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Research Article

Controlled Release Matrix Tablets of Olanzapine: Influence of Polymers on the *In Vitro* Release and Bioavailability

Amir Badshah,[1,2] Fazal Subhan,[1] and Khalid Rauf[1]

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Abstract. Controlled-release (CR) tablet formulation of olanzapine was developed using a binary mixture of Methocel® K100 LV-CR and Ethocel® standard 7FP premium by the dry granulation slugging method. Drug release kinetics of CR tablet formulations F1, F2, and F3, each one suitably compressed for 9-, 12-, and 15-kg hardness, were determined in a dissolution media of 0.1 N HCl (pH 1.5) and phosphate buffer (pH 6.8) using type II dissolution apparatus with paddles run at 50 rpm. Ethocel® was found to be distinctly controlling drug release, whereas the hardness of tablets and pH of the dissolution media did not significantly affect release kinetics. The CR test tablets containing 30% Methocel® and 60% Ethocel® (F3) with 12-kg hardness exhibited pH-independent zero-order release kinetics for 24 h. *In vivo* performance of the CR test tablet and conventional reference tablet were determined in rabbit serum using high-performance liquid chromatography coupled with electrochemical detector. Bioavailability parameters including C_{max}, T_{max}, and $AUC_{0-48\ h}$ of both tablets were compared. The CR test tablets produced optimized C_{max} and extended T_{max} ($P<0.05$). A good correlation of drug absorption *in vivo* and drug release *in vitro* ($R^2=0.9082$) was observed. Relative bioavailability of the test tablet was calculated as 94%. The manufacturing process employed was reproducible and the CR test tablets were stable for 6 months at 40±2°C/75±5% relative humidity. It was concluded that the CR test tablet formulation successfully developed may improve tolerability and patient adherence by reducing adverse effects.

KEY WORDS: bioavailability; controlled release; Ethocel®; olanzapine.

INTRODUCTION

Olanzapine, a second-generation antipsychotic, has been used widely for the clinical management of psychiatric illnesses, including acute mania, schizophrenia, and other psychotic disorders (1,2). Olanzapine serum level showed a tendency to increase with daily dose (3). The mean time for maximum concentration (T_{max}) and half-life ($t_{1/2}$) of olanzapine were observed as 6 and 33 h, respectively (4). Peak blood concentration (C_{max}) of olanzapine was detected as 5–50 ng/mL in the case of 2.5- to 17.5-mg daily doses (5) and 8–31 ng/mL in the case of 10- to 20-mg daily doses (3). The optimal therapeutic range of olanzapine was suggested as 20–50 ng/mL by Mauri *et al.* (6) and 20–60 ng/mL by Hiemke *et al.* (7).

Both first-generation antipsychotics and second-generation antipsychotics have increased risks of annoying extrapyramidal symptoms (8,9) and sudden cardiac deaths (10). Olanzapine and ziprasidone exhibited intermediate-level extrapyramidal side effect profiles (11,12). The most frequent side effects of olanzapine include sedation, somnolence, weight gain, hyperprolactinaemia, orthostatic hypotension increased appetite, dizziness, fatigue, elevated plasma glucose, triglycerides and liver enzyme levels, constipation, and dry mouth (13).

Non-adherence to antipsychotic medications has been a major subject of concern in clinical practice (14). There were many reasons for non-adherence, the important ones being side effect profiles and poor tolerability (15,16). The development of novel drug delivery systems of some antipsychotic drugs exhibited improved patient adherence by minimizing side effects and optimizing dosage regimen without compromising their therapeutic efficacy (17). In this context, extended-release tablet of quetiapine fumarate (Seroquel XR) showed improved efficacy and tolerability in patients with schizophrenia (18). Controlled-release tablets of olanzapine were designed in the present study to improve its safety and adherence profiles. Although olanzapine may not be an ideal drug for formulation in controlled-release tablet form, its side effect-dependent poor tolerability makes it a good candidate for formulating in such a form. Extended-release (ER) tablet of carbamazepine, instead of its long mean half-life of 37.5 h (19), has got official status in United States Pharmacopeia, USPXXXI, and a group of investigators prepared ER tablet of carbamazepine to improve its tolerability and adherence profile (20).

