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RESEARCH ARTICLE

# Comparison between Oral Delivery of Eudragit RSPO Microsphere-Based Matrix Tablet and Conventional Matrix Tablet

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## ABSTRACT

The study aims at the comparative study of once-daily ziprasidone loaded polymeric microspheres-based (ZEmsp) matrix tablets (ZEmsp-T) as a sustained delivery system with conventional matrix tablets. The effect of variation in the drug/polymer ratio on the physicochemical characteristics of the microspheres was investigated. The optimized ZEmsp formulation demonstrated favorable mean particle size and drug loading along with sustained release pattern. After the selection of the optimized microspheres, matrix tablets were compressed with different direct tableting agents. After successful preparation and evaluation of ZEmsp-T, we found that batch ZEmsp-T3 and ZEmsp-T4, respectively. The optimized matrix tablets showed sustained release pattern of the drug release. The same parameters were evaluated for conventional matrix tablets, but results were not complies. Thus, results of this study prove the suitability of using Eudragit RSPO as a sustained release polymeric material to develop microspheres combined with different tableting agents to prepared matrix tablets were designed successfully for once-daily oral administration to avoid dosing frequency.

**Keywords:** Ethocel, hydroxypropylmethyl cellulose, matrix tablets, microspheres, ziprasidone

## INTRODUCTION

In the past few decades, significant medical advances have been made in the area of drug delivery with the development of novel dosage forms for the treatment of schizophrenia. Modified release formulations (e.g., matrix tablets) are gaining popularity due to the advantages of lower dosing frequency, avoidance of first-pass metabolism and hence better patient compliance; reduced adverse effects as a result of small amounts of localized drug delivery, and improved therapeutic response due to consistent drug blood levels. The sustained release properties of the matrix tablet led to significant strides in the treatment of schizophrenia as it reduced relapse rates.[1]

Antipsychotic drugs can be of great benefit in a range of psychiatric disorders, including schizophrenia and bipolar disorder, but all are associated with a wide range of potential adverse effects. In general, atypical antipsychotic agents cause fewer extrapyramidal side effects (EPS) than conventional antipsychotics. However, some atypical antipsychotics also have a relative risk of EPS.[2-4]

Ziprasidone (ZPD) is an atypical antipsychotic agent used for the treatment of schizophrenia, mania, and bipolar disorder. Despite its high safety and efficacy, it suffers from low oral bioavailability (60%).[5] ZPD has high lipophilicity (c log $P$ = 3.6), and poor solubility (intrinsic solubility of 0.3 mg/ml) its solubility in simulated bio-relevant fluids was estimated to be 4–5 mg/mL.[6] Thus, ZPD shows solubility and dissolution rate limited absorption. Various approaches have been investigated to enhance the solubility and dissolution of ZPD such as complexation with beta-cyclodextrin, solid dispersions, ball milling, and cryo-grinding, coated crystal by spray drying, and lipid-based drug delivery systems.[5,7-11] At present, no work is available for solubility and dissolution enhancement through microspheres-based matrix tablet formulations for an antipsychotic drug, that

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is, ZPD. Thus, in this article attempts has been made to enhance the solubility and bioavailability of ZPD through microspheres-based matrix tablet formulations which is compared with normal matrix tablet of hydroxypropylmethyl cellulose (HPMC) and ethylcellulose (EC).

The purpose of the present research was to develop and compare the modified release tablet formulations containing Eudragit RSPO microspheres loaded with ZPD as well as matrix tablet of HPMC and EC. The emulsion solvent evaporation technique was used to prepare the ZPD loaded Eudragit RSPO microspheres, a freely soluble drug. Eudragit RSPO, which is a biocompatible copolymer synthesized from acrylic and methacrylic acid esters, was chosen as the matrix forming polymer due to its low permeability to water that is unaffected by pH.[12,13] The second formulation contains normal matrix tablet of a combination of HPMC and EC polymer. The effects of variations in the drug/polymer ratio on the physicochemical characteristics of the microspheres and the *in vitro* release performance of the microspheres were determined, evaluated and also compared with HPMC and EC-based matrix tablet. The morphological study of the prepared optimized formulations was evaluated by scanning electron microscopy. The most suitable microsphere formulation was then selected and compressed into tablets by direct compression using Compritol®888 ATO, Ludipress®, and Cellactose®80 as various excipients. Further, optimized microspheres-based matrix tablet formulation was evaluated for physical characterizations and *in vitro* release study was performed in phosphate buffer pH 6.8 and compared the *in vitro* release study of the HPMC and EC-based matrix tablet.

## MATERIALS AND METHODS

### Materials

The following materials were obtained from commercial suppliers and used as received: ZPD (Mylan Laboratories Ltd., Nashik, India); Eudragit RSPO (Evonik Pharma GmbH, Weiterstadt, Germany); aluminum tristearate (Merck, Darmstadt, Germany); triethyl citrate (Morflex, Greensboro NC, USA); Compritol®888 ATO (Gattefosse, St. Priest, France); Kollidon SR and Ludipress® (BASF, Ludwigshafen, Germany); and Cellactose®80 (Meggle GmbH, Hamburg, Germany). Methocel® K100 LV-CR (HPMC) and Ethocel® Standard 7FP Premium (fine particle EC) were obtained as a gift from the Colorcon Asia Ltd, India. All other chemicals were of analytical or reagent grade and used without further purification.

