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RESEARCH ARTICLE

Once daily controlled release matrix tablet of Prochlorperazine maleate: Influence of Ethocel® and/or Methocel® on *in vitro* drug release and bioavailability

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Abstract

Context: Controlled release (CR) matrix tablet of Prochlorperazine maleate was developed to improve its patient compliance.

Methods: Tablet formulations F1, F2 and F3 based on different concentrations of Methocel® K100 LV-CR Premium, were compacted by direct compression method while tablet formulations F4, F5 and F6, based on distinct blends of Methocel® K100 LV-CR Premium and Ethocel® Standard 7FP Premium, were compressed by flow-bound dry granulation-slugging method. The prepared powder mixtures, granules and tablets were evaluated for their physicochemical performance. Bioequivalence study of the optimized test tablet versus reference-conventional Stemitil® tablet was conducted on rabbits, using HPLC-UV system at λ_{max} 254 nm.

Results: The test tablet, containing 28% Methocel® and 58% Ethocel® (F6) exhibited desired zero order kinetics for 24 h and was found stable at accelerated storage conditions for 6 months. *In vitro* drug release rate decreased as the Ethocel® content in the blend was increased, perhaps due to slower penetrability of water. Hydrodynamic conditions and hardness of tablets could not affect drug release kinetics. The tablet displayed significantly ($p < 0.05$) optimized peak drug concentration-C_{max} (45 ± 3.42 vs. 64.5 ± 4.03), extended half life-$t_{1/2}$ (16.071 ± 3.97 vs. 5.257 ± 1.314 h) and bioequivalence to the reference tablet taken three times a day (1409 ± 15 ng·h/mL vs. 1346 ± 23 ng h/mL). The tablet showed strong Level A correlation ($R^2 = 0.8458$) between drug absorbed *in vivo* and drug released *in vitro*.

Conclusions: The developed tablet may be adopted by pharmaceutical industry to improve patient compliance of the Prochlorperazine maleate.

Keywords: Dry granulation-slugging method, bioequivalence, *in vivo-in vitro* correlation, Prochlorperazine, polymers

Introduction

Prochlorperazine, a phenothiazine derivative; is a well-known typical antipsychotic drug which acts by dopamine receptors blockade. Prochlorperazine and its salts are mostly used in the prevention and treatment of nausea and vomiting associated with radiotherapy[1], chemotherapy[2], surgery[3] and acute migraine[4,5]. Clinical studies showed that adverse effects of Prochlorperazine were directly proportional to its plasma levels[1,6]. Drug market of Pakistan is short of the GSK-marketed extended release Compazine® capsules of Prochlorperazine maleate. The unique clinical utility of Prochlorperazine maleate coupled with some serious side effects and shorter half life of 5–8 h[7], makes it an ideal candidate for development in controlled release tablet form.

A large number of controlled releases oral products, with better performance than their conventional counterparts; are commonly using the most simple

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Table 1. Composition of tablet formulations.

Ingredient	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
Prochlorperazine maleate, drug	12	12	12	12	12	12
Methocel® K100 LV-CR Premium, polymer	28	58	86	58	43	28
Ethocel® Standard 7FP Premium, copolymer	0	0	0	28	43	58
Lactose, diluent	58	28	0	0	0	0
Magnesium stearate, lubricant	1	1	1	1	1	1
Aersil®, glidant	1	1	1	1	1	1
Total (%)	100	100	100	100	100	100

Note: Weight of each tablet was 200 mg.

and cost-effective hydrophilic matrix technology. Hydroxypropyl methylcellulose (HPMC-2208) is widely used in formulation of extended/controlled release matrix and/or film coated tablets of some drugs[8,9]. The HPMC has been a very popular polymer, perhaps because of its wide regulatory acceptance, well established safety, nonionic nature, excellent stability, consistent reproducible release profiles, easy and cheap availability in the market. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion affect drug release profiles. The HPMC-based matrices commonly show pH-independent release profiles where drug solubility is pH independent but they may exhibit pH-dependent release profiles where drug solubility is pH dependent such as acidic drugs (e.g. Prochlorperazine maleate) or basic drugs (e.g. Olanzapine)[10–12]. HPMC based matrices may exhibit burst release in case of very soluble drugs[13,14].

Dow chemical company manufactures the HPMC-2208 under the trade name of Methocel®. Methocel® E and Methocel® K (e.g. Methocel® K100 LV CR Premium) are popular in formulation of controlled drug release matrix tablets because of their inherent potential for controlling drug release, robustness, rapid hydration and gel layer formation to cause immediate control on drug release[8,15]. They fulfill the exact requirements of many Official Compendia's, including United States Pharmacopoeia (USP) and British Pharmacopoeia (BP). Drug release from such matrices is not influenced by alcohol intake[16]. The Methocel® K100 LV CR Premium was used successfully in formulation of controlled matrix tablets. Various versions of fine particle ethylcellulose have exhibited higher potential as a binder and release retarding matrix former than its granular counterparts[17,18].

