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Effect of inclusion of citric acid and Lutrol® F-68 on ziprasidone and β-cyclodextrin complexation: Characterization, solubility and dissolution studies

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RESEARCH ARTICLE

ABSTRACT

Ziprasidone (ZPR) is an antipsychotic agent having less solubility. It is used for the treatment of schizophrenia. Complexation of hydrophobic drugs with cyclodextrins leads to enhanced solubility and dissolution. In this study, inclusion complexes were prepared by different methods, using ZPR, β-cyclodextrin (β-CD), and different auxiliary agents like hydrophilic polymer and hydroxy acid (1:1:0.5) to improve the aqueous solubility. The characterization of the ternary complexes was carried out using solubility study, Differential scanning calorimetry (DSC), Powder X-ray diffraction (PXRD), Fourier transformation infrared spectroscopy (FT-IR) and *in vitro* dissolution studies. DSC, XRD, and FT-IR studies showed interaction in drug, cyclodextrin, and auxiliary agents which are confirmed by enhancement of solubility and dissolution. Spray-dried dispersion showed less crystallinity and higher solubility as compared to the kneading method for both citric acid and Lutrol® F-68. Thus, the investigation concludes that the presence of the auxiliary agent has a synergistic action on complexation with cyclodextrin, which helps to modify the physicochemical properties of the drug.

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1. Introduction

The solubility of a drug is an important parameter for the safe and effective delivery of a dosage form. Moreover, to exhibit its therapeutic activity, a drug needs to possess some amount of water solubility and to permeate through the biological membrane via passive diffusion. Thus, only those drugs are absorbed which are in the solubilized form at its site of action. However, more than 90% of the new chemical entities in the pharmaceutical industry are poorly water-soluble [1].

The solubility of drugs can be enhanced using surfactants, co-solvents, polymers, particle size reduction, and cyclodextrins (CDs), etc. [2,3]. CDs are oligosaccharides which can accommodate the hydrophobic drug molecules within their cavity to form inclusion complexes. Inclusion complexes have gained importance in the pharmaceutical field due to their ability to modify chemical, biological, and physical characteristics of drug molecules. These modifications have an imperative role in drug delivery due to an increase in solubility [4-7]. It has been realized that a large amount of CD is required for the solubilization of a small amount of drug due to its low complexation efficiency. The addition of third agent i.e. auxiliary agent was found to increase complexation efficiency and thus to improve the solubilization process [8-21]. Hydroxy acids [13,14], hydrophilic polymers [8-12], and amino acids [7,15] were found as AAs to improve the complexation efficiency thus solubility of hydrophobic drugs. Water-soluble polymers showed synergistic action with inclusion complexes to improve their solubility [15,16]. Hydroxy acids modify the intramolecular hydrogen bond system involving the secondary hydroxy groups of CDs and/or affect their interaction with surrounding water molecules [17,18]. High concentrations of citric acid have been reported to increase the aqueous solubility of β-cyclodextrin [14,18,19]. Amino acids, meglumine were also used as auxiliary agents to enhance the solubility of drug-cyclodextrin complexes [20,21].

Ziprasidone is a benzothiazolyl piperazine derivative that belongs to a typical class of antipsychotics for the treatment of schizophrenia [22]. It is the new atypical antipsychotic drug that acts as a selective monoaminergic antagonist with high affinity for the serotonin Type-2 (5HT2), dopamine Type-2 (D2), 1 and 2 adrenergic, and H1 histaminergic receptors. ZPR

has a p*K*a value of 6.5 and it is poorly water-soluble (0.007 mg/mL at 37 °C) and highly lipophilic [23]. Many researchers have tried different methods to improve the solubility of ZPR by modifying the physicochemical characteristics like nanocrystal approach by the process of media milling [23,24], solid dispersion technique using carriers like soluplus, pluronic, hydroxypropyl β-CD, sulfobutyl ether β-CD, β-CD [24-28] and self-nano emulsifying pellets [29].