### Methods

#### *Preparation of microspheres*

The microspheres were prepared by the emulsion solvent evaporation technique.[14,15] Eudragit RSPO was dissolved in acetone by stirring at 500 rpm with a magnetic stirrer. Accurately weighed amounts of ZPD, aluminum tristearate and triethyl citrate were dispersed in this solution and stirred at the same rate with a magnetic stirrer at a temperature of <20°C. This mixture was rapidly poured into liquid paraffin. The resultant emulsion was continuously agitated at room temperature using a high-speed digital overhead stirrer (WiseStir® HS-D, DAIHAN) at 1200 rpm for 5 h and acetone was removed completely by evaporation. The solidified microspheres were filtered, washed twice with 200 ml n-hexane, then dried under vacuum at room temperature overnight and stored in a desiccator.

In this research, drug/polymer ratio (3/1, 2/1, 1/1, 1/2, 1/3, and 1/4) was varied, maintaining a constant amount of polymer and solvent volume, but decreasing the amount of the drug in all formulations. The composition of each microsphere formulation prepared is given in Table 1. Aluminum tristearate was used as an emulsifier to prevent coalescence during the formation of Eudragit RSPO microspheres and was added to the dispersed phase due to its hydrophilic structure. During the emulsification process, it formed a protective layer around Eudragit RSPO droplets and prevented the aggregation of small droplets into larger ones. This would lead to a reduced particle size after the solvent evaporation and particle hardening.[13,16-17] The amount of aluminum tristearate (3%) was calculated from the dispersed phase volume (w/v%). Triethyl citrate was used as a plasticizer and added to the dispersed phase with DH and aluminum tristearate to improve the flexibility of the polymer chains and the compressibility of Eudragit RSPO microspheres.[15,18] The concentration of triethyl

citrate (10%) was calculated from the polymer amount (w/w%).

***Encapsulation efficiency of microspheres***

An adequate quantity of microspheres was weighed and dissolved in methanol. The drug concentration was determined by UV-visible spectrophotometry (Shimadzu UV-1202 Visible) at 225 nm (n¼6). The analytical validation of the method was checked for precision (repeatability and reproducibility), accuracy, specificity, linearity, and range according to USP 30/NF 25 criteria (USP 30/NF 25 2007).

***Mean particle size and size distribution of microspheres***

The mean particle size and size distribution of the microspheres were determined by Metasizer 2000 (Malvern Panalytical, UK). Small amounts of microspheres were dispersed in purified water in the sample unit and then analyzed. Each determination was carried out in triplicate. From the data obtained, mean particle size and standard deviation were calculated.

***Preparation of matrix tablet formulations from microspheres***

The ZPD powder or an adequate amount of Eudragit RSPO microspheres corresponding to the weight of ZPD was weighed accurately and mixed with Compritol®888 ATO, Ludipress®, or Cellactose®80 at different ratios in geometric proportion for 20 min. The mixtures were compressed using a 12 mm flat-faced punch and a hydraulic press under a pressure of 3000 kgf/cm$^{-2}$(294MPa) for 20 s of dwell time uniaxially. The compositions of the tablet formulations are provided in Table 2.

***Characterization of tablets***

The tablets were evaluated from the standpoint of some physical parameters such as weight variation, thickness, and hardness. 20 tablets of each formulation (T3 and T4) were weighed using an electronic balance (Sartorius BL 210 S) according to an official method (EP 5.0 2005). The mean weight was expressed in mg. For each formulation, the hardness of 10 tablets was measured using a Strong-Cobb hardness tester to determine the crushing strength of the tablets. The mean hardness was calculated and expressed as kg/cm$^2$. The thickness was measured using a micrometer (Somet INOX). 10 tablets of each formulation were used, and the average value for thickness was expressed in mm.

***In vitro release studies of microspheres and tablets***

The *in vitro* dissolution studies of the microspheres and tablets were carried out according to the USP

**Table 1:** Contents of the microsphere formulations prepared with different drug/polymer ratios

| **Formulation code and quantities** | | | | | | |
|---|---|---|---|---|---|---|
| **Composition** | **ZEmsp1** | **ZEmsp2** | **ZEmsp3** | **ZEmsp4** | **ZEmsp5** | **ZEmsp6** |
| Ziprasidone (mg) | 400 | 300 | 200 | 100 | 50 | 25 |
| Eudragit RSPO (mg) | 100 | 100 | 100 | 100 | 100 | 100 |
| Triethylcitrate (mg) | 10 | 10 | 10 | 10 | 10 | 10 |
| Aluminum tristearate (g) | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| Acetone (ml) | 15 | 15 | 15 | 15 | 15 | 15 |
| Liquid paraffin (ml) | 250 | 250 | 250 | 250 | 250 | 250 |
| Drug/polymer | 4/1 | 3/1 | 2/1 | 1/1 | 1/2 | 1/4 |
| Emulsifier (%) | 1 | 1 | 1 | 1 | 1 | 1 |

**Table 2:** Compositions of the different tablet formulations

| **Formulation code and quantities (%)** | | | | | | |
|---|---|---|---|---|---|---|
| **Composition** | **ZEmsp-T1** | **ZEmsp-T2** | **ZEmsp-T3** | **ZEmsp-T4** | **ZEmsp-T5** | **ZEmsp-T6** |
| ZEmsp | 100 | 60 | 60 | 60 | - | - |
| ZPD powder | - | - | - | - | 60 | 60 |
| Compritol® 888 ATO | - | 40 | 38 | 38 | 38 | 38 |
| Ludipress® | - | - | - | 2 | - | 2 |
| Cellactose® 80 | - | - | 2 | - | 2 | - |