As per the available literature, only one study was found reporting the preparation of olanzapine sustained-release nanoparticles (21). Based on olanzapine proven efficacy along with frequent and serious side effects discussed above, the present study was aimed at the development of controlled-

[1] Department of Pharmacy, University of Peshawar, Peshawar, 25120 N.W.F.P, Pakistan.
[2] To whom correspondence should be addressed. (e-mail: amir_bad shah@upesh.edu.pk)

release (CR) matrix tablets of olanzapine to minimize fluctuation in serum drug level and subsequent lowering of side effects with improved tolerability and patient adherence. The widely recommended Methocel® K100 LV-CR and Ethocel® standard 7FP premium (22–24) were used in combination to prepare the controlled-release tablets of olanzapine, as proposed by a research team (25).

MATERIALS AND METHODS

Materials

Olanzapine (RPG Life Sciences Ltd, India) was provided as a gift sample by Danis Pharma, Islamabad, Pakistan. Methocel® K100 LV-CR (hydroxypropylmethylcellulose, HPMC-2208) and Ethocel® standard 7FP premium (fine particle ethylcellulose) were obtained as gifts from the Colorcon Asia Ltd, India. Conventional tablets (Zyprexa® by Eli Lilly Pvt Ltd, Karachi; Pakistan) containing 10 mg olanzapine were purchased from a local market. High-performance liquid chromatography (HPLC) grade acetonitrile and methanol were purchased from Merck's (Germany) authorized local supplier. All the other chemicals were either of analytical or pharmaceutical grades.

Preparation of Tablets

Methocel® K100 LV-CR (abbreviated as M) and Ethocel® standard 7FP premium (abbreviated as E) were blended together in three different proportions to constitute a 90% portion of the 200-mg tablet. Formulation F1 contained 60%M and 30%E, formulation F2 contained 45%M and 45%E, and F3 contained 30%M and 60%E. The blends were mixed with fixed amounts of olanzapine (5%), lactose (3%), colloidal silicon dioxide-Aerosil® (0.5%), and magnesium stearate (0.5%) in a polythene bag. Geometric dilution method was employed for mixing the ingredients weighed for 600 tablets in the case of each formulation. Powder mixture was passed through sieve no. 40 and then compressed into slugs with a manually run Tablet Press ZP-17, Shanghai China, equipped with 17-mm flat-faced tooling. The slugs (weighing 700–800 mg) were crushed in an oscillating granulator equipped with a 20-mesh screen. Additional quantities of Aerosil® (0.5%) and magnesium stearate (0.5%) were thoroughly mixed with the well-sized granules (70% being of size>200 μm to <1 mm) in a polythene bag. The prepared granules of each formulation were then suitably compressed to manufacture tablets (each one weighing 200 mg) of 9-, 12-, and 15-kg hardness, using the same Tablet Press mentioned above, but equipped with 8.00×3.50-mm tetragonal tooling.

In Vitro Evaluation

Physicochemical Evaluation of Powders, Granules, and Tablets

Angle of repose (AR) of the powder mixture and granules was determined by funnel method, while compressibility index (CI) and Hausner ratio (HR) of the powder mixture and granules were determined by cylinder method as per the United States Pharmacopeia, USPXXXI procedure for powder flow determination. Friability of tablets was determined using friability testing apparatus (FB 994, Curio Pakistan). Hardness and physical dimensions of the tablets were determined using a hardness and dimension tester (CHT 901, Curio Pakistan). Weight variation and drug content of tablets were determined according to the standard procedures of United States Pharmacopeis, USPXXXI. Briefly, tablets were individually crushed and olanzapine was extracted with 100 mL methanol from the finely powdered material. Olanzapine was assayed with UV–Visible Spectrophotometer (Shimadzu, model 1700) at λ_{max} 270 nm.

Tablets placed in 900-mL dissolution media of either pH 1.5 or pH 6.8 (kept at 37±0.5°C) were stirred at 50 rpm in type II paddle dissolution apparatus (Erweka, Germany). The amount of olanzapine released after 1, 2, 4, 6, 8, 10, 12, 16, and 24 h was determined with the UV–Visible Spectrophotometer at wavelength λ_{max} 270 nm.

Drug Release Kinetics

The drug release data were plotted in various kinetic models, including zero-order and first-order, Higuchi's square root of time equation (26), Hixon and Crowel's cube root equation (27), and Korsemeyer–Peppas exponential equation (28) to determine the rate and mechanism of olanzapine release.