Blending of ionic, nonionic and water insoluble polymers with HPMC were recommended by some investigators to modulate its functionalities and/or achieve desired release profiles of certain drugs[14,19,20].

In the backdrop of the above-stated works, this study was designed, to assess first three formulations (F1, F2 and F3), based on the Methocel® K100 LV-CR Premium only and other three formulations (F4, F5 and F6), based on distinct blends of Methocel® K100 LV-CR Premium and Ethocel® Standard 7FP Premium; to develop a once daily controlled release matrix tablet of Prochlorperazine maleate.

Materials and methods

Materials

The following materials were used as received: Prochlorperazine maleate (Sanofi Aventis), obtained as gift from Drug Testing Laboratory, Khyber Pakhtunkhawa; Peshawar, Pakistan; Methocel® K100 LV-CR Premium (Hydroxypropyl methylcellulose, HPMC-2208) and Ethocel® Standard 7FP Premium (Fine particle ethyl cellulose, FPEC), obtained as gift samples from the M/S Colorcon Asia Pvt. Ltd, India; Stemetil® tablets-conventional (batch No.564; 2008; Sanofi Aventis Pvt. Ltd. Pakistan); containing 8.1 mg Prochlorperazine maleate (5 mg Prochlorperazine base) were purchased from local market and used as reference during the *in vivo* studies; Acetonitrile and Methanol (HPLC grade) were purchased from authorized local supplier of Merck, Germany. The rest of chemicals used were of analytical grade.

Preparation of tablets

The compositions of tablet formulations F1, F2, F3, F4, F5 and F6 are given in Table 1. The various components of formulations F1, F2 and F3 were mixed together by geometric dilution method in a polythene bag and then compacted to 6 kg hard tablets by direct compression method. The polymers Methocel® K100 LV CR Premium (M®) and the Ethocel® Standard 7FP Premium (E®) were blended together in three different proportions to constitute formulation F4 (58% M® & 28% E®), F5 (43% M® & 43% E®) and F6 (28% M® & 58% E®). The drug, the blend, the Aerosil® (0.5%) and the magnesium stearate (0.5%) were mixed together by geometric dilution method in a polythene bag. The powder mixtures, after passing through sieve # 40; were compressed to slugs (700–800 mg) with a manually run Tablet Press ZP-17, Shangai China; using 17 mm flat-faced tooling. The slugs were crushed in an oscillating granulator, fitted with sieve # 20 to prepare proper size granules (250 to 840 μm). The remaining quantities of the magnesium stearate (0.5%) and Aerosil® (0.5%) were mixed with the granules in a polythene bag. The granulation of each formulation,

thus prepared; was divided into three portions and then suitably compressed to 9-, 12- and 15 kg hard tablets, with the Tablet Press mentioned above, equipped with 8.00 × 3.50 mm tetragonal tooling. The batch size was 600 tablets.

Physicochemical evaluation of powders, granules and tablets

It is a well-known fact the powder mixture shall fulfill the basic requirements of good flow (commonly measured by Angle of repose) and compressibility characteristics (commonly assessed by compressibility index and Hausner's Ratio) prior to tablets manufacture. Therefore the prepared powder mixture and granules were evaluated for flow ability and compressibility. Angle of repose (AR) was determined with funnel method while compressibility index (CI) & Hausner's ratio (HR) were determined by cylinder method as per the Powder Flow Monograph # 1174, United States Pharmacopeia, USP XXX (2007. Hardness and dimensions of sampled tablet ($n = 10$) were determined with a hardness and dimensions tester (CHT 901, Curio Pakistan) while weight variation and friability of the sampled tablets ($n = 20$) were determined with an analytical balance (AX 200, Shimadzu; Japan) and friability testing apparatus (FB 994, Curio Pakistan), respectively. The tablets were tested for uniformity of drug content in the light of USP procedure for the assay of Prochlorperazine maleate tablets. Briefly, a sample of 20 tablets was weighed and then finely powdered. A portion of the powder (equivalent to 20 mg Prochlorperazine maleate) was put into a 100 mL volumetric flask. The powder was extracted with a mixture of ion-pairing solution, acetonitrile and methanol (45:40:15) using a vortex mixer for shaking and then assayed with UV-Visible Spectrophotometer; Shimadzu (Model-1700) at λ_{max} 254 nm.

Drug dissolution

Drug release studies were conducted in 900 mL simulated gastric fluid; 0.1 N HCl, pH-1.2 and in 900 mL simulated intestinal fluid; Phosphate buffer, pH-6.8, with Type II Paddle dissolution apparatus (Erweka, Germany) run at 50 RPM. The temperature of dissolution medium was thermostatically controlled at 37 ± 0.5°C. Samples (10 mL) were withdrawn (and then replaced with the fresh corresponding medium) at predetermined time intervals (i.e. at 1, 2, 4, 6, 8, 10, 12, 16 and 24 h) and then assayed with the UV-Visible Spectrophotometer at λ_{max} 254 nm.