24/NF 19 2000 paddle method (Sotax AT 7 Smart) under sink conditions. The dissolution medium for the microspheres and matrix tablets was phosphate buffer (pH 6.8). A stirring speed of 100 rpm was used for all formulations, and the temperature of the media was maintained at 37 ± 0.5°C. The drug amount released at pre-determined time intervals was determined spectrophotometrically at 225 nm. The data obtained from the drug release studies were kinetically evaluated using SPSS 9.0 for Windows (SPSS, Chicago, IL). The *in vitro* release experiments were conducted in triplicate.

***Preparation of matrix tablet of HPMC***

The powders-mix of ZPD, Methocel®, Ethocel®, Microcrystalline cellulose (102) colloidal silicon dioxide-Aerocel®, and magnesium stearate was prepared for 1000 tablets, using the dry mix method blended in a polybag, Table 3.

***Tableting***

Matrix tablets were prepared by direct compression method using 12 mm flat faced round punch and a hydraulic press under a pressure of 32–39 Kp.

***Physicochemical evaluation of matrix tablet of HPMC***

Physicochemical characteristics, such as the angle of repose (AR), compressibility index (CI), and Hausner ratio (HR) of the matrix tablet of HPMC were determined, and the prepared matrix tablets of ZPD were also evaluated for various physicochemical characteristics such as friability, hardness, weight variation, and drug content.

***In vitro drug dissolution of HPMC matrix tablets***

The *in vitro* dissolution studies of the HPMC matrix tablets having 9 kg, 12 kg, and 15 kg of the selected optimized formulation F3 were carried out according to the USP 24/NF 19 2000 paddle method (Sotax AT 7 Smart) under sink conditions. The dissolution medium for the matrix tablets was pH 1.2 and phosphate buffer (pH 6.8). A stirring speed of 100 rpm was used for all formulations, and the temperature of the media was maintained at 37 ± 0.5°C. The drug amount released at pre-determined time intervals was determined spectrophotometrically at 225 nm. The data obtained from the drug release studies were kinetically evaluated using SPSS 9.0 for Windows (SPSS, Chicago, IL). The *in vitro* release experiments were conducted in triplicate. The drug release data were fitted to various models including zero-order kinetics, first-order kinetics, Higuchi's square root of time equation, Hixson and Crowell's cube root equation, and power law equation.

## RESULTS AND DISCUSSION

The preparation of matrix type microspheres of ZPD was achieved using the W/O emulsion solvent evaporation technique. According to several researchers, an acetone/liquid paraffin system was chosen as the most suitable solvent system to prepare Eudragit RSPO microspheres due to the solubility properties of the drug and the polymer.[13,15,16,19-21] During the preparation of the microsphere formulations by the solvent evaporation technique, various microsphere formulations with different drug/polymer ratios were tried in an effort to obtain spherical microspheres. When the polymer amount was too low (drug/polymer ratio 3/1), no spherical particles were obtained. This result showed that the amount of polymer was a very important parameter for the formation of Eudragit RSPO microspheres and influenced the physical properties of the final microspheres.

The encapsulation efficiencies of ZPD into Eudragit RSPO microspheres were in the range of 85.44–96.23%, which indicated good reproducibility. These results have shown that Eudragit RSPO is a good polymer for the preparation of microsphere formulation containing a hydrophilic drug by the emulsion solvent evaporation technique.

Particle size analysis of the Eudragit RSPO microspheres containing ZPD showed that the

**Table 3:** Compositions of the different tablet formulations

| Drug | Formulation code | Methocel (%) | Ethocel (%) | MCC 102 (%) | Magnesium stearate (%) | Colloidal silicone dioxide |
|---|---|---|---|---|---|---|
| ZPD 20 mg | F1 | 50 | 20 | 8 | 1 | 1 |
| | F2 | 35 | 35 | 8 | 1 | 1 |
| | F3 | 20 | 50 | 8 | 1 | 1 |

mean microsphere diameter was affected by variation in the drug/polymer ratio, as shown in Table 4. The mean particle size of microspheres increased with a decreasing polymer ratio. As the drug amount was increased and the polymer ratio decreased (drug/polymer ratio 2/1), a more viscous dispersion was obtained which formed larger droplets in the dispersion medium, resulting in an increase in particle size. Other researchers have also shown that the particle sizes of microspheres were dependent on the dispersed phase viscosities.[19] As seen in Table 3, the $D_{90}$ values of the microsphere size are in the range of 298.12–390.55 µm.