Testing Dissolution Equivalency

A simple model-independent approach that uses a similarity factor, proposed by Shah *et al.* (29) and adopted by US Food and Drug Authority (30), was employed for comparing the release profiles of olanzapine from the selected formulation F3 obtained at pH 1.5 and pH 6.8.

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

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

Reproducibility and Stability of the Tablets

Reproducibility of the manufacturing process was determined by preparing three repeated batches of the selected test formulation (F3 with 12-kg hardness) on three different occasions. The optimized tablets were stored in well-closed, high-density polyethylene jars and kept under accelerated storage conditions of 40±2°C/75±5% relative humidity (RH) in a stability chamber (Ti-Sc-THH-07-0400, Faisalabad, Pakistan) in accordance with International Commission for Harmonization guidelines for a period of 6 months. The samples were tested for appearance, percent drug contents, percent friability, and hardness at 0 time (pre-storage) and after storage for 1, 2, 4, and 6 months, respectively.

In Vivo Evaluation

The *in vivo* studies on Himalayan angora rabbits (of either sex with average weight of 2.0±0.2 kg) were conducted according to the standard protocol approved by the Research and Ethical Committee of Post-Graduate Medical Institute,

Hayatabad Medical Complex, Peshawar. Rabbits fasted for 24 h before the experiment and were divided into two groups, each having six animals. The selection of rabbits as animal model for the present study was based on previously published pharmacokinetic studies (31–33). The first group received orally the 10-mg reference tablets (Zyprexa® by Eli Lilly) and the second group received orally 10-mg CR test tablets of olanzapine. Briefly, for administration, the tablet was placed in the smoothly cut (opened) end of a 3-mL syringe (plastic) and pushed it ahead with a plunger toward the base of the rabbit's tongue for ingestion, followed by a few draughts (nearly 10 mL) of water. The rabbits were allowed free access to water during the whole period of study, but kept fasted for 12 h after tablet administration.

Blood samples (0.7 mL each time) were collected from the marginal ear vein of each rabbit at 0, 1, 2, 4, 6, 8, 12, 24, and 48 h in 3-mL test tubes and allowed to clot. Serum sample measuring 200 μL was withdrawn into another 3-mL test tube and centrifuged at 2,800 rpm for 10 min. Only 100 μL of the so obtained cleared serum was transferred to a 10-mL test tube and stored at −20°C until the time of sample preparation.

Extraction of olanzapine from serum samples was carried out using a previously published method (3). Briefly, to the 100-μL processed serum sample, 100 μL of 1 M sodium hydroxide and 6 mL mixture of pentane and dichloromethane (85:15) were added and thoroughly mixed for 2 min with vortex mixer. The mixture was centrifuged at 2,800 rpm and the supernatant (organic) layer was collected and transferred to a 10-mL test tube for subsequent drying under nitrogenous atmosphere. The residue so obtained was dissolved in 100 μL of acetonitrile by vortex mixing for 1 min and refrigerated at −20°C until the time of analysis.

Chromatographic Conditions

The serum level of olanzapine was determined by HPLC coupled with electrochemical detector (ECD) using a previously published method (34). Briefly, the HPLC system (Shimadzu, Japan) consisted a communication boss module (model 20A), two independently working pumps (model LC-20AT), and an analytical column Shim pack, RP.C18, CLC-ODS 150 mm×6 mm×5 μm, connected to an electrochemical detector, ESA Choulchem III (model 5300) equipped with an analytical cell (model 5011A). Electrodes 1 and 2 of the cell were set at +200 and −200 mV, respectively, while the guard cell (model 5020) was set at 300 mV. The mobile phase, consisting of 75 mM phosphate buffer, methanol, and acetonitrile (48:26:26), was used at a flow rate of 1.0 mL/min. Linearity, precision, and accuracy of the method and percentage recovery of olanzapine were determined using spiked serum of rabbits (with olanzapine concentrations of 0.5, 10, 50, and 100 ng/mL) run parallel to the same strength dilutions (*i.e.*, 0.5, 10, 50, and 100 ng/mL) of olanzapine stock solution. The validation experiments were carried out three times a day for three consecutive days.