In the present study, the effect of a hydrophilic polymer and hydroxy acid on the solubilization and dissolution of β-cyclodextrin with ziprasidone was investigated and these complexes were further characterized using different techniques.

2. Experimental

2.1. Materials

Ziprasidone hydrochloride with 99.7% purity was a gift sample from Macleods Pharma (Mumbai, India). β-Cyclodextrin and Lutrol® F-68 were procured from Gangwal Chemicals (Mumbai, India) and BASF, India, respectively. Citric acid, tartaric acid, and PEG 6000 were purchased from S.D. Fine (Mumbai, India). Kolllidon® 30 and HPMC E5 were obtained as gift samples from BASF, India and Dow Pharma Solutions, respectively. Milli-Q water was used in the research. All the other reagents used were of analytical grade.

2.2. Methods

2.2.1. Screening of hydrophilic polymers and acids [15]

Saturation solubility study of ZPR was carried out in 0.1-0.5 % solutions of hydrophilic polymers, namely, Kollidon-30, Lutrol® F-68, HPMC E5, and PEG 6000 and organic acids, namely citric acid and tartaric acid. UV spectrophotometer was used to analyze the solubility of the drug (Shimadzu UV 1800, Japan).

2.2.2. Phase solubility study

Higuchi and Connors's method was followed to carry out the phase solubility study [30]. For the phase solubility study of a ternary system, ZPR was added in excess to the series of β-CD aqueous solutions (3-15 mM) with 0.5% Lutrol® F-68 and citric acid separately. Lutrol® F-68, and citric acid are considered as AAs. The solutions were kept on a rotary shaker for 48 h at 25 °C. After equilibration, solutions were filtered using a 0.45 μ membrane filter. Furthermore, these were diluted appropriately. These solutions were analyzed at 316 nm using a UV spectrophotometer.

The same study was also performed in the absence of AA. The graphs of ziprasidone concentration and cyclodextrin concentration (with and without AA) were plotted. The apparent stability constants (K_c) of the binary (ZPR: β-CD) and ternary complexes (ZPR: β-CD: AA) were calculated from the phase solubility diagrams using the Equation (1),

$$K_c = \text{Slope}/ S_0 (1\text{-Slope}) \tag{1}$$

where S_0 is the intrinsic solubility of the drug in water in the absence of AA.

It has been stated that for the selection of complexation conditions, it is more convenient to obtain complexation efficiency (CE) values for CDs [5,15]. Thus, the CE was also calculated according to the Equation (2),

$$CE = \text{Slope} /1\text{-Slope} \tag{2}$$

2.3. Preparation of inclusion complexes

Ternary complexes were prepared by kneading, spray drying, and physical mixing methods using ZPR: β-CD: AA in the ratio of 1:1:0.5% as described below [15,31].

2.3.1. Physical mixture (PM)

The physical mixture (PM) was prepared by geometric mixing of ZPR, β-CD, and Lutrol® F-68. Furthermore, this mixture was passed through the #40 sieve.

2.3.2. Kneading method (KN)

The accurately weighed quantities of ZPR, β-CD, and Lutrol® F-68 were mixed geometrically and transferred to a mortar. A small portion of water: methanol (1:1, *v:v*) solution was added to this mixture and triturated for 1 hour to form a homogenous paste. The paste was dried at 45 °C in an oven. The dried mass was pulverized and passed through the #40 sieve.

2.3.3. Spray drying (SD)

The weighed amount of a drug along with β-CD and Lutrol® F-68 was dissolved in water:methanol (1:1, *v:v*) mixture with sonication and further spray dried. Spray drying was carried out using Lab Spray Dryer Model LU-222 Advanced (Labultima, Mumbai, India) with the drying capacity of 1 L/h. Parameters of spray drying were: inlet temperature 60 °C, outlet temperature 55 °C, aspirator flow 53 Nm³/h and the flow rate was 2 mL/min. The spray-dried mass was passed through the #40 sieve.