The dissolution profiles of ZPD released from Eudragit RSPO microsphere formulations and the dissolution profile of pure drug are given in Figure 1. All of the dissolution results showed that the drug amount dissolved was significantly different at each time point for all microsphere formulations. When the dissolution profile of pure drug was examined, it was seen that the dissolution rate of ZPD powder was quite fast, with more than 90% of the drug released in ~3 hr, as expected. ZPD-loaded microspheres lead to modulation of *in vitro* drug release, based on the drug/polymer ratio in the formulations. As the drug amount increased in the formulation, the matrix content of the microsphere increased, thereby increasing the diffusion path length of the drug to the surface of the microsphere. This result showed that the dissolution rate of the drug could be modified by increasing the drug concentration, as put forward by Amperiadou and Georgarakis,[14] Bhalerao *et al*.[22]

The microsphere formulation coded ZEmsp3 and ZEmsp4, respectively, was determined as the most suitable microsphere formulation for tableting based on the mass of microspheres with the excipients for oral application. This formulation was tableted by direct compression method. The tablet formulations were successfully compressed at 294MPa pressure. Trials to compress the microspheres into tablets without excipients were not successful. This result showed that Eudragit RSPO microspheres have poor binding properties. For this reason, the ZEmsp2-coded tablet formulation was prepared using a waxy material, Compritol®888 ATO, as a sustained release matrix material and compressibility agent. However, at the 40% wax level, the compaction failed due to punch sticking and capping problems. Since these problems were serious, two matrix

**Table 4:** Physicochemical properties of the different microspheres compositions

| Formulation code | Theoretical drug loading (%) | Practical drug loading (%) | Encapsulation efficiency (%) | D10 (Mean Diameter; µm) | D50 (Mean Diameter; µm) | D90 (Mean Diameter; µm) |
|---|---|---|---|---|---|---|
| ZEmsp1 | 78.39 | 75.44±3.44 | 96.23 | 237.43 | 246.94 | 298.12 |
| ZEmsp2 | 73.12 | 70.33±2.45 | 96.18 | 278.89 | 298.56 | 315.78 |
| ZEmsp3 | 64.46 | 59.78±3.56 | 92.73 | 301.66 | 312.45 | 356.67 |
| ZEmsp4 | 47.56 | 42.89±1.78 | 90.18 | 288.79 | 311.56 | 344.47 |
| ZEmsp5 | 31.20 | 28.83±2.67 | 92.40 | 256.34 | 298.45 | 378.88 |
| ZEmsp6 | 18.48 | 15.79±0.98 | 85.44 | 298.45 | 321.78 | 390.55 |

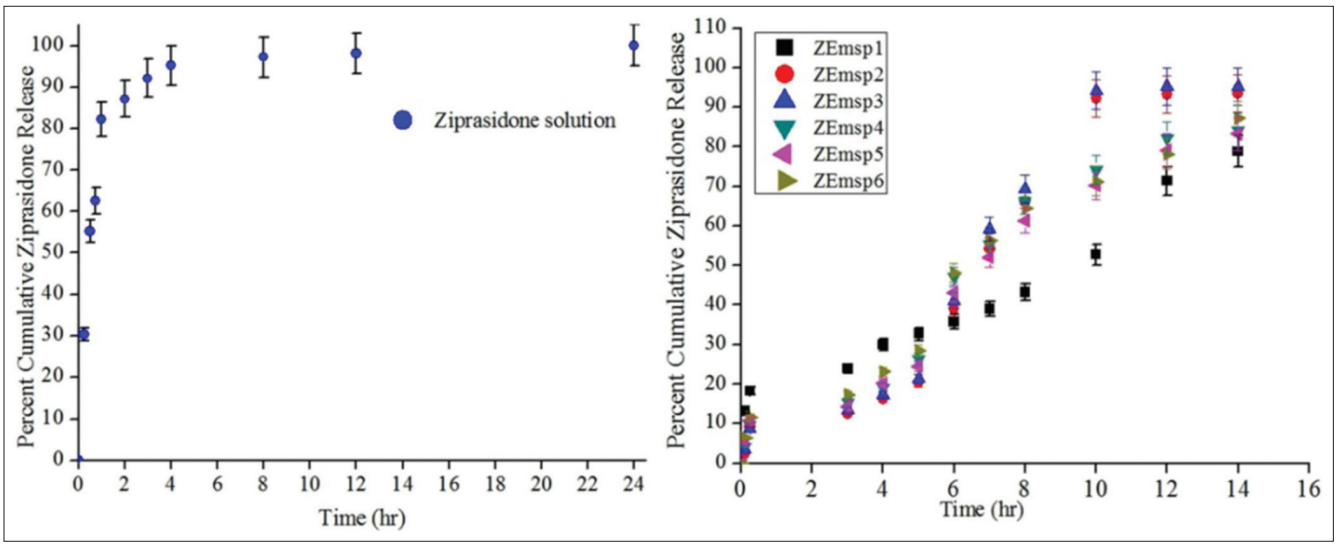


**Figure 1:** (a) *In vitro* release profile of pure ziprasidone solution; (b) *in vitro* release profile of ziprasidone loaded Eudragit RSPO microspheres of each batch in phosphate buffer pH 6.8, vertical bars represent, mean±SD ($n$ = 3)

tablet formulations, coded ZEmsp3 and ZEmsp4, respectively, were designed with direct tableting agents (Ludipress® and Cellactose® 80) to maintain the compression of the microspheres. It can be seen that compression into tablets caused no breakage of the microspheres.

Characterization of the compressed tablets is displayed in Table 5. The thickness of ZEmsp-T3 and ZEmsp-T4 matrix tablet formulations ranged from 5.05 to 5.20 mm. Tablet weight was found to be uniform among the matrix tablet formulations and complied with EP 5.0 2005. The tablets had suitable hardness in the both optimized matrix tablet formulations, that is, 4.4 kg/cm$^2$. These results confirmed that all tablet formulations were compressed with suitable weight uniformity, thickness, and hardness, as indicated by the very low standard deviations obtained. There was no significant difference between the tablet formulations coded ZEmsp-T3 (Cellactose® 80-containing) and ZEmsp-T4 (Ludipress®-containing) due to the type of - lactose-based direct tableting agents used in the matrix tablets.