Drug release data was fitted to various kinetic models, including zero order, first order; Higuchi's square root of time equation; Hixon and Crowell's cube root equation to assess the drug release rates (K values) and linearity of curves (R^2). To elucidate the mechanism of drug release, dissolution data for the first 60% of drug release was fitted in to Power law[21,22] Equation 1, and calculated the value of exponent "n" (showing mechanism of drug release) from the slope of the straight line.

$$M_t/M_\infty = kt^n \quad (1)$$

Where M_t and M_∞ were the amounts of drug released at time t (hours) and at infinite (∞) time, respectively. In case of a cylinder (tablet) values of "n" < 0.45 indicate Fickian release, values of "n" ≥ 0.45 to < 0.89 indicate non-Fickian (anomalous) release while the values of "n" ≥ 0.89 indicate zero order (Case II) release kinetics[23]. Goodness of fit test (linearity of curve) and/or values of the exponent "n" were used as criteria for selecting the most appropriate model.

Pair-wise model independent approach of similarity factor, f_2; was also employed to compare the release profiles of optimized formulation F6. Two release profiles are considered similar if value of the similarity factor, f_2 is close to 100. Generally, the values of $f_2 \geq 50$, indicates an average difference of not more than 10%[24–26].

Reproducibility and stability of the tablets

Three batches of the test formulation (F6 with optimum hardness of 12 kg) were produced on three different occasions to assess reproducibility of the manufacturing process. The tablet samples were tested for variation in weight, drug content, hardness and friability. The test tablets were stored in well closed high-density polyethylene plastic jars and kept under accelerated storage conditions (40 ± 2°C / 75 ± 5% RH), for a period of 6 months; using a stability chamber (Ti-Sc-THH-07-0400, Faisalabad, Pakistan). The samples were tested for changes in appearance, percent drug content, percent friability and tablet hardness at 0 time (prestorage) and after storage for 1, 2, 4 and 6 months, respectively.

Pharmacokinetics study

The *in vivo* pharmacokinetic studies were performed on Himalayan angora rabbits (either sex with 2.6 ± 0.3 kg, weight) in the light of standard protocol approved by Research and Ethical Committee of Post Graduate Medical Institute, Hayatabad Medical Complex, Peshawar. Selection of rabbits as animal model for the present study was based on some successfully conducted published studies[10,27,28]. The rabbits fasted for 20 h before experiment; were divided into two groups ($n = 6 + 6$). The first group received the test tablets of 24 mg Prochlorperazine maleate (15 mg Prochlorperazine base), while the second group received the reference-conventional Stemetil® tablets (8 hourly) containing 8 mg Prochlorperazine maleate (5 mg Prochlorperazine base), followed by a few draughts (nearly 10 mL) of water. The rabbits were kept fasting for 12 h after tablet administration but allowed free access to water during the whole period of study.

Blood samples (0.6 mL each time) were withdrawn from the marginal ear vein of rabbit in 3 mL test tubes at predetermined time intervals, 0, 1, 2, 4, 6, 8, 10, 12, 24 and 28 h in case of the test tablet and at predetermined

time intervals, 0, 1, 2, 4, 6, 8, 9, 10, 12, 14, 16, 24 and 28 h in case of the 8-hourly administered Stemetil® tablets. The blood samples were allowed to clot. Serum sample measuring 200 µL was withdrawn into another 3 mL test tube and centrifuged at 3000 RPM for 10 min. Cleared serum measuring 100 µL was transferred to a 10 mL test tube and stored at minus (–) 20°C till the time of analysis.

Extraction of Prochlorperazine from serum samples was carried out using a published method[29]. Briefly, to the 100 µL processed serum sample, 100 µL of 1M sodium hydroxide and 6 mL chloroform were added and thoroughly vortex mixed for 2 min. The mixture was centrifuged at 3000 RPM and then the supernatant (organic) layer was collected and transferred to 10 mL test tube for subsequent drying under nitrogenous atmosphere. The residue so obtained was dissolved in 100 µL of the mobile phase by vortex mixing for 1 min and then analyzed.

Determination of serum drug concentration

Serum level of Prochlorperazine was determined using high-performance liquid chromatography coupled with ultraviolet detector (HPLC-UV) by an assay method for Prochlorperazine maleate tablets USP XXX, 2007, with minor modifications. Briefly, the HPLC system (Shimadzu, Japan) was constituted by Communication Boss Module (CBM, Model 20A), two independently working pumps (model LC-20AT) and an analytical column, PurospharR Star RP.C18e, HibarR RT 250-4.6 (5 µM); Merck, Germany.