PMLutrol, KNLutrol and SDLutrol are ternary complexes of drug, β-CD and Lutrol F-68 prepared by physical mixing, kneading and spray drying, respectively. Similarly, ternary complexes were prepared using citric acid instead of Lutrol® F-68 by above three methods. PMCA, KNCA and SDCA are ternary complexes of drug, β-CD and citric acid prepared by physical mixing, kneading and spray drying, respectively. All these mixtures were characterized as follows:

2.4. Characterization of inclusion complexes

Saturation solubility studies, Fourier transform infrared spectroscopy, differential scanning calorimetry, powder X-ray diffractometry were performed to characterize the complexes as per the protocol mentioned in literature [31].

2.4.1. Assay (Percentage of drug content)

A UV spectrophotometric method was developed to estimate the concentration of ZPR in prepared complexes. The complex equivalent to 10 mg of ZPR was dissolved in 10 mL methanol to examine the drug content. Furthermore, suitable dilution was obtained using methanol. This solution was then filtered using a 0.45 μ membrane filter and the concentration of ZPR was determined by a previously developed UV analytical method to calculate percent drug content.

2.4.2. Dissolution testing

In vitro dissolution studies were performed in triplicate by taking a complex equivalent to 20 mg of pure ZPR. Dissolution studies on the formulations were performed in 900 mL of phosphate buffer (pH = 6.4) with 2% sodium lauryl sulphate (SLS) using the United States Pharmacopeia (USP) type II paddle-type dissolution apparatus at 37±0.5 °C and stirred at 75 rpm. At predetermined time intervals, aliquots of 10 mL were withdrawn and filtered through the Whatman filter paper.
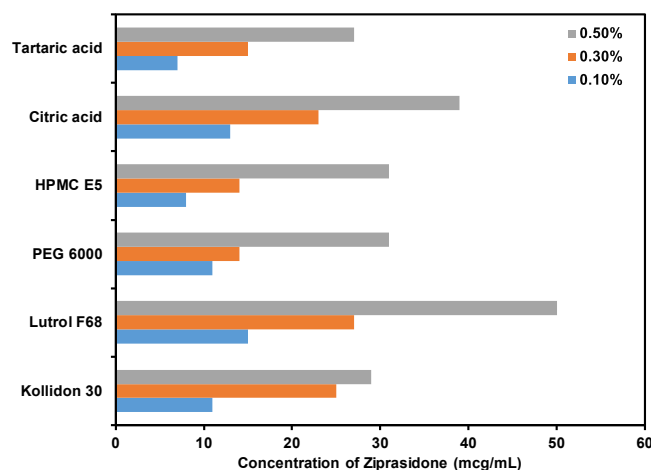
Figure 1. Solubility of the drug in different polymers and hydroxy acids.
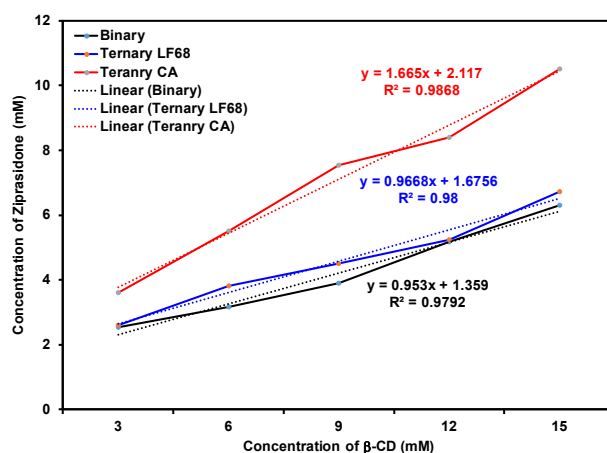

Figure 2. Phase solubility curves of binary and ternary systems. (Binary: ZPR: β-Cyclodextrin, Ternary LF68: ZPR: β-Cyclodextrin and Lutrol® F-68, Ternary CA: ZPR: β-Cyclodextrin and citric acid).