Pharmacokinetic Analysis

The peak serum concentration (C_{max}) and time of its occurrence (T_{max}) were read directly from olanzapine concentration–time data. For other pharmacokinetic parameters, the concentration–time data were 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 olanzapine serum concentration–time data. Area under the plasma level–time curve (AUC) and moment plasma level–time curves (AUMC) were calculated by trapezoidal method. The ratio of AUC and AUMC was used to estimate the mean residence time (MRT) of the drug. 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 percent relative bioavailability of the test tablet was calculated with the following formula (35):

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

In vitro–in vivo correlation of the optimized formulation (F3 with 12-kg hardness) was investigated by plotting the percent drug absorbed (P_a) against the percent drug released (P_r). Percent drug dissolved values were taken from the *in vitro* release data and the percent drug absorbed values were calculated by Wagner–Nelson method (36).

Statistical Analysis

Unpaired *t* tests, using Prism Graph Pad, were carried out to compare the pharmacokinetic parameters of CR test tablets and reference tablets. *P* values of <0.05 were considered as significant.

RESULTS

In Vitro Evaluations

Physicochemical Evaluation of Powder Mixtures, Granules, and Tablets

The measured AR and compressibility index for powder mixtures indicated poor flowability and compressibility as compared to the same for granules which showed good flowability and compressibility characteristics (Table I). The HR of powder mixtures and granules followed the same trend (see Table I). Drug content of granules varied from 102±2% to 103±3%. The tablets from each lot of three formulations were found uniform with respect to physical dimensions, percent weight variation, percent friability, and percent drug content, represented by the results of the selected formulation F3 (see Table II), fulfilling the dosage uniformity requirements of United States Pharmacopeia, USPXXXI.

Drug Release Kinetics and Dissolution Equivalency

The three designed formulations, F1, F2, and F3, exhibited release periods of 8, 12, and 24 h, respectively (Figs. 1, 2, and 3). The drug release data of the three formulations revealed that the hardness of tablets and the pH

Table I. Physicochemical Characteristics of Powder Mix and Granules Prepared for the Manufacture of Controlled-Release Matrix Tablets of Olanzapine (Mean ± SD, n=6)

Angle of repose (deg)		Compressibility index (%)	Hausner ratio	Drug content
Powders mix				
F1	46±3	27±3	1.32±0.11	–
F2	51±3	32±4	1.43±0.13	–
F3	60±3	33±3	1.56±0.13	–
Granules				
F1	31±3	11±2	1.14±0.12	103±3
F2	33±2	13±2	1.16±0.10	103±2
F3	33±2	12±1	1.17±0.13	102±2

of dissolution media did not significantly affect the drug release rate and mechanism (Figs. 1, 2, and 3). The value of R^2 (coefficient of determination) measured highly fit in the zero-order model. Values of the release exponent "n" were also found as ≥0.89, indicating a zero-order release pattern (Figs. 1, 2, and 3). The values of similarity factor f_2 for the selected formulation F3 were calculated as 68.29, 66.55, and 72.53 for 9-, 12-, and 15-kg hard tablets, respectively, indicating that the dissolution profiles determined at pH 6.8 *vs* pH 1.5 at all the three hardness levels were highly comparable, indicating that the pH did not affect significantly the drug dissolution/release profiles.

Reproducibility of Manufacturing Process and Stability of Tablets

The CR test tablets containing 30% Methocel® and 60% Ethocel® (F3) with 12-kg hardness were selected as the optimized formulation based on optimum flow (AR=33±2), compressibility (CI=12±1) of its granules, hardness (12 kg), and drug release period of 24 h. The formulation followed the zero-order release pattern in both dissolution media of pH 1.5 and pH 6.8. In the three batches of the CR test tablets produced on three different occasions, no significant (P<0.05) difference was observed with respect to drug contents (103±2, 102±3, and 100±4). The data on the stability parameters, including drug content, weight variation, friability, hardness, and appearance for the CR test tablets, indicated that there was no significant (P<0.05) effect of the accelerated storage conditions (40°C/75% RH) after storage for 1, 2, 4, and 6 months (Table III).

