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Research Article

Development of Controlled-Release Matrix Tablet of Risperidone: Influence of Methocel®- and Ethocel®-Based Novel Polymeric Blend on *In Vitro* Drug Release and Bioavailability

Amir Badshah,[1,4] Fazal Subhan,[1] Khalid Rauf,[1] Nadeem Irfan Bukhari,[2] Kifayatullah Shah,[3] Samiullah Khan,[1] Zia Ahmed,[1] and Ihsanullah Khan[1]

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Abstract. Controlled-release (CR) matrix tablet of 4 mg risperidone was developed using flow bound dry granulation–slugging method to improve its safety profile and compliance. Model formulations F1, F2, and F3, consisting of distinct blends of Methocel® K100 LV-CR and Ethocel® standard 7FP premium, were slugged. Each batch of granules (250–1,000 μm), obtained by crushing the slugs, was divided into three portions after lubrication and then compressed to 9-, 12-, and 15-kg hard tablets. *In vitro* drug release studies were carried out in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) using a paddle dissolution apparatus run at 50 rpm. The CR test tablet, containing 30% Methocel® and 60% Ethocel® (F3) with 12-kg hardness, exhibited pH-independent zero-order release kinetics for 24 h. The drug release rate was inversely proportional to the content of Ethocel®, while the gel layer formed of Methocel® helped in maintaining the integrity of the matrix. Changes in the hardness of tablet did not affect the release kinetics. The tablets were reproducible and stable for 6 months at 40±2°C/75±5% relative humidity. Risperidone and its active metabolite, 9-hydroxyrisperidone, present in the pooled rabbit's serum, were analyzed with HPLC-UV at λ_{max} 280 nm. The CR test tablet exhibited bioequivalence to reference conventional tablet in addition to the significantly ($p<0.05$) optimized peak concentration, C_{max}, and extended peak time, T_{max}, of the active moiety. There was a good association between drug absorption *in vivo* and drug release *in vitro* ($R^2=0.7293$). The successfully developed CR test tablet may be used for better therapeutic outcomes of risperidone.

KEY WORDS: controlled release; dry granulation slugging method; risperidone.

INTRODUCTION

Risperidone, a water-insoluble second-generation antipsychotic drug, is widely used in the clinical management of schizophrenia, bipolar disorder, and irritability in children. 9-Hydroxyrisperidone, a major metabolite of risperidone, was pharmacologically as much potent as the parent compound. The serum concentration of the active moiety is thus the sum of serum concentrations of risperidone and 9-hydroxyrisperidone (1,2).

Noncompliance to antipsychotic drugs has been a major problem since long (3). Noncompliant psychiatric patients suffered an almost double re-hospitalization from relapse, resulting in poor quality of life and increased economic burden (4). Noncompliance to antipsychotic drugs was mainly caused by their side effects (5), including dose-dependent cardiac arrest deaths (6), extrapyramidal side effects, dry mouth, constipation, difficulty in urinating, and loss of accommodation (7). There was a strong association between plasma levels of risperidone and its adverse effects (8,9).

The combined peak concentration (C_{max}) of risperidone and its active metabolite, 9-hydroxyrisperidone, was reported as 30 ng/mL for once-daily 4-mg tablets (10) and 50 ng/mL for once-daily 6-mg tablets (11), while their combined elimination half-life was approximately 20 h both in poor and extensive metabolizers (12). A group of investigators (13) suggested 20–60 ng/mL as the optimal concentration of the active moiety for therapeutic activity. Another group of researchers observed 74 ng/mL active moiety as the threshold limit for causing extrapyramidal side effects (14).

Novel formulations of some antipsychotic drugs have become popular because of convenience in dosage, reduced side effects, and improved efficacy (15). Better therapeutic outcomes were exhibited by the OROS-based extended-release tablet of 9-hydroxyrisperidone (an active metabolite of risperidone) commercially known as Paliperidone, Invega® (16). Similar results have been exhibited by the oral monolithic matrix tablets of carbamazepine (17). A therapeutically favorable drug release profile was shown by the lipid matrices of olanzapine (18).

Matrix tablets meant for oral route are popular because of the simplicity in manufacture, ease and safety in use, and

[1] Department of Pharmacy, University of Peshawar, Peshawar 25120, Khyber Pakhtoonkhwa, Pakistan.
[2] University College of Pharmacy, Punjab University, Punjab, Pakistan.
[3] Faculty of Pharmacy, Gomal University, D.I.Khan, Khyber Pakhtoonkhwa, Pakistan.
[4] To whom correspondence should be addressed. (e-mail: amir_badshah@upesh.edu.pk)

cost effectiveness. Hydroxypropyl methylcellulose (HPMC, hydrophilic) has been a popular release-retarding polymer in simple matrix tablets (19,20) and floating gastro-retentive tablets (21,22). Fine particle ethyl cellulose (FPEC) was successfully used in the formulation of extended-release tablets of some non-ionizable drugs (23). Blending of HPMC with other polymers (*e.g.*, ethyl cellulose) has been recommended for the alteration of its functionalities (24). Blends of HPMC with FPEC have shown promising results in our previously published investigation (25).