The mobile phase, consisting of ion pairing solution, methanol and acetonitrile (45:15:40) was de aerated with sonication after filtering through the 0.45 µM nylon filter. The compound was eluted isocratically using the mobile phase with a flow rate of 1.0 mL/min (pump pressure of 185 kgf). Briefly, the ion pairing solution (USP) was prepared by dissolving 4.33g of sodium 1-octanesulfonate in 500 mL water and then adding 4.0 mL glacial acid and sufficient purified water to make the final volume 1000 mL

Pharmacokinetic analysis

The peak serum concentration (C_{max}) and time of its occurrence (T_{max}) were read directly from Prochlorperazine concentration-time data. For other pharmacokinetic parameters, the concentration-time data was analyzed, using a computer based PK (pharmacokinetic) Software, WinNonlin® Ver. 5.2.1 (Pharsight Corporation, Mountain View, CA, USA). Noncompartmental approach could describe successfully the Prochlorperazine serum concentration-time data. Area under the plasma level-time curve (AUC) was calculated by trapezoidal method. For the computation of the terminal elimination rate constant (K_{el}), the program used a minimum of three data points. Where the computation of K_{el} was not possible for all the animals, best fit implemented in software was used. The $t_{1/2}$, was estimated as, $t_{1/2} = 0.693/K_{el}$.

Relative bioavailability and in vitro-in-vivo correlation

The extent of drug absorption from the CR test tablet relative to the reference Stemetil® tablet was calculated with the following formula[30].

$$\%\,\text{Relative Bioavailability} = \frac{AUC_{0-t}(\text{Test})}{AUC_{0-t}(\text{Reference})} \times 100$$

In vitro-in vivo correlation for the test tablet was investigated by plotting point to point percent drug absorbed (Pa) against the percent drug released (Pr). The percent drug dissolved values were taken from the *in vitro* release data and the percent drug absorbed values were calculated by the following formula[31]

$$Fa = [(C_t + k_{el}\ AUC_{0\text{-}t}) / ke\ AUC_{0\text{-}\infty}] \times 100$$

Where F_a indicates the fraction of drug absorbed, C_t denotes the drug serum concentration at time *t*. The k_e shows overall elimination rate constant while the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ are the areas under curve between time zero to time *t* and from time zero to time infinity, respectively.

Statistical analysis

Unpaired student *t*-test with Prism Graph Pad, Version-5 was employed to compare the test tablet and the reference-Stemetil tablet with respect to their half life, $t_{1/2;}$ peak concentration, C_{max}; peak time T_{max} and area under curve, $AUC_{0\text{-}28}$. The "p" values of less than 0.05 were considered as significant.

Results

Physicochemical evaluation of powder mixtures and granules

The powder mixtures of formulation F1, F2 and F3 exhibited good flow profiles as indicated by the values of angle of repose (30 ± 2° to 33 ± 3°), good compressibility profiles inferred from compressibility indexes (12 ± 1 to 13 ± 2) and Hausner's ratios (1.12 ± 0.0.09 to 1.15 ± 0.07). Therefore, the formulations F1, F2 and F3 were compacted to 6 kg hard tablets by direct compression method. Percent drug content of the powder-mixtures (103 ± 3, 100 ± 4 and 101 ± 5) and tablets (102 ± 4, 101 ± 3 and 103 ± 3) were well within the USP limits.

The powder mixtures of formulation F4, F5 and F6 exhibited poor flow ability profiles inferred from angle of repose (46 ± 2° to 52 ± 4°) and poor compressibility profiles implied from compressibility indexes (27 ± 3 to 32 ± 3) and Hausner's ratios ((1.38 ± 0.17 to 1.45 ± 0.18). As the compaction of these powder-mixtures by direct compression method was not possible, therefore the powder mixtures were compressed to slugs' by dry granulation-slugging method. The granules obtained by crushing of slugs, were tested for flow ability and compressibility characteristics. The granules exhibited good flow ability concluded from angle of Repose (31 ± 2° to 34 ± 2°); good compressibility inferred

from compressibility indexes (11 ± 2% to 13 ± 2%) and Hausner's ratios (1.13 ± 0.12 to 1.17 ± 0.15). Percent drug content of the granules (101 ± 4, 102 ± 3 and 102 ± 2) were well within the USP limits.

Physicochemical evaluation of tablets

The prepared tablets were found satisfactory with respect to their dimensions (length × width, 8.0 ± 0.1 × 3.5 ± 0.1 mm to 8.1 ± 0.1 × 3.6 ± 0.1 mm), weight variation (3 ± 0.4% to 5 ± 0.4%), friability (0.39 ± 0.08 % to 0.56 ± 0.06 % and percent drug content (103 ± 4 % to 102 ± 3 %).

