respect to its physicochemical parameters as evident developed Metoclopramide hydrochloride sustained release tablets are stable at long term storage conditions at 25°C and 60% RH, and accelerated conditions at 40°C and 75% RH for a period of six months.

3.5 Swelling Index

The swelling index calculated with respect to time and weight. As time increases, the swelling index increased, because weight gain by tablet increased proportionally with rate of hydration up to 10 hrs for all Metoclopramide hydrochloride SR tablets (i.e. E2 Slow release, E4 Medium release & E5 Fast release).

3.6 Bioavailability Study

The plasma concentration values obtained were calculated for pharmacokinetic parameters like Cmax, Tmax and AUC(0-∞) by using Phoenix 6.4.0 version software. The Cmax and Tmax data showed higher for immediate release compare to sustain release formulation. The mean pharmacokinetic parameters for developed sustained release and marketed immediate release are summarized in Table 6 and graphical representation as in Fig. 5.

Table 6: Mean Pharmacokinetic Parameter of Metoclopramide Hydrochloride for Marketed Immediate Release and Sustained Release Tablet (fast, medium & slow)

Formulation	Tmax (hr)	Cmax (ug/mL)	AUC(0-∞) (hr*ug/mL)
Immediate Release Tablet	1.11	49.06	273.694
Fast Sustained Release Tablet	0.89	48.433	214.506
Medium Sustained Release Tablet	0.89	48.004	238.671
Slow Sustained Release Tablet	1.002	48.366	230.834

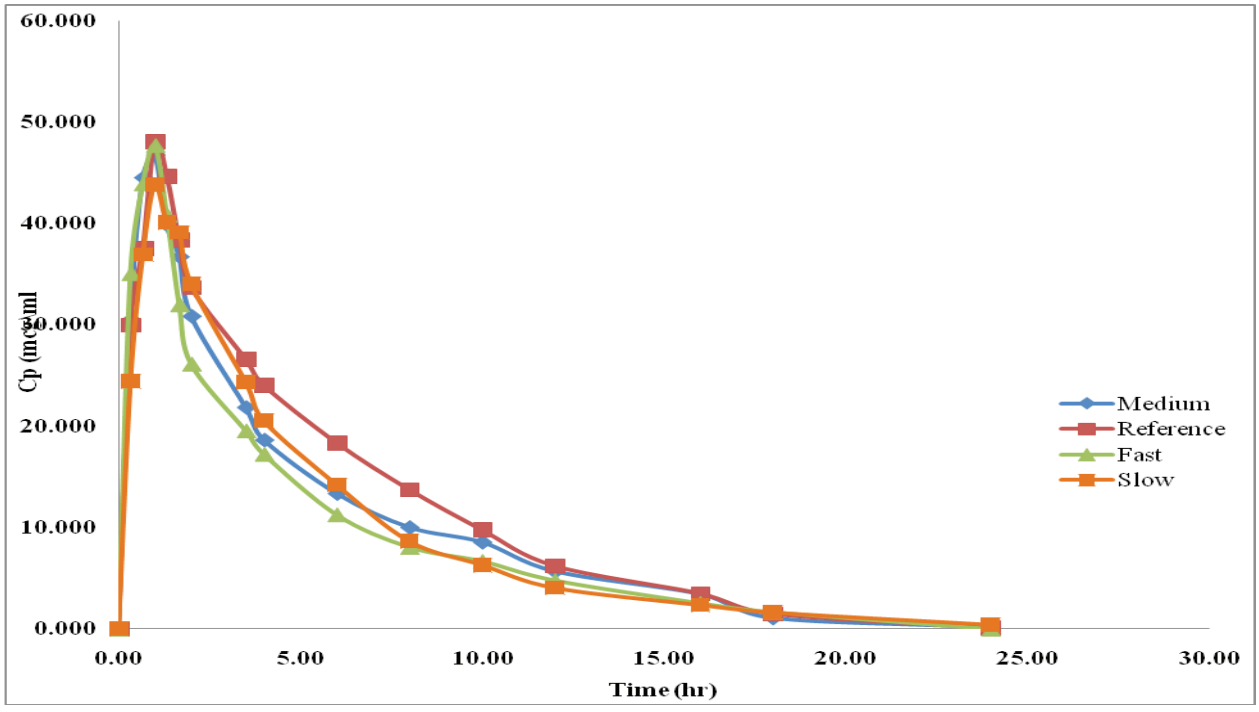

Fig 5: Mean Plasma Concentration-Time Profile of Metoclopramide Hydrochloride Immediate Release and Sustained Release (Slow, Medium, Fast) tablet