No study has been reported so far regarding the preparation of risperidone controlled-release matrix tablets. Blends of Methocel® K100 LV-CR and Ethocel® standard 7FP premium, novel versions of HPMC and ethyl cellulose respectively, were employed in the present study to prepare the controlled-release matrix tablets of risperidone. The study also attempted to assess the impact of the novel blend on drug release kinetics and bioavailability.

MATERIALS AND METHODS

Risperidone (Jubilant Organosys Science Active Ltd., India) was provided by Bryon Pharma, Khyber Pakhtoonkhwa, Pakistan, as a gift sample, and 9-hydroxyrisperidone was purchased from TLC PharmaChem, Canada. Methocel® K100LV-CR and Ethocel® Standard 7FP Premium were gratefully provided as gift samples by Colorcon Asia Ltd., India. Conventional Risperdal® tablets (batch no. 6914 dated May, 2007; Johnson and Johnson (Pvt.) Ltd., Pakistan) of 4-mg risperidone strength were used as reference during *in vivo* studies. HPLC grade acetonitrile and methanol (Merck, Germany) were purchased from the authorized dealer in the local market. Other chemicals used were of analytical grade.

Preparation of Tablets

Model formulations F1, F2, and F3 were prepared by blending Methocel® K100 LV-CR (M) and Ethocel® standard 7FP premium (E) in three different proportions. The polymeric blends constituted 90% portion of formulations F1 (60% M and 30% E), F2 (45% M and 45% E), and F3 (30% M and 60% E). The polymeric blends were thoroughly mixed with preset fixed amounts of risperidone (2%), lactose (6%), colloidal silicon dioxide (Aerosil®, 0.5%), and magnesium stearate (0.5%) in a polybag by a geometric dilution method. The powder mixture, thus prepared for a batch of 600 tablets, was initially passed through sieve #40 and then compressed into slugs with a manually run Tablet Press ZP-17, Shanghai, China, using 17-mm flat-faced tooling. The slugs were crushed first in a pestle and mortar and then in an oscillating granulator (fitted with 20 mesh screen) for sizing the granules (≥200 μm to ≤1 mm). Aerosil® (0.5%) and magnesium stearate (0.5%) were mixed well with the pre-sized granules in a polybag. The material thus prepared was divided into three portions and then compressed suitably to alter into tablets of 9-, 12-, and 15-kg hardness with the Tablet Press ZP-17, equipped with 8.00×3.50-mm tetragonal tooling. Each tablet, containing 4 mg risperidone, weighed 200 mg

Physicochemical Evaluation of Powder Mixture, Granules, and Tablets

The powder mixture and granules thus prepared were evaluated for flow and compressibility characteristics. The angle of repose (AR) of the powder mixture and granules was determined using a fixed funnel, while the compressibility index (CI), and Hausner ratio (HR) were determined with a 100-mL cylinder in accordance with Monograph #<1174>, United States Pharmacopoeia XXX (USP XXX). The granules were assayed for risperidone content with a UV–Visible spectrophotometer (Shimadzu, Japan, model 1700) set at λ_{max}=280 nm using methanol as the extraction solvent. The friability of the tablets was determined with a friability tester (FB 994, Curio, Pakistan), while the hardness and physical dimensions of the tablets were determined with a hardness plus dimensions tester (CHT 901, Curio). Weight variation was determined as given in Monograph #<905>, USP XXX. To determine content uniformity, ten tablets were individually crushed, extracting each one with 100 mL methanol for assay of risperidone, as mentioned above.

Drug release studies were conducted in 900 mL of 0.1 N HCl (pH 1.2) and 900 mL of phosphate buffer (pH 6.8) kept at thermostatically controlled temperatures of 37±0.5°C using a type II paddle dissolution apparatus (Erweka, Germany) run at 50 rpm. The samples withdrawn were replaced with similar dissolution media. Percent drug release after 1, 2, 4, 6, 8, 10, 12, 16, and 24 h was determined with the UV–Visible spectrophotometer at λ_{max}=280 nm.

The drug release data were fitted to the usual kinetic models, including zero-order, first-order, Higuchi's square root of time, and Hixon and Crowell's cube root of time to determine the release rate (K) and coefficient of determination (R^2). Korsemeyer–Peppas's equation was applied to determine the linearity of the drug release curves (coefficient of determination, R^2) and release exponent (n) with the following equation (26):

$$\text{Korsemeyer} - \text{Peppas's equation, } Q_t/Q_\infty = kt^n \qquad (1)$$

where Q_t is the percent drug release at time t; Q_∞ the percent drug release after infinite time, usually taken as 100; Q_t/Q_∞ is the fraction of drug released at time t; and k in the Korsemeyer's model is a release constant incorporating the structural and geometric characteristics of the system; n is the release exponent, indicative of the drug release mechanism.

Release profiles of the 9-, 12-, and 15-kg hard tablets of the selected formulation F3, determined in dissolution media of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8), were also compared using the model-independent approach of similarity factor f_2 as a determinant parameter (27,28).