In Vivo Evaluation

Method Validation

During the HPLC-ECD analysis, rabbit serum collected at zero time showed no peak, while spiked samples exhibited a single peak of olanzapine, indicating high level selectivity of the method. The retention time and absolute recovery of olanzapine were found as 9.23 min and 93%, respectively. Accuracy of the method was shown by coefficient of variations being 7% for interday and 9% for intraday determinations. A good level linearity of the method was shown by coefficient of determination being 0.897. Sensitivity of the method was observed as 0.5 ng/mL

Pharmacokinetics of Olanzapine

Significantly higher values of peak time, T_{max} (14.00± 2.00 *vs* 8.0±0.89, P<0.05); mean residence time, $MRT_{0–48\ h}$ (26.59±0.81 *vs* 17.61±0.36, P<0.0001); and half life, $t_{1/2}$ (17.00± 1.59 *vs* 13.13±0.65, P<0.05), were observed for CR test tablets as compared to the same for reference tablets, indicating extended absorption phase and presence of the drug for a longer time in the body. Significantly optimized values of peak concentration, C_{max} (43.17±1.47 *vs* 82.17±2.21, P< 0.0001) were exhibited by the test tablets. Area under curve up to 48 h $AUC_{0–48\ h}$ (1,980±45.06 *vs* 2,108±69.69) and area under the curve up to infinite time $AUC_{0\text{-}inf}$ (2,140±79.08 *vs* 2,342±107.2) for test and reference tablets were not significantly different at P<0.05, indicating bioequivalence of the CR test tablets to the reference conventional tablets.

Relative Bioavailability and In Vitro–In Vivo Correlation

The relative bioavailability of test tablet was calculated as 94%. The CR test tablet showed an extended absorption phase. The percent drug absorbed (P_a) plotted against percent drug released (P_r) exhibited a good correlation with R^2 value of 0.9082 (Fig. 4).

DISCUSSION

Drug tolerability is a key parameter in clinical practice while prescribing a drug. As antipsychotic therapies are usually prescribed for longer times, the significance of tolerability and safety increases manifold. Therefore, the widely used antipsychotic drug, olanzapine, was developed in the form of controlled-release matrix tablets.

In a published study, the concentration of olanzapine in serum showed a tendency to increase with the administered daily dose (3), which in turn caused an increase in side effects and poor tolerability, leading to poor compliance (15,16,37). Therefore, the CR tablets of olanzapine were developed to manage optimization of olanzapine blood level. The present study using rabbits as animal model shows the ability of the CR test tablet formulation to maintain a fairly constant and an optimum blood level for 24 h as compared to a rapid rise followed by a similar decline in olanzapine serum concentration from reference tablets (Fig. 5). Significant extension in half-life

Table II. Physicochemical Characteristics of Controlled-Release Matrix Tablets of the Selected Formulation F3 (Mean ± SD, n=20)

Hardness of tablets (kg)	Friability (%)	Weight variation (%)	Drug content (%)	Dimensions (length and width in mm)
9	0.46±0.08	5±0.5	100±4	8.0±0.1×3.6±0.1
12	0.49±0.07	4±0.3	101±3	8.1±0.1×3.5±0.1
15	0.42±0.04	5±0.4	102±3	8.1±0.1×3.5±0.1

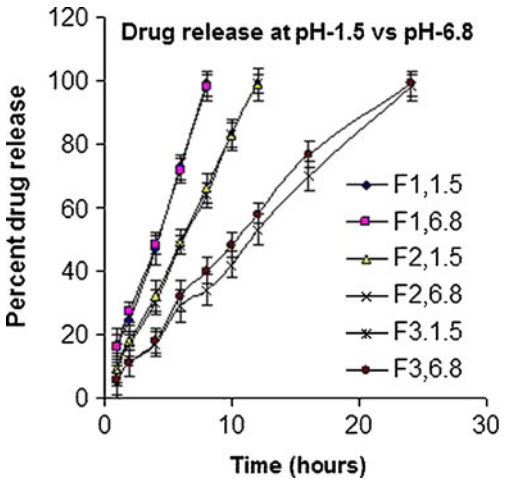

Fig. 1. Release profiles of olanzapine from 9-kg hard tablets of model formulations F1 (60% Methocel®, 30% Ethocel®), F2 (45% Methocel®, 45% Ethocel®), and F3 (30% Methocel®, 60% Ethocel®) using dissolution media of 0.1NHCI with pH 1.5 (F1,1.5; F2,1.5, F3,1.5) and phosphate buffer with pH 6.8 (F1,6.8; F2,6.8; F3,6.8), stirred with paddles run at 50 rpm (mean ± SD, n=6)