Drug dissolution

The *in vitro* drug release studies of formulations F1 (based on 28% Methocel®), F2 (based on 58% Methocel®), and F3 (based on 86% Methocel®), produced drug release periods of round about 2.5 h, 6.5 h and 8 h, respectively in both 0.1 N HCl, pH-1.2 and phosphate buffer, pH-6.8 (results not shown). These release periods were of little value in the present context. To further extend the release period, the Methocel® was replaced sequentially with 28%, 43% and 56% Ethocel® (hydrophobic) to constitute formulations F4, F5 and F6 for achieving the target release period of 24 h. A detailed account of the *in vitro* drug release studies of the promising formulations F4, F5 and F6, using simulated gastric fluid and simulated intestinal fluid can be seen in Table 2. The *in vitro* drug release data of these promising formulations is also presented selectively in Figure 1 and Figure 2. The changes in hydrodynamic conditions[10] and tablet hardness could not affect drug release kinetics[10,32,33] (see Table 2). The values of similarity factor, f_2, calculated for 9-, 12- and 15 kg hard tablets of formulation F6 at pH 1.2 versus pH 6.8 were 61.82, 78.70 and 79.58, respectively, indicating that there was insignificant difference in the release profiles, that is, there was no effect of the hydrodynamic conditions on drug release kinetics.

Selection of the optimized test tablets

Tablet formulation F6 with 12 kg hardness was selected as the optimized one based upon its optimum hardness and zero order release kinetics for 24 h at both pH-1.2 and pH-6.8.

Reproducibility and accelerated stability study

Among the manufactured three lots of formulation F6 with 12 kg hardness, there was no significant difference in drug content (100 ± 3%, 101 ± 3% and 103 ± 2%). The friability levels found were 0.4 ± 0.07%, 0.36 ± 0.06% and 0.5 ± 0.08% for the three batches, falling well within the USP limit. There was no significant effect of ICH recommended accelerated storage conditions (40° ± 2° C/75 ± 5 % RH) on percent drug content, percent weight variation, percent friability and tablets hardness obtained at 0 time (prestorage) and after storage for 1, 2, 4 and 6 months as shown in Table 3. The tablets maintained their original white appearance for the whole period of 6 months.

Pharmacokinetics study

The Chromatographic (HPLC-UV) method was validated in the light of International guidelines[34,35]. The retention time for Prochlorperazine maleate was approximately 2.19 min. There was no interference of endogenous substances with the detection of Prochlorperazine. The mean absolute recovery of Prochlorperazine determined from five aliquots of quality control samples was calculated as 87 ± 5%.

The mean serum concentrations-time profiles of Prochlorperazine for the test tablet and reference Stemetil® tablet are shown in Figure 3. The test tablet exhibited a significantly ($p < 0.01$) optimized peak concentration, C_{max} (45.50 ± 3.42 ng/mL vs. 64.50 ± 4.03 ng/mL) and extended time of peak concentration, T_{max} (14.33 ± 7.16 h vs. 4.17 ± 0.37 h) against the reference

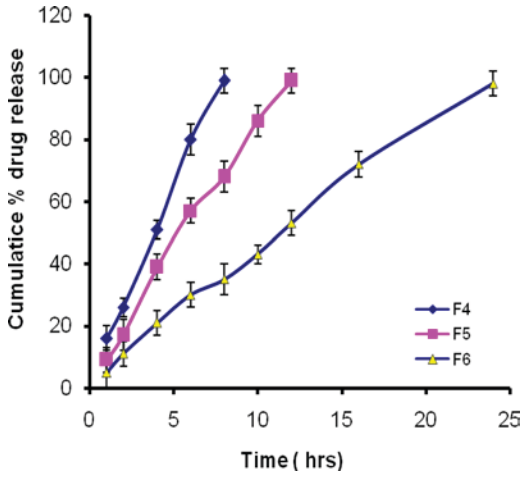

Figure 1. Comparative release profiles of Prochlorperazine maleate from 12 kg hard tablets of the promising formulations F4, F5 and F6 in dissolution media of pH 1.2 (Mean ± SD, $n = 6$).

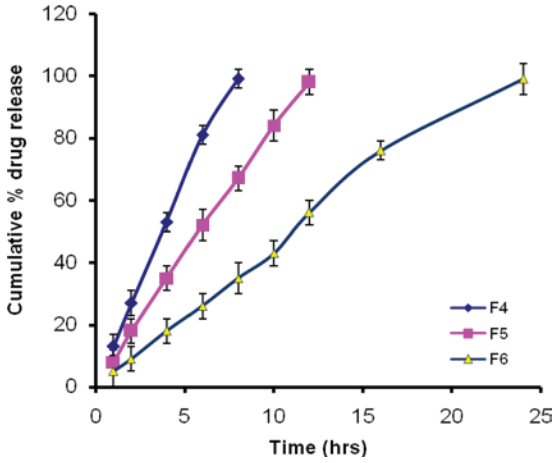

Figure 2. Comparative release profiles of Prochlorperazine maleate from 12 kg hard tablets of the promising formulations F4, F5 and F6 in dissolution media of pH 6.8 (Mean ± SD, $n = 6$).