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}W_t\sum_{t-1}^{a}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \qquad (2)$$

where n is the number of data points collected, R_t and T_t are the percent drug dissolved at each time point for the reference and test tablets, respectively, and W_t is an optional weight factor.

Three batches of the selected test formulation (F3 with 12-kg hardness) were prepared at three different occasions to

find out the reproducibility of the manufacturing process. The optimized tablets (F3 with 12-kg hardness), sealed in plastic bags, were stored in well-closed high-density polyethylene jars and kept under accelerated storage conditions (40±2°C/75±5% relative humidity, RH) for 6 months in a stability chamber (Ti-Sc-THH-07-0400, Faisalabad, Pakistan). To determine stability at accelerated storage conditions, the tablets were tested for appearance, friability, hardness, and drug content at 0 times (pre-storage) and after 1, 2, 4, and 6 months' storage.

In Vivo Evaluations

The *in vivo* studies on rabbits (Himalayan angora, either sex, weighing 2.2±0.3 kg) were carried out in accordance with the standard protocol approved by the Research and Ethical Committee of Postgraduate Medical Institute, Hayatabad Medical Complex, Peshawar. Rabbits fasted for 24 h before trial and were divided into two groups, each one having six animals. Selection of rabbits as the animal model for the present study was based on some successfully conducted previously published pharmacokinetic studies (22,29,30). The first group received 4-mg reference conventional tablets and the second group received 4 mg controlled-release (CR) test tablets of risperidone. The rabbits were kept fasted for 12 h after tablet administration, but given free access to water during the whole period of study. Blood samples (0.7 mL each time) were collected from the marginal ear vein at 0, 1, 2, 4, 6, 8, 12, 24, and 48 h in 3-mL test tubes and allowed to clot. A 200-μL serum was withdrawn from the clot into another 3-mL test tube and centrifuged (Table Top Centrifuge, model DSC 200A-2; Digisystem Lab, Taiwan) at 2,800 rpm for 10 min. Of the cleared serum, 100 μL was transferred to a 10-mL test tube and stored at −20°C until analysis.

Risperidone and 9-hydroxyrisperidone were extracted from the serum samples using an already published liquid–liquid extraction method (11). To the 100 μL so processed serum sample, 100 μL of 1 M sodium bicarbonate and 7 mL blend of pentane and dichloromethane (85:15) were added and thoroughly mixed with Vortexer (Gyromixer, Pakland, Pakistan) for 2 min. The mixture was centrifuged at 2,800 rpm for 3 min and the supernatant (organic) layer transferred to 6-mL test tubes for drying under nitrogenous flux. The residue so obtained was dissolved in 100 μL acetonitrile with the help of a vortex mixer run for a minute.

Risperidone and its active metabolite (9-hydroxyrisperidone) in rabbit sera were quantified by HPLC-UV by means of a reported method (31) with minor modifications. The HPLC system (Shimadzu) included a communication boss module (model 20A), two independently working pumps (model LC-20AT), and an analytical column (PurospharR Star RP, C18e, HiberR RT 250-4.6 (5 μM) connected to a UV-Visible detector (SPD-20A). The mobile phase, composed of 130 mM ammonium acetate–methanol–acetonitrile (40:20:40), was run at the flow rate of 0.9 mL/min.

The concentration–time data of risperidone and 9-hydroxyrisperidone from single-dose 4-mg reference tablet and single dose 4-mg CR test tablet were analyzed with Win Nolin® Ver. 5.2.1 (Pharsight Corporation, Mountain View, CA, USA). Standard non-compartmental approach (32) was implemented to find out various pharmacokinetic parameters including half-life ($t_{1/2}$), area under the curve (AUC), and mean residence time (MRT). Unpaired *t* test with Prism Graph Pad, version 5, was carried out to conclude for the treatment effect (test tablets *versus* reference tablets). Percent relative bioavailability of the test tablet was calculated with the following equation (33):

$$\text{Percent relative } \textit{bioavailability} = \frac{\text{AUC}_{0-t}(\text{Test})}{\text{AUC}_{0-t}(\text{Reference})} \times 100 \quad (3)$$

Percent risperidone absorbed (P_a) was plotted against percent risperidone released to determine *in vivo–in vitro* correlation. Percent risperidone absorbed was determined by the Wagner–Nelson method (34), while percent risperidone released values were taken from the *in vitro* drug release data.

Statistical Analysis

Unpaired *t* test was conducted with Prism Graph Pad, version 5, to compare the *in vitro* drug release profiles and the *in vivo* pharmacokinetic parameters.