The sink conditions were maintained by replacing equal amounts of fresh media. Furthermore, samples were analyzed spectrophotometrically. The graph of percent drug release of ZPR against time (minutes) was plotted.

3. Results and discussion

3.1. Screening polymers and acids to be used for complexation

For optimization of the concentration of hydrophilic polymers and hydroxy acids to be used for ternary complexation, saturation solubility of ZPR was carried out at three different concentrations in water. Maximum solubility was obtained by using Lutrol® F-68 as polymer and citric acid as hydroxy acid at a concentration of 0.5% as shown in Figure 1, so they were selected as AAs. It was also observed that as the concentration of the AA increases, the solubility of the drug also increases as shown in Figure 1.

3.2. Phase solubility studies

Phase solubility analysis is the primary crucial evaluation test in the development of CD-based inclusion complexes of the drugs. The phase solubility curves of ZPR in aqueous β-CD solutions with and without the addition of different AAs were carried out. As shown in Figure 2, a linear increase in ZPR concentration was observed with an increasing β-CD concentration in the presence as well as the absence of AAs, indicating A_L-type diagram. As reported in literature, A_L-type diagram represents first order dependency of the interaction on the β-CD concentration and the water-soluble complex formation without precipitation in binary and ternary systems [28].

The slope was found less than unity and the stability constant was found between 50 and 2000 M^{-1} as shown in Table 1 indicating a 1:1 ratio for complexation. Intrinsic solubility was found increased due to the presence of AA. The presence of citric acid enhanced solubility 1.5 times more as compared to Lutrol® F-68. Lutrol® F-68 showed marginal improvement in intrinsic solubility. Complexation efficiency (CE) with citric acid improved 2.5 times as compared to Lutrol® F-68, and binary system. The higher CE value indicate the formation of a more stable complex. Kim *et al.* have shown an increase in apparent intrinsic solubility which led to an increase in complexation efficiency in the presence of hydroxypropyl β-CD and sulfobutyl ether β-CD due to formation of salts [26]. The marginal increase in complexation efficiency is found in the presence of Lutrol® F-68. Co-complexes or aggregates showing higher stability constant (K_c) values were observed as a result of polymer interaction with the outer surface of CDs and with drug-CD complexes. The developed aggregates are capable of solubilizing drugs and other hydrophobic molecules [4].

Table 1. The phase solubility parameters for the effect of citric acid and Lutrol® F-68.

System *	AA	Slope	Intrinsic solubility (μg/mL)	K_c [1/M]	Complexation efficiency
Binary	-	0.318	1.36	343.1	0.46
Ternary	Lutrol® F-68	0.322	1.66	349.9	0.48
Ternary	Citric acid	0.555	2.12	917.7	1.25

* Binary: ZPR:β-Cyclodextrin (1:1), Ternary: ZPR:β-Cyclodextrin:AA (1:1:0.5%).

Table 2. Drug content and saturation solubility for drug and ternary complexes *.

System	Method	Solubility (μg/mL)	Drug content (%)
ZPR	-	1.070±0.66	-
ZPR + β-CD + Lutrol® F-68	Physical mixture	4.23±0.88	99.24±0.22
ZPR + β-CD + Lutrol® F-68	Kneaded dispersion	17.05±0.76	100.78±0.49
ZPR + β-CD + Lutrol® F-68	Spray-dried	39.59±0.36	100.36±0.91
ZPR + β-CD + Citric acid	Physical mixture	6.99±0.27	99.53±0.88
ZPR + β-CD + Citric acid	Kneaded dispersion	18.60±0.19	99.02±0.34
ZPR + β-CD + Citric acid	Spray-dried	45.69±0.15	97.97±0.56

* Results are the mean of three determinations (n=3) ± standard deviation (SD).

Table 3. % Dissolution from drug and inclusion complexes *.