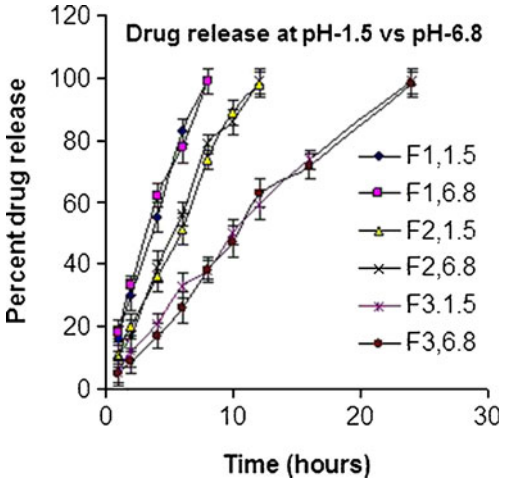

Fig. 3. Release profiles of olanzapine from 15-kg hard tablets of model formulations F1 (60% Methocel®, 30% Ethocel®), F2 (45% Methocel®, 45% Ethocel®), and F3 (30% Methocel®, 60% Ethocel®) using dissolution media of 0.1 N HCI with pH 1.5 (F1,1.5; F2,1.5; F3,1.5) and phosphate buffer with pH 6.8 (F1,6.8; F2,6.8; F3,6.8) stirred with paddles run at 50 rpm (mean ± SD, n=6)

($t_{1/2}$) and time required to achieve peak concentration (T_{max}) of the test CR tablets is indicative of drug release at a slower rate for an extended period of time. No significant difference in mean AUCs of test and reference tablets indicates that both the formulations were bioequivalent.

As both Methocel® and Ethocel® have sufficient binding characteristics (38,39), tablets of optimum friability and desired hardness at each level of compression force were produced. 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 (25,40).

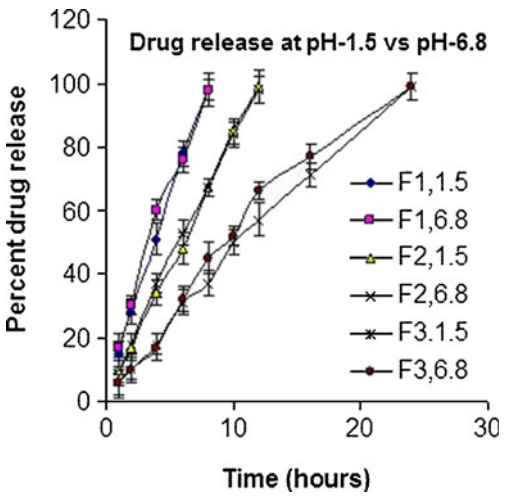

Fig. 2. Release profiles of olanzapine from 12-kg hard tablets of model formulations F1 (60% Methocel®, 30% Ethocel®), F2 (45% Methocel®, 45% Ethocel®), and F3 (30% Methocel®, 60% Ethocel®) using dissolution media of 0.1NHCI with pH 1.5 (F1,1.5; F2,1.5; F3,1.5) and phosphate buffer with pH 6.8 (F1,6.8; F2,6.8; F3,6.8), stirred with paddles run at 50 rpm (mean ± SD, n=6)

To elucidate the mechanism of drug release from olanzapine controlled-release tablets, dissolution data for the first 60% of drug release (41) were fitted to the exponential equation. The release exponent "n" was calculated through the slope of the straight line of the data after fitting in the model (28,42). In the case of cylinders (*i.e.*, tablets), the value of "n" ≤ 0.45 shows Fickian release, 0.45<"n"<0.89 shows anomalous transport, while the value of "n" ≥ 0.89 shows zero-order release (43,44). Fickian diffusion refers to the diffusion of drug through pores of the matrix, zero-order demonstrates the release of drug with erosion of the polymeric chains, and anomalous transport refers to the release of drug by a combined process of diffusion and erosion (42). The criterion for selecting the most appropriate model (among the mathematical models mentioned above) was chosen on the basis of "n" values and/or goodness-of-fit test (*i.e.*, coefficient of determination R^2 value falling near 1.0, which shows linearity of regression line) where necessary.