RESULTS

Physicochemical Evaluation of Powder Mix, Granules, and Tablets

The angle of repose (AR), compressibility index (CI) and Hausner's ratio (HR) for the powder mixture of formulation F1 were found as 47±2, 26±3, and 1.36±0.16, respectively, indicating poor flow ability and compressibility. The AR, CI, and HR (49±3, 28±4, and 1.42±0.13, respectively) values for the powder mix of formulation F2 and the AR, CI, and HR (55±4, 31±2, and 1.45±0.18, respectively) values for formulation F3 also indicate poor flow ability and compressibility. For the prepared granules, the values of AR, CI, and HR were noted as 31±2, 11±2, and 1.13±0.12, respectively for formulation F1; as 33±2, 13±2, and 1.16±0.15, respectively, for formulation F2; and as 32±2, 12±1, and 1.18±0.12, respectively, for formulation F3, indicating their good flow ability and compressibility properties. Drug contents of granules of F1, F2, and F3 were observed as 103±4%, 102±3%, and 104±3%, respectively. The tablets from each lot (9-, 12-, and 15-kg hardness) of formulations F1, F2, and F3 showed <2% variation in physical dimensions, <5% variation in weights, <0.5% friability, and <5% variation in drug content, fulfilling the dosage uniformity requirements of Monograph #<905>, USP XXX

Drug Release Kinetics

The model formulations F1, F2, and F3, tested for drug release, exhibited drug release periods of nearly 8, 12, and 24 h, respectively, as represented in Fig. 1. The dissolution data obtained during the present study were fitted to the generally used kinetic models; a detailed account of the exploration is presented in Table I. Release rates (*K* values) ranged from 11.45% to 12.09% per hour in the case of formulation F1, from 8.13% to 8.26% per hour in the case of

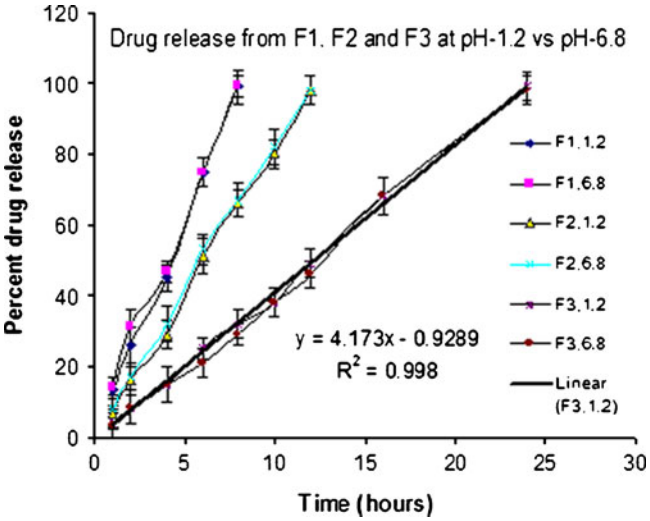

Fig. 1. Comparative release profiles of risperidone from 12-kg hard tablets of model formulations F1 (60% Methocel® and 30% Ethocel®), F2 (45% Methocel® and 45% Ethocel®), and F3 (30% Methocel® and 60% Ethocel®) using dissolution media of 0.1 N HCl with pH 1.2 (F1, 1.2; F2, 1.2; F3, 1.2) and phosphate buffer with pH 6.8 (F1, 6.8; F2, 6.8; F3, 6.8), stirred with paddles run at 50 rpm

formulation F2, and from 4.10% to 4.20% per hour using 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) as dissolution media, as shown in Table I. Release exponent n and/or goodness-of-fit test (linearity of the curve) were used as standards for selecting the most appropriate model. The observed values of the release exponent n more or less ranged from 0.86 to 1.14 of formulations F1, F2, and F3 in both 0.1 N HCl and phosphate buffer. Changes in the hardness of tablets and pH of the dissolution media did not affect significantly ($p>0.05$) the release rates and mechanism (see Table I and Figs. 2 and 3). The drug release profiles of the various lots (*i.e.*, 9-, 12-, and 15-kg hard tablets) of formulation F3, determined in the dissolution media of 0.1 N HCl and phosphate buffer, were compared using a model-independent pairwise approach of similarity factor f_2. The similarity factor f_2 values, calculated as 80.96, 82.53, and 84.95 for 9-, 12-, and 15-kg hard tablets, respectively, of formulation F3, showed a good level of equivalence in dissolution profiles obtained for the tablets at pH 6.8 (used as test) *versus* pH 1.2 (used as reference).

The test tablet containing 30% Methocel® and 60% Ethocel® (F3) with 12-kg hardness was selected as the optimized one (based on its release kinetics of zero order) for further studies. Insignificant difference was observed in the drug contents (102±3, 103±2, and 100±3) of the test tablets produced at three different occasions. Accelerated storage conditions, 40±2°C/75±5% RH (mean±SD) did not affect significantly the drug content, weight variation, friability, hardness, and appearance of the CR test tablets for the whole 6-month study period (Table II).

In Vivo Evaluation

During HPLC-UV analysis, the retention times for 9-hydroxyrisperidone and risperidone were noted as 4.02 and 4.62 min, respectively. The mean absolute recoveries of

Table I. Effect of Formulation (F1, F2, and F3), Dissolution Media (pH 1.2 and 6.8) and Tablet Hardness (9, 12, and 15 kg) on the Release Kinetics of Risperidone from Its Extended-Release Tablets