Auxiliary agent		Lutrol® F-68			Citric acid		
Parameter (% drug release at end of)	Drug	Physical mixture	Kneaded dispersion	Spray-dried	Physical mixture	Kneaded dispersion	Spray-dried
15 min	1.9±0.3	31.6±1.2	73.1±1.5	75.4±0.1	43.5±0.3	59.8±0.5	80.5±0.1
30 min	8.6±1.0	81.6±0.8	84.8±0.6	87.8±0.9	81.1±0.2	86.2±1.2	91.3±0.4

* Results are the mean of three determinations (n=3) ± relative standard deviation.

3.3. Saturation solubility of inclusion complexes

The results of the saturation solubility testing of ZPR, physical mixtures, and inclusion complexes in water are represented in Table 2. The improved water solubility of ZPR resulted due to the formation of ternary inclusion complexes of ZPR with β-CD. SD showed 40 folds increase as compared to the plain drug for both AAs. Citric acid showed a comparable increase in solubility when compared with Lutrol® F-68. The general trend in the increase in solubility was Spray-dried > Kneaded dispersion > Physical mixture for both AAs.

3.4. Assay (Percentage of drug content)

Percent drug content was found between 90-110 % for all complexes as shown in Table 2. As per any Pharmacopeia, assay should be 100%. Similar results are reported by Dua *et al*. for acceclofenac β-CD complexes [32].

3.5. Fourier transformation infrared spectroscopy

FT-IR is a useful methodology to estimate a possible guest (drug)-host (cyclodextrin) solid-state interaction. The characteristic peaks due to various functional groups in the guest molecule were affected due to an interaction between guest and host molecule [28]. The FT-IR spectrum of ZPR showed the presence of characteristic bands at 3421 (OH stretch), 3197 (Aromatic C-H stretch), 1713 (C=0 stretch), 1630 (C=N stretch), 2927 (C-H stretch), 972 (C-N) and 742 cm^{-1} (C-Cl stretch). The FT-IR spectrum of β-CD exhibited bands at 3300-3500 cm^{-1} due to O-H stretching vibrations and the bands due to CH and CH$_2$ groups appear in 2800-3000 cm^{-1} region. The IR spectra obtained for ternary inclusion complexes using Lutrol® F-68 and citric acid showed a shift in IR bands, reduction in intensity, and/or disappearance of some characteristic bands of ZPR. The significant shift characteristic peaks of ZPR suggest the interaction of ZPR with β-CD, Lutrol® F-68, and citric acid.

3.6. Differential scanning calorimetry

The DSC thermal analytical technique can be used to study the interaction between drug (guest) and host molecule. ZPR showed a broad endotherm for the presence of water and the characteristic endothermic peak corresponding to its melting point at 300 °C with decomposition [33]. DSC graph of β-CD showed a broad endotherm at 60-122 °C indicating the

presence of water. DSC graphs of ternary inclusion complexes containing Lutrol® F-68, and citric acid showed the intensity of the endothermic peak of ZPR at its melting point is considerably reduced compared to their PMs. The endotherm of ZPR was also found to shift in all inclusion complexes indicating the interaction of drugs, β-CD, and AA. The disappearance of endotherm was observed for SD complexes of both AAs reflecting strong interaction.

3.7. Powder X-Ray Diffraction

X-ray powder diffraction (PXRD) study was carried out to confirm the formation of a new solid system. The diffraction pattern of ZPR showed several sharp high-intensity peaks at diffraction angles (2θ) of 10.6, 12.2, 16.3, 24.2, 25.2, and 27.1° indicating its crystalline nature [25]. The X-ray diffractograms of β-CD also showed several intense peaks due to its crystalline nature. The intensity of diffractograms of inclusion complexes was compared with that of the plain drug to understand the interaction. The intensity of some characteristic diffraction peaks of ZPR was significantly reduced in spray-dried and kneaded ternary complexes as compared to their physical mixtures. Reduction in intensity and sharpness was consi-derably observed in SD complexes with both AAs indicating amorphous nature resulting in a considerable increase in solubility as seen in Table 2.