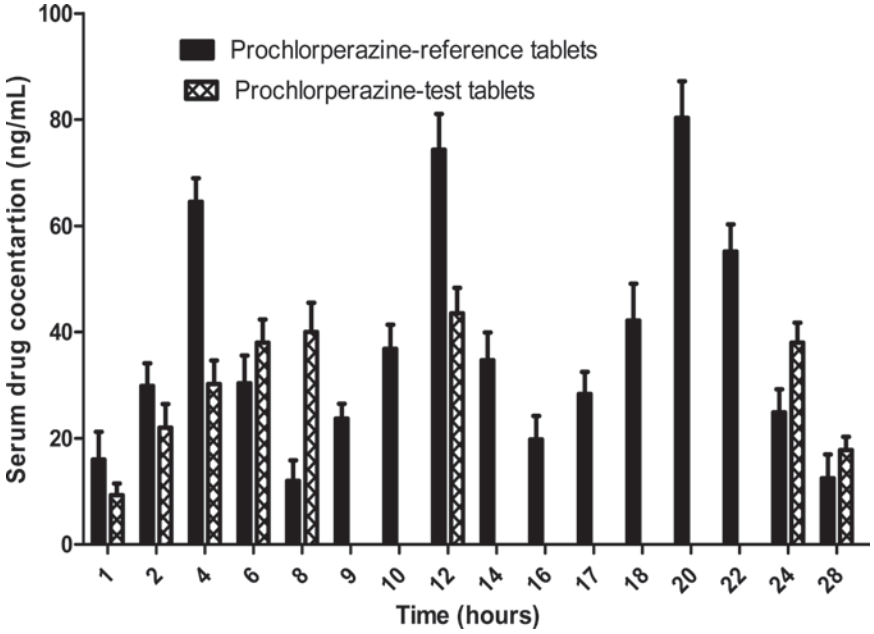

Figure 3. Serum drug concentration-time profiles of Prochlorperazine, following oral administration of the Reference conventional-Stemetil tablet (5 mg) 8 hourly and Test controlled release tablet from formulation F6 (15 mg) once a day to rabbits. Each points represent mean ± SD, $n = 6$.

Table 2. Comparative drug release profiles of some promising controlled release formulations of Prochlorperazine maleate using dissolution media of pH-1.2 and pH-6.8.

		Zero order		Higuchis		First order		Hixon-Crowel		Korsemeyer		Results
Formulation No.	Hardness	K	R^2	K	R^2	K	R^2	K	R^2	n	R^2	Mechanism of drug release
Dissolution medium, 0.1N HCl, pH-1.2												
F4												
	9 kg	12.38	0.997	47.17	0.976	−0.216	0.840	−0.320	0.978	0.942	0.987	Zero order
	12 kg	12.24	0.996	46.79	0.981	−0.252	0.820	−0.305	0.973	0.877	0.991	Zero order
	15 kg	12.13	0.991	46.48	0.982	−0.219	0.878	−0.301	0.967	0.861	0.983	Zero order
F5												
	9 kg	8.29	0.999	37.05	0.901	−0.146	0.754	−0.231	0.940	1.0719	0.991	Zero order
	12 kg	8.22	0.993	37.05	0.990	−0.147	0.778	−0.223	0.929	1.008	0.993	Zero order
	15 kg	8.19	0.987	36.99	0.991	−0.149	0.803	−0.217	0.923	0.944	0.980	Zero order
F6												
	9 kg	4.09	0.997	23.86	0.958	−0.075	0.789	−0.123	0.909	0.983	0.994	Zero order
	12 kg	4.05	0.995	23.63	0.969	−0.065	0.838	−0.118	0.899	0.921	0.995	Zero order
	15 kg	4.11	0.991	24.49	0.971	−0.076	0.819	−0.118	0.893	0.904	0.996	Zero order
Dissolution medium, Phosphate buffer, pH-6.8												
F4												
	9 kg	12.23	0.997	46.69	0.979	−0.251	0.811	−0.306	0.974	0.892	0.997	Zero order
	12 kg	12.51	0.995	48.12	0.991	−0.254	0.834	−0.320	0.951	1.018	0.999	Zero order
	15 kg	12.35	0.993	47.39	0.986	−0.245	0.807	−0.310	0.955	0.953	0.996	Zero order
F5												
	9 kg	8.13	0.997	36.51	0.988	−0.146	0.766	−0.219	0.938	0.976	0.997	Zero order
	12 kg	8.17	0.999	36.62	0.986	−0.128	0.812	−0.226	0.943	1.019	0.997	Zero order
	15 kg	8.12	0.996	36.51	0.989	−0.128	0.824	−0.220	0.943	0.956	0.995	Zero order
F6												
	9 kg	4.17	0.981	24.70	0.983	−0.067	0.875	−0.122	0.873	0.998	0.999	Zero order
	12 kg	4.27	0.990	24.88	0.964	−0.077	0.826	−0.126	0.908	0.964	0.998	Zero order
	15 kg	4.21	0.990	24.67	0.970	−0.077	0.827	−0.122	0.907	0.924	0.994	Zero order

Note: K, R^2 and "n" represent release rate constant (percent/hour), coefficient of determination and release exponent, respectively.