		Zero order		Higuchi		First order		Hixon–Crowel		Korsemeyer		Results
Formulation	Hardness (kg)	K	R^2	K	R^2	K	R^2	K	R^2	n	R^2	Mechanism of drug release
pH of the dissolution medium = 1.2												
F1	9	12.09	0.998	45.94	0.971	−0.213	0.816	−0.311	0.982	0.88	0.994	Zero order[a]
	12	12.29	0.996	46.74	0.969	−0.247	0.778	−0.0317	0.977	0.94	0.994	Zero order[b]
	15	11.91	0.998	45.30	0.973	−0.212	0.821	−0.302	0.979	0.86	0.997	Zero order[a]
F2	9	8.13	0.999	36.22	0.974	−0.124	0.768	−0.231	0.952	1.05	0.993	Zero order[b]
	12	8.26	0.997	36.87	0.976	−0.126	0.783	−0.235	0.952	1.07	0.995	Zero order[b]
	15	8.13	0.996	36.29	0.976	−0.113	0.794	−0.229	0.962	1.14	0.994	Zero order[b]
F3	9	4.11	0.997	23.75	0.954	−0.059	0.839	−0.128	0.906	1.07	0.987	Zero order[b]
	12	4.17	0.998	24.06	0.949	−0.075	0.782	−0.127	0.928	1.01	0.998	Zero order[b]
	15	4.10	0.998	23.45	0.962	−0.065	0.819	−0.125	0.917	0.99	0.997	Zero order[b]
pH of the dissolution medium=6.8												
F1	9	11.45	0.998	43.57	0.975	−0.189	0.833	−0.287	0.978	0.81	0.998	Zero order[a]
	12	11.85	0.993	45.18	0.973	−0.246	0.780	−0.297	0.861	0.88	0.980	Zero order[a]
	15	11.55	0.994	44.23	0.982	−0.212	0.840	−0.285	0.958	0.83	0.985	Zero order[a]
F2	9	8.40	0.997	37.14	0.976	−0.143	0.728	−0.242	0.951	1.11	0.993	Zero order[b]
	12	8.19	0.998	36.69	0.982	−0.127	0.799	−0.229	0.948	1.02	0.998	Zero order[b]
	15	8.18	0.994	36.21	0.956	−0.115	0.799	−0.234	0.965	1.01	0.978	Zero order[b]
F3	9	4.17	0.997	23.85	0.954	−0.076	0.789	−0.125	0.926	0.98	0.992	Zero order[b]
	12	4.18	0.996	23.98	0.939	−0.065	0.811	−0.131	0.927	1.08	0.994	Zero order[b]
	15	4.20	0.995	24.25	0.947	−0.074	0.761	−0.126	0.924	0.99	0.992	Zero order[b]

K, R^2, and n represent the release rate constant, coefficient of determination, and release exponent, respectively. F1 contains 60% Methocel® and 30% Ethocel®; F2 contains 45% Methocel® and 45% Ethocel®; and F3 contains 30% Methocel® and 60% Ethocel®

[a] Decision was made on the basis of the values of R^2

[b] Decision was made on the basis of the values of both n and R^2

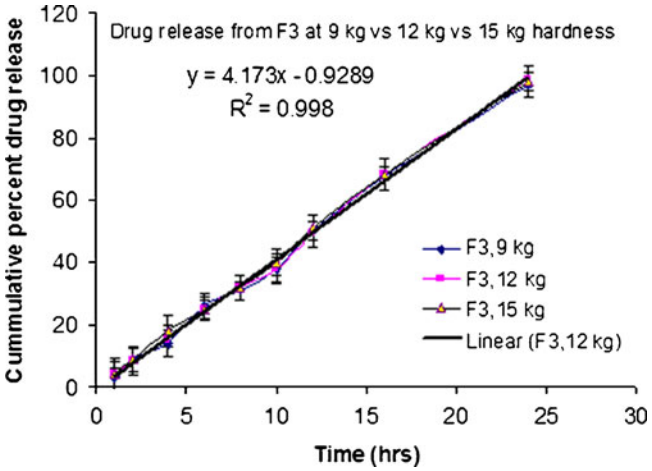

Fig. 2. Comparative release profiles of risperidone from 9- 12-, and 15-kg hard tablets of model formulation F3 (30% Methocel® and 60% Ethocel®) using dissolution media of 0.1 N HCl, pH 1.2, stirred with paddles run at 50 rpm

risperidone and 9-hydroxyrisperidone were observed as 91.5±3% and 90±2%, respectively.

The CR test tablet exhibited a significantly ($p<0.05$) optimized peak serum concentration (C_{max}) and a significantly ($p<0.05$) extended peak time (T_{max}, hours) and mean residence time ($MRT_{0-48\ h}$) with respect to the active moiety, risperidone alone, and 9-hydroxyrisperidone alone. The areas under the curves ($AUC_{0-48\ h}$ and AUC_{0-inf}) of the active moiety for the test and the reference tablets were not significantly ($p<0.05$) different (see Fig. 4 and Table III), indicating bioequivalence of the CR test tablets with the reference conventional tablets. Significant extension ($p<0.05$) in the half-lives of risperidone alone and 9-hydroxyrisperidone alone were shown by the CR test tablet, indicating the success of the formulation (see Fig. 4 and Table III). The half-life of the active moiety from the CR test tablet was noted as 18.14±3.45 h, while that of the reference tablet was 15.27±2.092 h, indicating successful development of the CR formulation.