3.8. In vitro dissolution study

The dissolution profile of pure drug and complexes (PM, KN, and SD) with both AAs is shown in Figure 3. An increase in the dissolution rate was achieved with all complexes. Table 3 gives a % drug release at the end of 15 and 30 min. As shown in Figure 3 and Table 3, the faster release was obtained with citric acid as compared to Lutrol® F-68 in all types of complexes. Dissolution was found faster for SD complexes as compared to KN for both AAs indicating better interaction which is also supported by XRD, DSC studies. PMs for both AAs showed slower dissolution as compared to KN and SD. These results are in tune with those reported in literature [31,34].

4. Conclusion

Ziprasidone has low solubility in water. The inclusion complexes of the drug were prepared using β-CD and citric acid, Lutrol® F-68 as AA.
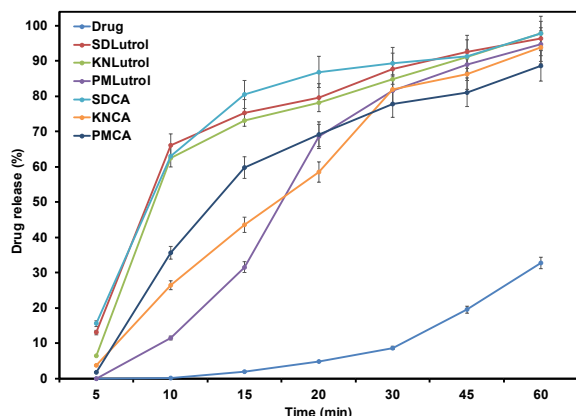
Figure 3. Dissolution studies for ziprasidone and its complexes. (Drug: Ziprasidone, PMLutrol, KNLutrol, SDLutrol: Physical mixture, Kneaded, Spray-dried ternary complex with Lutrol® F-68, respectively, PMCA, KNCA, SDCA: Ternary complexes with citric acid prepared by Physical mixing, kneading, and spray drying, respectively)

The apparent stability constant was considerably increased in the presence of citric acid as compared to Lutrol® F-68. DSC, XRD, FT-IR studies showed an interaction between 3 components for both AAs. Saturation studies showed an increase in solubility in the following order: Spray dried > Kneaded > Physical mixture > drug, but not much difference was observed between citric acid and Lutrol® F-68. The dissolution studies showed a considerable increase due to the presence of citric acid as compared to Lutrol® F-68 which is due to pH-dependent solubility of the drug forming a stable complex. Thus, the use of polymer or hydroxy acid increases the dissolution of the drug as a result of enhanced solubility.

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Disclosure statement DS

Conflict of interests: The authors declare that they have no conflict of interest.
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Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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References