The *in vitro* release profiles of the matrix tablet formulations coded ZEmsp-T3 and ZEmsp-T4, respectively, in pH media, 6.8 as given in the monograph of USP 24/NF 19 2000 for ZPD, are shown in Figure 2. When the dissolution profiles of the tablet formulations coded ZEmsp-T3 and ZEmsp-T4 in the medium of the pH 6.8 were evaluated, the drug release from ZPD microspheres-containing tablet formulations ZEmsp-T3 and ZEmsp-T4, respectively, was slower than the pure ZPD solution. During burst effect <20% and <22% of ZPD was released from the tablet formulations coded ZEmsp-T3 and ZEmsp-T4, respectively, up to 1.5 h. The results of dissolution profiles in the dissolution media at pH 6.8 showed that two tablet formulations ZEmsp-T3 and ZEmsp-T4 were successfully designed, maintaining release of ZPD, a highly water-soluble drug, for a period of 24 h; Compritol®888 ATO appeared to be a suitable sustained release matrix material due to its waxy structure. Matrix delivery systems utilizing waxy materials usually employed a core of drug embedded in the wax or a compressed physical blend of drug and matrix-forming agent. As the system was immersed into the dissolution medium, the dissolution medium slowly penetrated the matrix feature and the waxy material blocked the pores of the matrix, inhibiting the drug release and resulting in a sustained or modified release of the drug.[23-25]

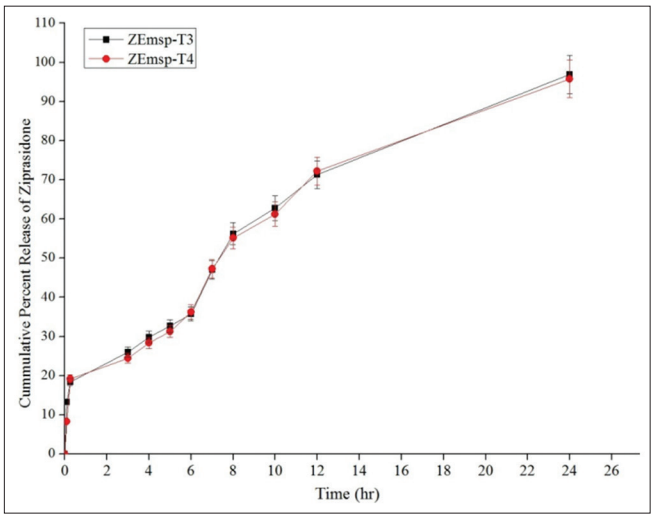


**Figure 2:** (a) *In vitro* release profile of optimized ziprasidone loaded microsphere-based matrix tablet in phosphate buffer pH 6.8, vertical bars represents, mean±SD ($n$ = 3)

As shown in Table 6, the angle of repose for powders-mix varied from 46 ± 3° to 60 ± 3°, indicating poor flowability as compared to granules, for which the AR varied from 31 ± 3° to 33 ± 2°, indicating good flowability. The CI of powders-mix varied from 27 ± 3% to 33 ± 3%, indicating poor compressibility as compared to granules, for which it ranged from 11 ± 2% to 12 ± 1% indicating good compressibility. HR followed the same trend (1.32 ± 0.11–1.56 ± 0.13 for powders and 1.14 ± 0.12–1.17 ± 0.13 for granules) as was noted for AR and CI of powders-mix and granules. Drug content of granules varied from 102 ± 2% to 103 ± 3%.

The tablets from each batch were found uniform with respect to dimensions (length × width, 8.0 × 3.6–8.1 × 3.5 mm), the percent weight variation (4 ± 0.3–5 ± 0.5), percent friability (0.42 ± 0.04–0.49 ± 0.07), and percent drug content (100 ± 4%–102 ± 3%), as represented by the results of

**Table 5:** Characterizations of the optimized matrix tablet formulations

| Characteristics of Tablets | | | | Thickness (mm) ($n$=10) |
|---|---|---|---|---|
| **Tablet code** | **Weight uniformity (mg) ($n$=20)** | **Hardness (kg/cm$^2$) ($n$=10)** | **Friability (%)** | **Before Dissolution** |
| ZEmsp-T3 | 750.34±0.01 | 4.4±0.08 | 0.5±0.01 | 5.05±0.01 |
| ZEmsp-T4 | 750.24±0.01 | 4.4±0.07 | 0.6±0.01 | 5.20±0.03 |

the selected formulation F3 [Table 7]; fulfilling requirements of the USP.