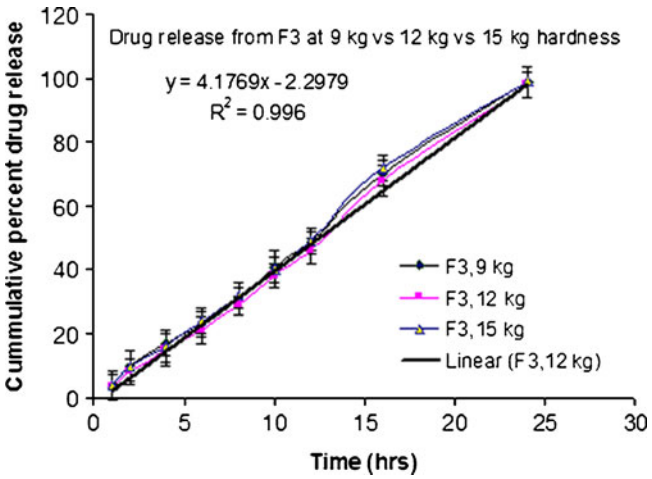

Fig. 3. Comparative release profiles of risperidone from 9-, 12-, and 15-kg hard tablets of model formulations F3 (30% Methocel® and 60% Ethocel®) using dissolution media of phosphate buffer, pH 6.8, stirred with paddles run at 50 rpm

Relative Bioavailability and *In Vitro* and *In Vivo* Correlation

The percent risperidone absorbed (P_a) when plotted against the percent risperidone released (P_r) showed a good correlation ($R^2=0.7293$) between the drug absorbed *in vivo* and the drug released *in vitro* (Fig. 5).

DISCUSSION

Commonly encountered noncompliance to antipsychotic drug therapy (3,35) leads to an almost double re-hospitalization from relapse (36). Therefore, a controlled-release tablet of risperidone was developed to optimize its blood level, minimize its side effects, and ultimately improve its treatment adherence.

During pilot studies, the widely used release-retarding hydrophilic polymer Methocel® K100LV-CR was tried alone starting from 20% up to 60% of tablet weight (with 10% increments), but it could hardly extend the drug release period from 2 h up to 8 h. Then, the percentage of the Methocel® was further increased step by step in the same way up to 90% of tablet weight, but the release period was not extended to any appreciable extent. Therefore, a part of the Methocel® was substituted by the hydrophobic Ethocel® standard 7FP premium for extending the release period up to 24 h.

In a total 90% polymeric blend, 60% Methocel® and 30% Ethocel® (F1) could hardly maintain the release period of 8 h. However, the value of the release exponent n was raised from an anomalous drug release ($n<0.89$) to a zero-order drug release ($n\geq0.89$) pattern using 0.1 N HCl (pH 1.2). Nearly the same results were observed for the tablets in phosphate buffer (pH 6.8). A major difficulty experienced after the inclusion of 30% Ethocel® in formulation F1 was the poor flowability and compressibility of the powder mixture, which led us to use the dry granulation–slugging method for manufacturing the tablets. The flow and compressibility characteristics of the powder mixtures were sufficiently improved by the successful use of the dry granulation–slugging method. The method was selected because it does not allow a chance of decomposition of drugs by hydrolysis, as occurs in the case of wet granulation method. Thereafter, further substitution of 15% Methocel® by Ethocel® (F2, 45:45%) extended the release period up to 12 h, with n values ≥0.89 and/or R^2 falling near to 1 (linear curve), indicating zero-order kinetics. In the case of formulation F3, further substitution of 15% Methocel® by Ethocel® (30% Methocel® and 60% Ethocel®) could extend the release period up to 24 h with zero-order kinetics, as shown in Fig. 1 and Table I.

An expected but disproportional reduction in the release rates with an increase in the concentration of the hydrophobic Ethocel® might be caused by the slow penetrability of water for hydration of the matrix due to the hydrophobic character of the Ethocel® particles. Additionally, the insoluble particles of Ethocel® entangled in the gel layer of Methocel® were perhaps performing the role of barrier to drug release. This idea is in line with some previously published studies (25,37).

Table II. Stability Indicating Parameters Determined for the Test Tablet of Risperidone at 40±2°C/75±5% RH (Mean±SD)

Testing time	Drug content (%)	Weight variation (%)	Friability (%)	Hardness (kg)	Appearance
At 0 time (pre-storage)	103±3	4±0.3	0.45±0.02	12.0±0.3	whitish
After 1 month	104±2	4±0.4	0.41±0.03	12.0±0.3	whitish
After 2 months	103±3	3±0.4	0.51±0.03	12.0±0.3	whitish
After 4 months	101±3	3±0.3	0.43±0.02	12.2±0.4	whitish
After 6 months	100±2	4±0.4	0.68±0.02	12.4±0.4	whitish

Since both Methocel® and Ethocel® possess binding and matrix-forming characteristics (38), tablets of high quality (optimum friability and desired hardness level) were produced. As zero-order drug release supplies a constant amount of drug for absorption and maintains a constant level of plasma concentration (39), many researchers have sought to formulate matrices for zero-order release pattern, but few have been successful (24,25).