[1]. Gribbon, P.; Andreas, S. *Drug Discov. Today* **2005**, *1*, 17-22.
[2]. Kim, C. K.; Park, J. S. *Am. J. Drug Deliv.* **2004**, *2*, 113-130.
[3]. Leuner, C.; Dressman, J. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 47-60.
[4]. Brewster, M. E.; Loftsson, T. *Adva. Drug Deliv. Rev.* **2007**, *59*, 645-666.
[5]. Loftsson, T.; Duchene, D. *Inter. J. Pharm.* **2007**, *329*, 1-11.
[6]. Conceicao, J.; Adeoye, O.; Cabral-Marques, H. M.; Lobo, J. *Curr. Pharm. Design* **2018**, *24*, 1405-1433.
[7]. Sherje, A.; Londhe, V. *Curr. Drug Discov. Tech.* **2014**, *11*, 271-278.
[8]. Sigurdardottir, A. M.; Loftsson, T. *Int. J. Pharm.* **1995**, *126*, 73-78.
[9]. Danel, C.; Azaroual, N.; Chavaria, C.; Odou, V.; Martel, B.; Vaccher, C. *Carbohydr. Polym.* **2013**, *92*, 2282-2292.
[10]. Gaspar de Araujo, M. V. *J. Mol. Struc.* **2017**, *1150*, 146-154.
[11]. Patel, P.; Agrawal, Y. K.; Sarvaiya, J. *Int. J. Bio. Macromol.* **2016**, *84*, 182-188.
[12]. Soliman, K. A.; Ibrahim, H. K.; Ghorab, M. M. *Int. J. Pharm.* **2016**, *512*, 168-177.
[13]. Pokharkar, V.; Khanna, A.; Venkatpurwar, V.; Dhar, S.; Mandpe, L. *Acta Pharm.* **2009**, *59*, 121-132.
[14]. Redenti, E.; Szente, L.; Szejtli, J. *J. Pharm. Sci.* **2000**, *89*, 1-8.
[15]. Sherje, A. P.; Londhe, V. *J. Pharm. Innov.* **2015**, *10*, 324-334.
[16]. Taupitz, T.; Dressman, J. B.; Buchanan, C. M.; Klein, S. *Eur. J. Pharm. Biopharm.* **2013**, *83*, 378–387.
[17]. Rakkaew, P.; Suksiriworapong, J.; Chantasart, D. *Pharm. Dev. Technol.* **2018**, *23*, 715-722.
[18]. Germain, P.; Bilial, M.; De Brauner, C. *Termochim. Acta* **1995**, *259*, 187-198.
[19]. Fenyvesi, E.; Vikmon, M.; Szema, J.; Redenti, E.; Del-canale, M.; Ventura, P.; Szejtli, J. *J. Incl. Phenom.* **1999**, *33*, 339-344.
[20]. Haque, N.; Prabhu, N. P. *Biochem. Biophys. Res. Commun.* **2018**, *499*, 907-912.
[21]. Li, X.; Yang, M.; Li, Y.; Gong, W.; Wang, Y.; Shan, L.; Shao, S.; Gao, C. *Current Drug Deliv.* **2017**, *14*, 1130-1143.
[22]. Daniel, D. G.; Zimbroff, D. L.; Potkin, S. G.; Reeves, K. R.; Harrigan, E. P.; Lakshmi Narayanan, M. *Neuropsychopharmacology* **1999**, *20*, 491-505.
[23]. Gauniya, A.; Mazumder, R.; Pathak, K. *Int. J. Pharm. Pharm. Sci.* **2015**, *7*, 146-150.
[24]. Thombre, A. G.; Shah, J. C.; Sagawa, K.; Caldwell, W. B. *Int. J. Pharm.* **2012**, *428*, 8-17.
[25]. Mogal, P.; Derle, D. *J. Drug Design Med. Chem.* **2017**, *3*, 37-48.
[26]. Kim, Y.; Oksanen, A. D.; Massefski, W.; Blake, F. J. Jr.; Duffy, M. E.; Chrunyk, B. *J. Pharm. Sci.* **1998**, *87*, 1560-1567.
[27]. Thombre, A. G.; Herbig, S. M.; Alderman, J. A. *Pharm. Res.* **2011**, *28*, 3159-3170.
[28]. Deshmukh, S. S.; Potnis, V. V.; Shelar, D. B.; Mahaparale, P. *Indian Drugs* **2007**, *44*, 677-682.
[29]. Miao, Y.; Chen, G.; Ren, L.; Pingkai, O. *Drug Deliv.* **2016**, *23*, 2163-2172.
[30]. Higuchi, T. K. A. C. *Adv. Anal. Chem. Instrum.* **1965**, *4*, 117-211.
[31]. Londhe, V. Y.; Deshmane, A. B.; Singh, S. R.; Kulkarni, Y. A. *J. Mol. Struc.* **2018**, *1157*, 395-400.
[32]. Dua, K.; Pubreja K.; Ramana, M. V.; Lather, V. *J. Pharm. Bioallied Sci.* **2011**, *3(3)*, 417-425.
[33]. National Library of Medicine, PubChem, Retrieved Mar 22, 2019, from https://pubchem. ncbi. nlm. nih. gov/compound/Ziprasidone
[34]. Londhe, V. Y.; Pawar A.; Kundaikar, H. *J. Mol. Struc.* **2020**, *1220*, 128615.