Table 3. Stability of the optimized controlled release tablets of Prochlorperazine maleate at accelerated storage conditions (Mean ± SD, $n=3$).

Testing time	Drug content (%)	Weight variation (%)	Friability (%)	Hardness (kg)	Appearance
At 0 time (prestorage)	101 ± 3	3 ± 0.4	0.49 ± 0.01	12.0 ± 0.3	White
After 1 month	103 ± 4	5 ± 0.4	0.57 ± 0.01	12.0 ± 0.4	White
After 2 months	101 ± 4	4 ± 0.3	0.62 ± 0.01	12.0 ± 0.2	White
After 4 months	102 ± 2	3 ± 0.5	0.53 ± 0.01	12.1 ± 0.3	White
After 6 months	101 ± 3	5 ± 0.3	0.48 ± 0.01	12.3 ± 0.2	White

Note: Accelerated storage conditions means storage at 40 ± 2°C/75 ± 5% RH.

tablet. A significantly prolonged ($p<0.05$) half life, $t_{1/2}$ was shown by the test tablets as compared to that of reference tablet (16.07 ± 3.97 h 5.26 ± 1.31 h). The test tablet exhibited nearly the same area under curve, $AUC_{0\text{-}28hour}$ (1409.35 ± 145.46 ng·h/mL) as that shown by the reference conventional tablet administered three times a day (1346 ± 229.98 ng·h/mL); indicating a good level of bioequivalence.

Relative bioavailability

The relative bioavailability of test tablet was calculated as 100%. The CR Test tablet showed an extended absorption phase with t_{max} of 14.33 ± 7.16 h.

In vitro and in vivo correlation

The percent drug absorbed (Fa on Y axis) when plotted against percent drug released (Fr on X axis) produced a high level linearity ($R^2=0.8458$) as shown in Figure 4, indicating a strong level A correlation between the drug absorbed *in vivo* and the drug released *in vitro*.

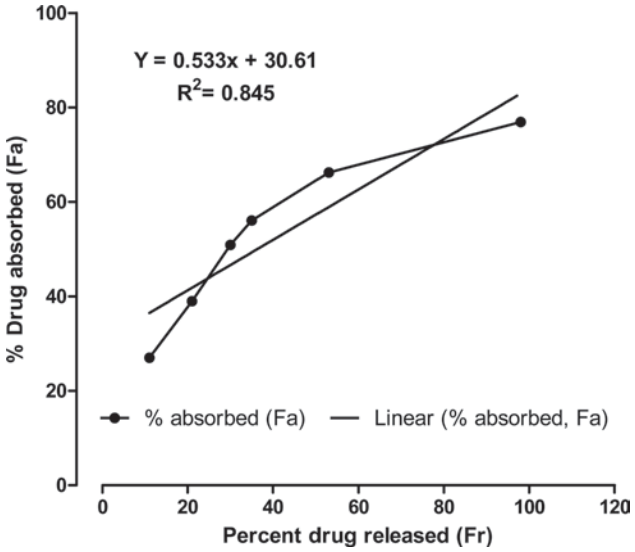

Figure 4. Correlation between percent drug absorbed and percent drug released at predetermined time intervals of 1, 2, 4, 6, 8, 12 and 24 h.

Discussion

Conventional tablets of Prochlorperazine maleate are normally taken 3–4 times a day based on its shorter half life (5–8 h). It is a typical antipsychotic drug which causes the bothersome extra pyramidal side effects. Therefore, the controlled release matrix tablet of Prochlorperazine maleate was developed to address its major issues of tolerability and compliance. Methocel® K 100 LV CR Premium was tried alone at the concentration level of 28%, 58% and 86%. Tablets of high quality were easily produced with the Methocel® by the most popular direct compression method, perhaps because of its granular nature and well established bonding qualities[36], but it could not extend the drug release period beyond 8 h. As the fine particle Ethylcellulose (FPEC) was used successfully as a matrix forming agent to develop controlled release matrix tablets of Ibuprofen by a group of investigators[18], therefore, the Ethocel Standard 7FP Premium (fine particle ethyl cellulose, hydrophobic) was employed to substitute portions of the Methocel® to further extend the release period up to 24 h.

Studies on flow ability and compressibility characteristics of powder mixtures from formulations F4, F5 and F6 showed that the material was not lending itself to direct compression; therefore the simple one dry granulation-slugging method was employed to manufacture the tablets[37].

Three formulations were designed, taking into consideration the previously developed blends for the same purpose (Badshah et al., 2010). The total concentration of the polymeric blends were reduced to 86% from that of 90% and Lactose present in the previously developed formulation was completely eliminated to make a space for 24 mg Prochlorperazine maleate. The formulations F4, contained 58% Methocel® and 28% Ethocel®. The F5 was prepared with 43% Methocel® and 43% Ethocel® while F6 contained 28% Methocel® and 58% Ethocel®. The other excipients such as silicon dioxide (Aerosil®) and magnesium stearate were kept fixed each at 1% level in order to determine clearly the effect of the polymers.