Interestingly, in a total of 90% of the polymeric blend, 60% Methocel® and 30% Ethocel® (F1) could hardly maintain the release period for 8 h. However, the value of release exponent "n" turned out to be 0.79, 0.89, and 0.89 (showing anomalous drug transport and/or zero-order mechanism) of 9-, 12-, and 15-kg hard tablets, respectively, in dissolution media of pH 1.5. Nearly similar "n" values ("n">0.81–0.91) of the aforementioned tablets were observed at pH 6.8. One major difficulty faced after inclusion of 30% Ethocel® in formulation F1 was dictation of using dry granulation (slugging) method for tablet manufacture (instead of direct compression method) because of poor flow ability and poor compressibility characteristics of the powder mixtures. Thereafter, further substitution of 15% Methocel® by Ethocel® (F2; 45% Methocel®/45% Ethocel®) extended the release period up to 12 h with "n" values ≥ 0.89, indicating zero-order kinetics. In the case of formulation F3, 15% Methocel® was further substituted by Ethocel® (30% Methocel® and 60% Ethocel®), leading to extension in the release period up to 24 h achieved.

Table III. Stability-Indicating Parameters (Drug Content, Weight Variation, Friability, Hardness, and Appearance) for the Optimized Controlled-Release Matrix Tablets of Olanzapine (Mean ± SD, n=20)

Readings taken for the determination of stability	Drug content (%)	Weight variation (%)	Friability (%)	Hardness (kg)	Appearance (color)
At 0 time (pre-storage)	103±2	3±0.3	0.49±0.02	12.0±0.4	Yellowish
After 1 month	102±3	4±0.5	0.61±0.03	12.0±0.3	Yellowish
After 2 months	101±2	3±0.4	0.56±0.03	12.0±0.4	Yellowish
After 4 months	100±3	3±0.5	0.48±0.03	12.2±0.3	Yellowish
After 6 months	100±2	4±0.3	0.60±0.03	12.4±0.3	Yellowish

The regular but disproportional reduction in release rates with increase in the concentration of Ethocel® was perhaps due to slow hydration of the matrix, based upon the hydrophobic character of Ethocel®. The insoluble particles of Ethocel® were probably acting as barrier to drug release in the gel layer of Methocel®.

A rather strange aspect of the formulations F1, F2, and F3 seems to be the usage of a higher percentage of the polymer blend *i.e.*, 90%. It was compromised for achieving the 24-h release period with zero-order kinetics. However, the above findings are consistent with a previously published study (23) where 89% of fine particle ethylcellulose was used to formulate extended-release tablets of some ionizable and non-ionizable drugs. Requirement of this much higher level of the polymers blend may be due to the lower viscosity of Methocel® K100 LV-CR and of Ethocel® standard 7FP premium (38), leading to rapid disentanglement and erosion of the matrices. Drug release mechanism based on release exponent, "n" and the higher goodness-of-fit values (R^2 approaching 1) indicated zero-order release of drug in both dissolution media of pH 1.5 and pH 6.8 for all the three formulations F1, F2, and F3.

The findings of the present study reveal that higher compression force led to increased tablet hardness in all formulations, F1, F2, and F3, but the 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 affected by an increase in tablet hardness from 9 to 15 kg. These findings of the present work were in line with the work of some other investigators (24,45).

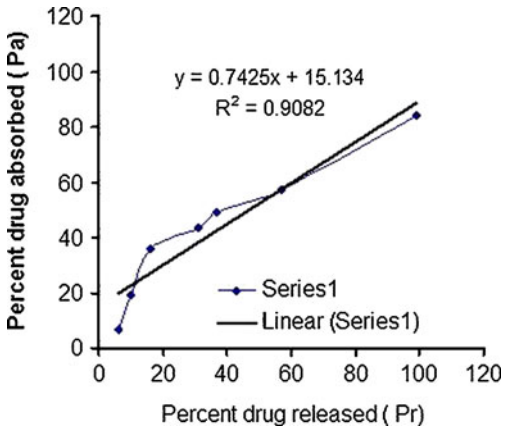

Fig. 4. Percent of drug absorbed (P_a) plotted against percent of drug released (P_a) at time intervals of 1, 2, 4, 6, 8, 12, and 24 h to show the *in vitro–in vivo* correlation of olanzapine controlled-release test tablet