Based on the data given in Table 8, Figures 3-8 demonstrate the maximum of 8 h, 12 h, and 24 h release periods from the designed formulations of F1, F2, and F3, respectively. The drug release rates (%/hour) were 11.85, 8.19, and 4.07 for F1, F2, and F3, respectively, with 9 kg hardness; 11.98,

**Table 6:** Physicochemical characteristics of powders-mix prepared for manufacture of extended-release tablets of ZPD (mean±SD, *n*=3)

| Powders mix | Angle of repose (degrees) | Compressibility index (%) | Hausner ratio | Drug content |
|---|---|---|---|---|
| F1 | 46±3 | 27±3 | 1.32±0.11 | 103±3 |
| F2 | 51±3 | 32±4 | 1.43±0.13 | 103±2 |
| F3 | 60±3 | 33±3 | 1.56±0.13 | 102±2 |

F1 contains 50% Methocel® and 20% Ethocel®; F2 contains 35% Methocel® and 35% Ethocel® while F3 contains 20% Methocel® and 50% Ethocel®

**Table 7:** Physicochemical characteristics of extended-release tablets of Ziprasidone for its selected formulation F3 (mean±SD, *n*=10)

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

F3 contains 30% Methocel® and 60% Ethocel®

**Table 8:** Effect of the formulation (F1,F2,and F3), dissolution media (pH-1.2 and pH-6.8) and tablet hardness (9 kg, 12 kg and 15 kg) on the release kinetics of ZPD from its extended-release tablets

| **pH of the dissolution medium=1.2** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Hardness** | **Zero-order** | | **Higuchi's** | | **First order** | | **Hixson-Crowell** | | **Korsmeyer** | | **Results** |
| **F1** | | **K** | **R2** | **K** | **R2** | **K** | **R2** | **K** | **R2** | **N** | **R2** | **Mechanism of drug release** |
| | 9 | 11.85 | 0.996 | 44.87 | 0.962 | −0.245 | 0.769 | −0.296 | 0.992 | 0.791 | 0.982 | Anomulous |
| | 12 | 11.98 | 0.998 | 45.87 | 0.986 | −0.215 | 0.849 | −0.301 | 0.968 | 0.896 | 0.999 | Zero order |
| | 15 | 12.11 | 0.992 | 46.64 | 0.991 | −0.254 | 0.846 | −0.297 | 0.954 | 0.895 | 0.999 | Zero order |
| **F2** | | | | | | | | | | | | |
| | 9 | 8.19 | 0.999 | 36.44 | 0.972 | −0.145 | 0.742 | −0.223 | 0.964 | 0.939 | 0.998 | Zero order |
| | 12 | 8.24 | 0.999 | 36.64 | 0.971 | −0.147 | 0.757 | −0.222 | 0.967 | 0.909 | 0.996 | Zero order |
| | 15 | 8.24 | 0.992 | 36.89 | 0.978 | −0.135 | 0.864 | −0.216 | 0.954 | 0.882 | 0.995 | Anomalous |
| **F3** | | | | | | | | | | | | |
| | 9 | 4.07 | 0.996 | 23.69 | 0.963 | −0.065 | 0.830 | −0.120 | 0.913 | 0.922 | 0.994 | Zero order |
| | 12 | 4.13 | 0.990 | 24.26 | 0.978 | −0.0757 | 0.812 | −0.120 | 0.892 | 0.921 | 0.994 | Zero order |
| | 15 | 4.12 | 0.987 | 24.34 | 0.985 | −0.076 | 0.826 | −0.118 | 0.872 | 0.949 | 0.993 | Zero order |
| **pH of the dissolution medium=6.8** | | | | | | | | | | | | |
| **F1** | | **K** | **R2** | **K** | **R2** | **K** | **R2** | **C** | **R2** | **N** | **R2** | |
| | 9 | 11.64 | 0.998 | 44.22 | 0.971 | −0.209 | 0.801 | −0.293 | 0.986 | 0.817 | 0.998 | Anomalous |
| | 12 | 11.49 | 0.989 | 44.34 | 0.993 | −0.210 | 0.844 | −0.284 | 0.946 | 0.910 | 0.997 | Anomulous |
| | 15 | 11.40 | 0.987 | 44.12 | 0.996 | −0.245 | 0.815 | −0.275 | 0.937 | 0.889 | 0.999 | Anomulous |
| **F2** | | | | | | | | | | | | |
| | 9 | 8.24 | 0.998 | 36.54 | 0.965 | −0.145 | 0.736 | −0.226 | 0.972 | 0.931 | 0.997 | Zero order |
| | 12 | 8.03 | 0.998 | 35.97 | 0.986 | −0.127 | 0.810 | −0.217 | 0.949 | 0.930 | 0.998 | Zero order |
| | 15 | 8.33 | 0.983 | 37.595 | 0.986 | −0.150 | 0.811 | −0.219 | 0.931 | 0.959 | 0.986 | Zero order |
| **F3** | | | | | | | | | | | | |
| | 9 | 4.19 | 0.986 | 24.70 | 0.979 | −0.077 | 0.837 | −0.120 | 0.889 | 0.921 | 0.995 | Zero order |
| | 12 | 4.26 | 0.965 | 25.35 | 0.984 | −0.078 | 0.858 | −0.122 | 0.859 | 0.993 | 0.981 | Zero order |
| | 15 | 4.22 | 0.979 | 24.89 | 0.973 | −0.067 | 0.864 | −0.125 | 0.886 | 0.889 | 0.993 | Zero order |

K, R2 and "n" represent release rate constant, coefficient of determination and release exponent respectively, F1 contains 50% Methocel® and 20% Ethocel®, F2 contains 35% Methocel® and 35% Ethocel®, F3 contains 20% Methocel® and 50% Ethocel®