As both Methocel® and Ethocel® have sufficient binding characteristics[36], therefore tablets of optimum friability and desired hardness at the three levels of compression force were produced easily. Drug release at a zero order rate provides a constant concentration of the drug for absorption and maintains plasma concentration within a therapeutic range. Such a behavior of dosage form effectively minimizes side effects and subsequently improves tolerability and adherence. Many researchers have sought to formulate

matrices for zero order release pattern but few have been successful[10,38].

To elucidate the mechanism of drug release from the Prochlorperazine controlled release tablets, dissolution data for the first 60% of drug release[39] was fitted to the Power law equation. The release exponent "*n*" was calculated from the slope of the straight line. In case of cylinders (i.e. tablets), the value of "*n*" < 0.45 indicates Fickian release; 0.45 ≤ "*n*" < 0.89 indicates anomalous transport, while the value of "*n*" ≥ 0.89 indicates the zero order release[22,23].

Interestingly, in a total 86% polymeric blend, 58% Methocel® and 28% Ethocel® (F4) could hardly maintained the release period for 8 h, but the mechanism of drug release was changed from that of anomalous to zero order. Inclusion of 28 % Ethocel® in formulation F4 also caused poor flow ability and compressibility of the powder-mixture, so alternatively the dry granulation-slugging method was employed to produce the tablets. Thereafter, further substitution of Methocel® by Ethocel® (F5; 43%:43%) could extend the release period up to 12 h with zero order kinetics. In case of formulation F6, a good portion of Methocel® was further substituted by Ethocel® (28% Methocel® and 58% Ethocel®), which could exhibited the desired release period of 24 hours with zero order kinetics.

Ethocel® content based reduction in drug release rates was noted which may be due to slow hydration of the matrix. The insoluble particles of Ethocel® perhaps acted as barrier to drug release in the gel layer of the Methocel®. This is in line with the findings of Howard and Timinis[40], where they used sodium alginate (a gelling agent which is insoluble at acidic pH) for avoiding the initial burst release of some basic drugs from the Methocel®-based matrices.

As the tablet hardness differ case to case at different times, so tablets of these formulations were compressed for different hardness levels to study their impact on drug release. The drug release studies of the tablet formulations F4, F5 and F6 were also carried out at the two commonly encountered extremes of pH, that is, pH-1.2 and pH-6.8. The drug release kinetics was not affected by the hydrodynamic conditions. Tablet hardness was increased with increase in compression forces in case of all formulations, F4, F4 and F6 but their release rates and mechanisms remained unaffected. It can be implied that the porosity and /or tortuosity of the prepared tablets, after their hydration; were not influenced by increase in tablet hardness from 9 kg to 15 kg. The findings of the present study were in line with some previously conducted studies[10,41].

The method of HPLC-UV analysis was validated in the light of the International Guidelines[35,42]. The conventional tablets of Prochlorperazine maleate are normally taken three times a day and the plasma levels of Prochlorperazine correlate with its adverse drug effects[6], therefore, side effects and frequency of dosage dependent noncompliance of the drug need to be addressed. Thus, the controlled release (CR) tablet of Prochlorperazine maleate was developed to reduce frequency of dosage and minimize fluctuations in blood levels of Prochlorperazine and hence reduce its side effects for improvement in compliance. The therapeutic blood level of Prochlorperazine has been reported as 10–40 ng/mL[43]. The test tablet of Prochlorperazine maleate exhibited nearly constant and optimum therapeutic concentration, that is, 43 ng/mL as compared to that of 65 ng/mL for the reference tablet. Significant extension in half life ($t_{1/2}$) and time required for achieving maximum concentration (T_{max}) of test formulation also indicate drug release occurring at a slower rate for extended time, eliminating the need for taking Prochlorperazine maleate tablets in multiple doses per day. An insignificant difference between mean area under curve $AUC_{0\text{-}28}$ (1409 ± 135) of 15 mg test tablet given once a day and $AUC_{0\text{-}28}$ of the reference tablets given 3 times a day (1347 ± 231) indicates their bioequivalent. Relative bioavailability of Prochlorperazine was noted as 1.05, indicating that the test and the Reference tablets were bioequivalent within the BE acceptance limits of 0.8–1.25. The test tablets were capable of releasing sufficient amount of the drug to maintain its therapeutic range for extended period of time. A relatively good level of *in vitro* and *in vivo* correlation was achieved with coefficient of determination (R^2) being 0.8458, which indicate that the formulation was successful enough for further promotion and clinical evaluation.

Conclusions

The novel blend of Methocel® K100LV-CR Premium and Ethocel® Standard 7FP Premium was successfully employed to formulate the once daily controlled release matrix tablets of Prochlorperazine maleate. The investigated tablet exhibiting bioequivalence to the Stemetil® tablet and a strong level "A" correlation between the drugs released *in vitro* and drug absorbed *in vivo*, may improve safety and compliance profiles of the Prochlorperazine maleate.

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Declaration of interest

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