To elucidate the mechanism of drug release from risperidone controlled-release tablets, dissolution data for the first 60% of drug release (40) were fitted to the exponential equation (26). The release exponent n was calculated through the slope of the straight line upon fitting data into the Korsemeyer–Peppas model (26,41). In the case of cylinders (*i.e.*, tablets), the value of $n \leq 0.45$ shows Fickian release; values of $0.45 < n < 0.89$ show anomalous transport, while the value of $n \geq 0.89$ shows a zero-order release (42,43).

Fickian diffusion proposes the diffusion of drug through pores of the matrix and zero-order express release of drug with erosion of the polymeric chains, while anomalous transport reveals release of drug by a combined process of diffusion and erosion (41). The decisive factor for selecting the most appropriate model (among the mathematical models usually employed in this connection) was based on the n value and/or goodness-of-fit test (*i.e.*, linearity of the curves, where the coefficient of determination R^2 approaches 1) values.

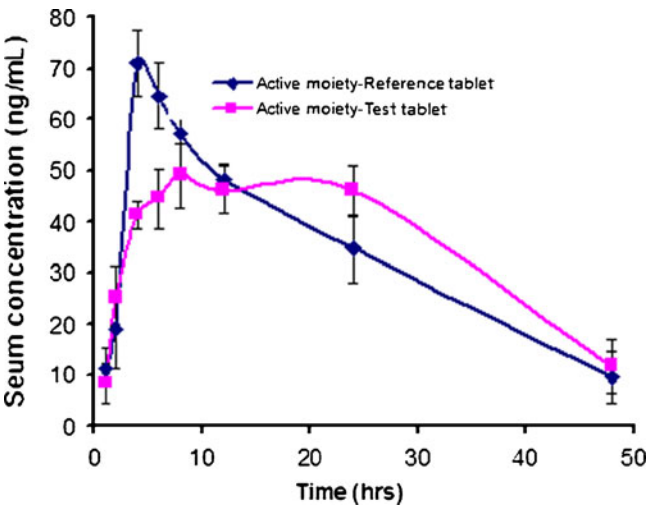

Fig. 4. Comparative serum concentration–time profiles of active moiety–reference tablet and active moiety–test tablet obtained from reference and test tablets, respectively, following their oral administration to rabbits (mean ± SD, $n=6$). Active moiety refers to the combined concentration of risperidone and 9-hydroxyrisperidone

Use of a larger proportion of the polymer blend (*i.e.*, 90%) was compromised for achieving the 24-h release period with zero-order kinetics. The aforementioned objectionable point is qualified by some earlier investigations where 89.5% of fine particle ethyl cellulose (23) and 90% Methocel- and Ethocel-based blends (25) were used to extend the drug release period up to 24 h. The need for so much higher concentrations of the polymeric blend in the present study may be due to the low-viscosity gel former Methocel®,K100 LV-CR (44), leading to rapid disentanglement and erosion of the matrices.

Drug release mechanism based on the values of n and/or R^2 showed a zero-order release pattern of risperidone at both pH 1.2 and pH 6.8 for all (9-, 12-, and 15-kg hard tablets) three formulations F1, F2, and F3.

Application of a higher compression force to the designed matrices regularly caused an increase in tablet hardness, but the drug release kinetics were not affected in both dissolution media, which is in line with some previous studies (25,45). It means that the porosity and/or tortuosity of the prepared tablets upon hydration were not affected by the increase in tablet hardness, which is in line with the observations of some other groups of investigators (45,46).

As the pH in GIT is not uniform, influence of changes in pH on the drug release kinetics was also studied (see Figs. 2 and 3). Methocel® K100 LV-CR (hydroxypropyl methylcellulose) is a cellulose derivative (with methoxyl and hydroxypropyl substituents on a β-*o*-glucopyranosyl ring backbone) resistant to changes in pH of the dissolution medium in the range of 2–13, so it is relatively stable (47). Similarly, Ethocel®, a cellulose derivative (with ethoxyl substitution on anhydroglucose ring backbone), is insoluble in water; thus, its release properties are less affected by the changes in pH (48). Therefore, in the present study, risperidone release from a blend of these polymers was not affected by changes in pH of the dissolution media.

The similarity factor $f_2 \geq 50$ indicates an average difference of not more than 10% at the sample time points (27,28). In the present study, higher values of the similarity factor f_2 (*i.e.*, >80) for the 9-, 12-, and 15-kg hard tablets of formulation F3 indicate negligible difference of the tablets' dissolution profiles in phosphate buffer (pH 6.8) *versus* in 0.1 N HCl (pH 1.2). The aforementioned values of f_2 calculated for the tablets have further strengthened our finding that the pH variations did not significantly affect the drug release from the matrices designed in the present study.