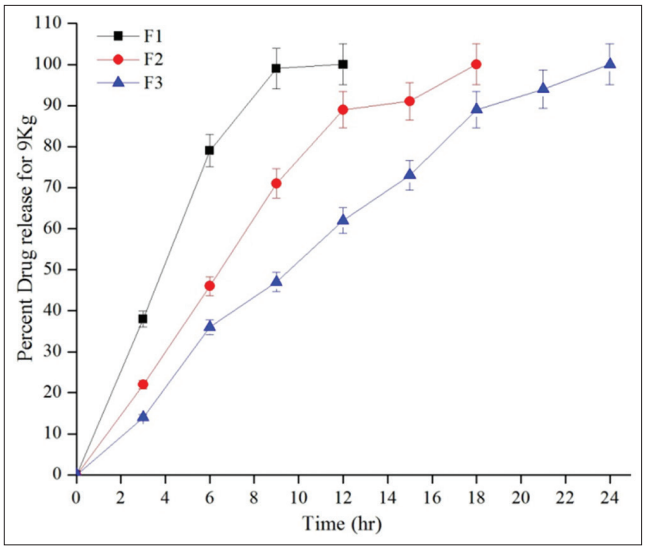


**Figure 3:** Comparative release profiles of ziprasidone from 9 kg hard tablets of formulations F1 (50% Methocel® and 20% Ethocel®), F2 (35% Methocel® and 35% Ethocel®), and F3 (20% Methocel® and 50% Ethocel®), in dissolution media of pH 1.2 (mean±SD, $n = 6$)

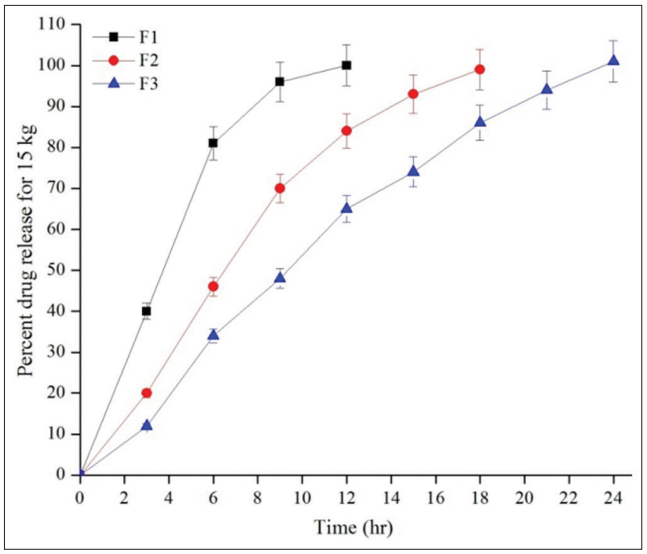


**Figure 5:** Comparative release profiles of ziprasidone from 15 kg hard tablets of formulations F1 (50% Methocel® and 20% Ethocel®), F2 (35% Methocel® and 35% Ethocel®), and F3 (20% Methocel® and 50% Ethocel®), in dissolution media of pH 1.2 (mean±SD, $n = 6$)

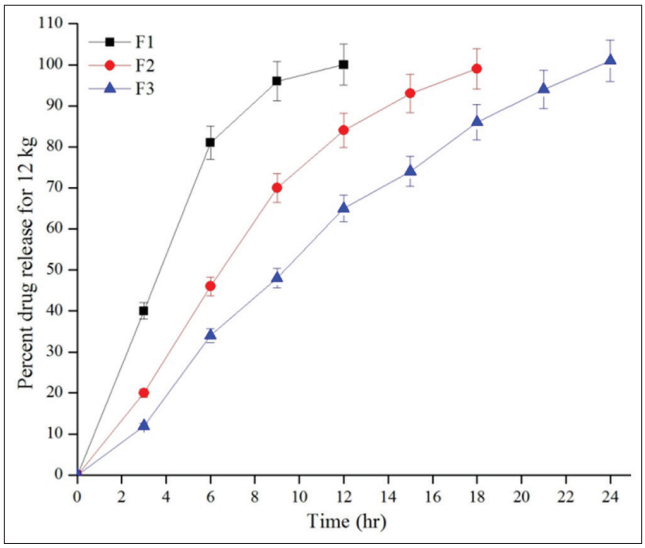


**Figure 4:** Comparative release profiles of ziprasidone from 12 kg hard tablets of formulations F1 (50% Methocel® and 20% Ethocel®), F2 (35% Methocel® and 35% Ethocel®), and F3 (20% Methocel® and 50% Ethocel®), in dissolution media of pH 1.2 (mean±SD, $n = 6$)

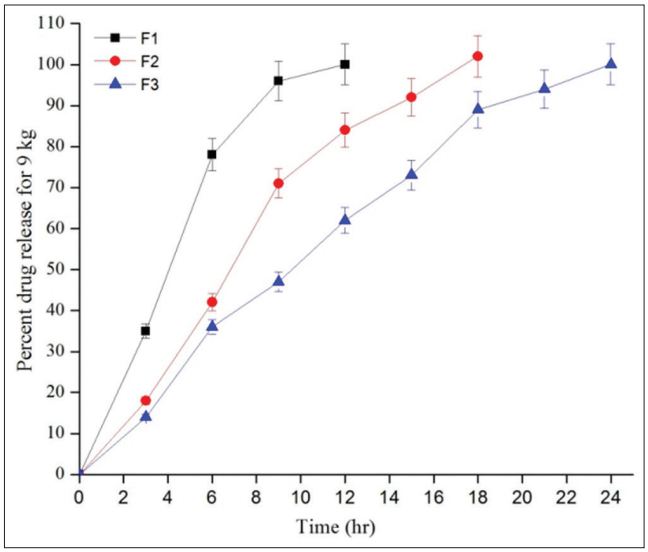


**Figure 6:** Comparative release profiles of ziprasidone from 9 kg hard tablets of formulations F1 (50% Methocel® and 20% Ethocel®), F2 (35% Methocel® and 35% Ethocel®), and F3 (20% Methocel® and 50% Ethocel®), in dissolution media of pH 6.8 (mean±SD, $n = 6$)