4. DISCUSSION

The individual excipients did not show any characteristic peaks. The powder flow properties were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), and Car r`s Hausner's ratio index. The good flow property (C.I (%) 11 – 15 and Hausner's Ratio 1.12 – 1.18) and (angle of repose < 25) were selected and used for the formulation. Weight variation of tablets fond with in the pharmacopeial limit. Thickness for the tablets demonstrated minor variation between the each batch of tablet. Hardness of the tablets were within the acceptance limit. Friability found less than 1% and drug content for the formulation were more than 90%. The *in vitro* drug release studies performed as per the USP method i.e. pH 6.8 pH condition at 50 rpm for developed sustained release and marketed immediate release formulation. The formulation with HPMC showed that an increase in polymer: drug ratio reduced the release rate. This was due to increase in polymer concentration caused an enlarge in the viscosity of the gel as well as the formation of a gel layer with a longer diffusion path. Drug release was found to follow Higuchi kinetics and slope (n) value obtained with all formulations ranged between 0.4426–0.5212. Since the slope values are near to 0.5, the dominant mechanism for drug release is Fickian diffusion. The slope values obtained with Koresmeyer-Peppas equation also appears to indicate a coupling of the diffusion and erosion mechanism-so-called inconsistent distribution and possibly indicates that the drug release is controlled by more than one method. The developed Metoclopramide hydrochloride sustained release tablets are stable at long term storage conditions at 25°C and 60% RH, and accelerated conditions at 40°C and 75% RH for a period of six months. The direct relationship was observed between swelling index and polymer concentration, and as polymer concentration increases, swelling index was increased. In vitro dissolution profiles of Metoclopramide hydrochloride showed a fast release compared to sustained release formulation. The developed tablets produced a higher AUC than the marketed immediate release product. Developed sustained release demonstrated high half-life and low elimination rate constant values is indicative, that drug leftover in the body for extended period of time and showed signs of prolonged effect. The prolonged effect of drug was further sustained by elevated values of mean residential time (MRT). Compared to previous study (Sayed IAR *et al*., 2009, Hasan EI *et al*., 2003) Metoclorpamide hydrochloride sustained release and immediate release tablet was compared by performing *in vitro and in vivo*

correlation study to support biowaivers in cse of alteration in composition, equipments, batch sizes and manufacturing process.

5. CONCLUSION

The present study made successful preparation of once daily Metoclopramide hydrochloride sustained release matrix tablets. The optimized formulation was found to be stable at all the stability conditions. The developed formulation had superior bioavailability compared to the marketed formulation. The sustained release tablets of Metoclopramide hydrochloride were well absorbed and the extent of absorption was higher than that of the marketed tablet. The sustained and efficient drug delivery system developed in the present study will maintain plasma Metoclopramide hydrochloride levels better, which resolve the drawbacks related with the conventional therapy.

are required to confirm the results of present study.

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Metoklopramit Hidroklorür Hpmc Tabletlerinin Sürekli Salım Özelliği Gösteren Formülasyonlarını Hazırlanması ve Değerlendirilmesi

ÖZ

Bu çalışmanın amacı, hidroksipropil metilselüloz (HPMC) kullanılarak direkt basım yöntemi ile metoklopramid hidroklorür'ün "günde bir kez" kullanımı amacıyla sürekli salım özelliği gösteren tabletlerini geliştirmektir. Saf ilaç etken maddesi, polimerler ve karışımlar incelendiğinde pik kayması, piklerin varlığı veya kaybolması bakımından belirgin bir değişiklik kaydedilmedi. Metoklopramid hidroklorür içeren sürekli salınımı ve klinik kullanıma sunulmuş olan hemen salım özelliğine sahip tabletler, görünüş, ağırlık değişimi, kalınlık, sertlik, kırılganlık ve *in vitro* serbest salım gibi fiziko-kimyasal parametreler açısından değerlendirildi. Metoklopramid hidroklorür'ün sürekli salım özelliği gösteren tabletlerinin fizikokimyasal özellikleri ve ilaç içerikleri dikkate alındığında 25^{0}C'de ve %60 bağıl nem (RH) koşullarında ve 40°C'de ve %75 RH şartlarını içeren uzun süreli, hızlandırılmış altı aylık saklama koşullarında kararlıdır. Metoklopramid hidroklorür'ün sürekli salım tabletlerinden *in vitro* ilaç salınımı, piyasaya sürülmüş olan derhal salım özellikli tabletler ile karşılaştırıldı. Metoklopramid hidroklorür'ün sürekli salım tabletlerinin çok iyi emildiği ve emilim oranının pazarlanan tabletinkinden daha yüksek olduğu belirlendi. Sürekli salım formülasyonuna kıyasla Cmax ve tmax verileri derhal salım tabletleri için daha yüksek bulundu. Geliştirilen metoklopramid hidroklorür sürekli salınma tabletlerinin, yüksek AUC, yarılanma ömrü ve daha düşük eliminasyon hız sabiti değerleri göstermesi ilacın uzun süre vücutta kaldığını ve uzamış etki belirtileri gösterdiğini düşündürdü. Bu çalışmada, geliştirilen sürekli salım özellikli ilaç verme sisteminin, plazma metoklopramid hidroklorür düzeylerinin sağlanmasında daha iyi sonuç vereceği ve bu durumun da geleneksel tedavi ile ilgili sorunları ortadan kaldıracağı önerilmektedir.

Anahtar kelimeler: Metoklopramid hidroklorür; Sürekli salım; Günde bir kez, Hidroksipropilmetil selüloz; Dissolüsyon çalışması; Farmakokinetik çalışma.

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