The comparative *in vivo* studies of the test tablet and the reference conventional Risperdal® tablet in rabbits exhibited the ability of the former tablet to maintain a fairly optimized serum concentration of the drug for an extended period (see Fig. 4). Significant extension in half-life ($t_{1/2}$) and time for

Table III. Pharmacokinetic Parameters Determined in Rabbit Sera Following Oral Administration of 4 mg Reference Conventional Tablets and 4 mg CR Test Tablets (Mean ± SEM)

Pharmacokinetic parameter determined as	Reference tablets	Test tablets
Active moiety (risperidone plus 9-hydroxyrisperidone)		
Half-life, $t_{1/2}$ (h)	15.27±2.092	18.14±3.45
Time of maximum plasma concentration, T_{max} (h)	4.67±0.42	11.00±2.72*
Maximum plasma concentration, C_{max} (ng/mL)	72.83±2.12	51.50±1.80***
Area under curve, $AUC_{0–48\ h}$ (ng h/mL)	1,609.00±70.72	1,702.00±54.20
Area under curve-$AUC_{0–inf}$ (ng h/mL)	1,853.00±146.80	2,061.00±184.80
Mean residence time, $MRT_{0–48\ h}$ (h)	17.24±0.64	19.40±0.55*
Risperidone (alone)		
Half-life, $T_{1/2}$ (ng h/mL)	5.07±0.34	15.32±2.08***
Time of maximum plasma concentration, T_{max} (h)	4.17±0.17	3.67±0.33
Maximum plasma concentration, C_{max} (ng/mL)	56.00±2.66	26.00±1.27***
Area under curve, $AUC_{0–48\ h}$ (ng h/mL)	499.8±26.72	589.0±19.60*
Area under curve, $AUC_{0–inf}$ (ng h/mL)	518.8±21.64	835.5±107.4*
Mean residence time, MRT_{all} (h)	7.289±0.57	15.01±1.09***
9-Hydroxyrisperidone (alone)		
Half-life, $t_{1/2}$ (ng h/mL)	17.50±2.11	74.72±16.06***
Time of maximum concentration, T_{max} (h)	14.67±3.04	14.67±3.04
Maximum plasma concentration, C_{max} (ng/mL)	33.83±1.276	21.00±1.789***
Area under curve, AUC_{0All} (ng × h/mL)	1,109±54.99	745.2±50.23***
Are under curve, $AUC_{0–inf}$ (ng h/mL)	1,594±291.0	2,280±384.5
Mean residence time, $MRT_{0–48\ h}$ (h)	21.05±0.7215	24.08±0.4496**

*P<0.05, **P<0.001, ***P<0.0001 (values are significantly different between means of reference and test tablets of risperidone, mean ± SEM)

peak concentration (T_{max}) of risperidone and 9-hydroxyrisperidone from the test tablet is indicative of drug release at a slower rate for an extended time interval. Bioequivalence of the test tablet to the reference conventional Risperdal® tablet is indicated by the AUCs of the tablets concerned (see Table II). The relative bioavailability of test tablets, calculated as 100%, also indicates the suitability of the formulation. An optimized serum drug concentration from the test tablet for an extended time (see Fig. 4) proves the successful development of the controlled-release formulation.

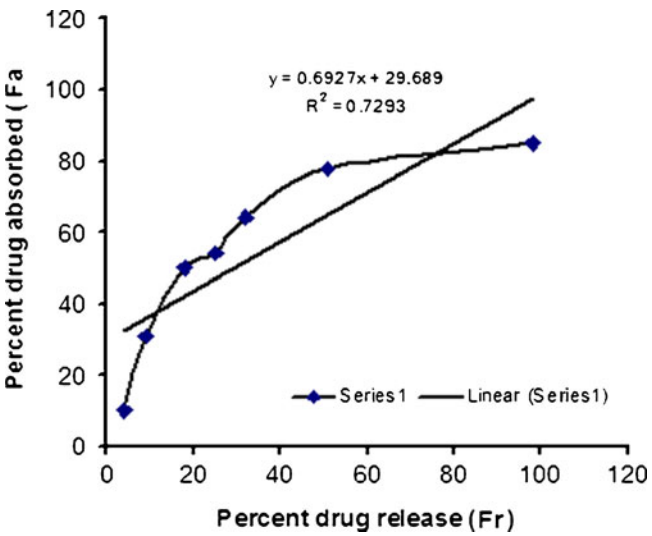

Fig. 5. Percent drug absorbed (P_a) plotted against percent drug released (P_r) at times 1, 2, 4, 6, 8, 12, and 24 h to determine the *in vitro* and *in vivo* correlation of risperidone controlled-release test tablet

The percent drug absorbed was calculated with the Wagner and Nelson method (34) followed by *in vitro–in vivo* correlation (R^2) determination, which turned out to be 0.7293 for the test tablet (see Fig. 5). The results revealed a good level A (point to point) correlation of drug absorbed with the amount of drug released.

CONCLUSION

The blend of Methocel® K100LV-CR and the Ethocel® standard 7FP premium was successfully used in preparing the CR tablet of risperidone. The blend exhibited a pH-independent zero-order kinetics. Ethocel® played a major role in controlling drug release, while the gel layer of Methocel® proved its worth in maintaining solidarity of the matrix. The CR test tablet, based on its optimized peak concentration and bioequivalence to the conventional Risperdal® tablet, may be used for better therapeutic outcomes of risperidone.

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Declaration of Interest The authors report no declaration of interest.

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