8.24, and 4.13, respectively, for F1, F2, and F3 with 12 kg hardness and 12.11, 8.24, and 4.12 for F1, F2, and F3, respectively, with 15 kg hardness in pH-1.2. Nearly, same trend and levels of release rates were observed for the above-mentioned tablets in pH-6.8 [Table 8].

## CONCLUSION

The present research, comparative evaluation of both microspheres-based once-daily modified release matrix tablets of ZPD with conventional matrix tablets was successfully designed and appeared to be a suitable dosage form for oral application. Drug/polymer ratio of the emulsion system played an important role in the formation of polymeric microspheres and affected the characteristics of the final microspheres prepared. It was established that physical properties of polymeric microspheres and the release rate of ZPD can be modified by variation of the drug/polymer ratio. Compritol®888 ATO, Ludipress®,

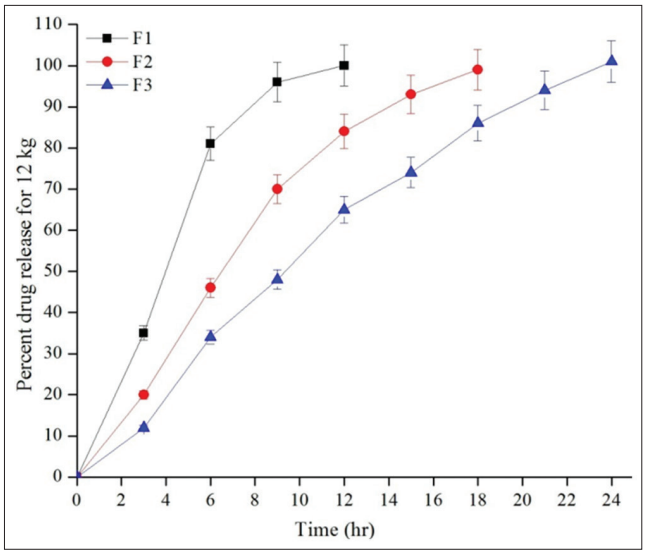


**Figure 7:** Comparative release profiles of ziprasidone from 12 kg hard tablets of formulations F1 (50% Methocel® and 20% Ethocel®), F2 (35% Methocel® and 35% Ethocel®), and F3 (20% Methocel® and 50% Ethocel®), in dissolution media of pH 6.8 (mean±SD, $n$ = 6)

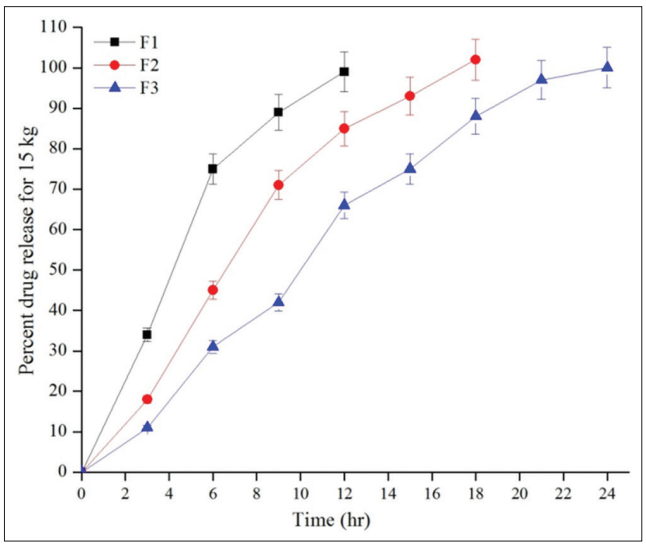


**Figure 8:** Comparative release profiles of ziprasidone from 15 kg hard tablets of formulations F1 (50% Methocel® and 20% Ethocel®), F2 (35% Methocel® and 35% Ethocel®), and F3 (20% Methocel® and 50% Ethocel®), in dissolution media of pH 6.8 (mean±SD, $n$ = 6)

and Cellactose®80 have been used to formulate matrix tablets of ZPD using direct compression method, maintaining the drug release for 24 h. It was shown that Compritol®888 ATO was a good sustained release matrix material for once-daily modified release of a ZPD. Cellactose®80 exhibited a considerable retardation effect on the drug release when compared with Ludipress®. After successful preparation and evaluation of ZEmsp-T, we found that batch ZDmsp-T3 and ZDmsp-T4, respectively, was optimized batches which were further characterized such as weight variations, hardness, friability, and thickness. The optimized matrix tablets were evaluated for *in vitro* dissolution study which showed sustained release pattern of the drug release. Further, same parameters were evaluated for conventional matrix tablet but the results of it not good as compared with microsphere-based matrix tablet, so we concluded that microsphere-based matrix tablet was showed excellent sustained release pattern.

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