As the pH in GIT is not uniform, the impact of pH on the drug release rate from the formulations was also studied. Methocel® K100 LV-CR (hydroxypropylmethylcellulose) 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 (46). Similarly, Ethocel®, a cellulose derivative (with ethoxyl substitution on anhydroglucose ring backbone) is insoluble in water; thus, its release properties are affected to a lesser extent by the changes in pH (47). Therefore, olanzapine release from these polymers was not affected by the change in pH.

Generally, similarity factor, $f_2 \geq 50$, indicates an average difference of not more than 10% at the sample time points (29,30). In the present study, the higher values (>66) of similarity factor f_2 for the F3 formulation with the hardness levels of 9, 12, and 15 kg at both pH 6.8 and pH 1.5 was another supporting point for the conclusion that the pH levels have no significant effect on the drug release from the designed matrices.

The relative bioavailability of 94% for the test tablets indicates nearly the same bioavailability of the drug from both the formulations. However, a nearly stable concentration of test tablet over 24 h as compared to that of the reference formulation (see Fig. 5) showed the appropriateness of the developed CR formulation. An *in vitro–in vivo* correlation (R^2) of 0.9082 of the optimized test tablet

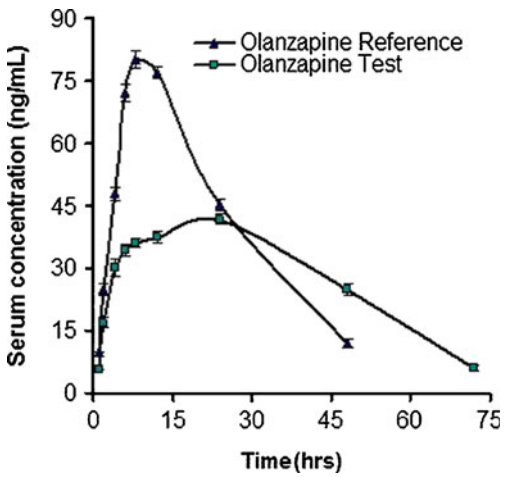

Fig. 5. Comparative serum concentration–time profiles of olanzapine reference tablets (*Olanzapine Reference*) and olanzapine controlled-release test tablets (*Olanzapine Test*) following oral administration to rabbits (mean ± SEM, n=6)

indicated a good correlation of absorption with the amount of drug release up to 85%. Percent drug absorbed was calculated by the Wagner and Nelson method (36) for this purpose. These results imply that the release and absorption of olanzapine occurs throughout the GIT, which is further indicative of suitability of olanzapine presenting in the controlled-release tablet form. The published method used for the extraction (3) of olanzapine was sufficiently reproducible with a good level of mean percent recovery (93%). Similarly, the HPLC-ECD method (34) used was doing well in the analysis of olanzapine. The published method had sufficient selectivity, sensitivity, linearity, and accuracy to carry out the bioavailability studies successfully.

The major objective in the development of a pharmaceutical product has been a good understanding of the *in vitro* and *in vivo* performance. *In vitro–in vivo* correlation (IVIVC) serves as a replacement for *in vivo* bioavailability and support for biowaivers if any. IVIVCs can also be employed to establish dissolution specifications and to support and/or validate the use of dissolution methods. All of the regulatory agencies, pharmaceutical industries, and academicians have accepted the value of IVIVCs. Therefore, the activity in this area for oral extended-release dosage forms has been in practice. As the controlled-release tablets of olanzapine does not qualify the biowaivers rule of FDA (48), we calculated IVIVC in the present work just to establish dissolution specifications and to support and validate the use of dissolution method.

CONCLUSION

Blend of Methocel® K100LV-CR and the Ethocel® standard 7FP premium was successfully used in the formulation of controlled-release matrix tablets of olanzapine. The investigated controlled-release matrix tablet has shown a good *in vitro* and *in vivo* correlation and optimized smooth blood levels of olanzapine for 24 h. So this olanzapine formulation seems a better and safer clinical choice for improved tolerability due to controlled-release behavior over prolonged time as compared to conventional tablets.

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