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Research Article

An *In-Vitro* Evaluation for the Effect of B-Cyclodextrin and PVP-K 30 on Drug Release Pattern of Sertraline Hydrochloride

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ABSTRACT
Solubility enhancement of poorly water soluble drug is an important aspect of formulation development. Sertraline hydrochloride is a selective serotonin reuptake inhibiter (SSRI) that exhibits antidepressant activities & is practically insoluble in water. Since Sertraline hydrochoride is a poorly water soluble drug, therefore to increase its solubility Solid dispersions were prepared in different molar ratios of drug/carrier by using kneading method. PVP K-30 & β-cyclodextrin (CD) were used as carriers. Various concentrations of drug and polymers were made (1:1, 1:2 ratios) to check the effect of polymer concentrations on drug release pattern of Sertraline hydrochloride. The release rate of sertraline hydrochloride from the resulting complexes was determined from dissolution studies by use of USP type 1 dissolution test apparatus (Basket type). After comparing the release from pure drug & Solid dispersion approaches, it was found that the solubility of sertraline hydrochloride was remarkably increased by use of 1:2 ratios (drug: polymer). The % release of the drug from solid dispersion of the drug & CD in the ratio 1:2 was found to be 94.79% & that of PVP K-30 it was found to be 94.14% after 15 mins. From the result it can be concluded that percent release of sertraline Hcl was improved from 35.14% to 94.79% by forming complexes of CD and PVP K-30 with drug.

Keywords: Solubility enhancement, Sertraline hydrochloride, PVP K-30, β-cyclodextrin.

INTRODUCTION

Today, 35-40% all new chemical entities suffer from poor aqueous solubility. The Biopharmaceutical Classification System (BCS) classifies them as class II substances.[1]. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability[2]. Improvement of the solubility of poorly water-soluble drugs is one of the most challenging aspects of drug development.[3]
Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor "drug-like" properties. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics. Less than 40 % of lipophilic drug candidates fail

to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmacodynamic activities. The lipophilic drug that reaches the market requires a high dose to attain proper pharmacological action.[4]
Sertraline hydrochloride selective serotonin reuptake inhibiter (SSRI) exhibit antidepressant activities & is practically insoluble in water. Its bioavailability is expected to be limited by its dissolution rate. Solid dispersion have great potential both for increasing the bioavailability of drugs and for developing controlled-release preparation , valuable preliminary studies of the use of solid dispersion to provide sustained- or controlled release of drugs have been reported.[5,6]

EXPERIMENTAL

Materials

The drug Sertraline Hydrochloride was procured as gift sample from (Shreya Pharmaceuticals Limited, Aurangabad, India), PVP K-30, β-cyclodextrin, were procured from (Loba Chemicals, Mumbai, India). All other chemicals purchased were of analytical grade.

Characterization of sertraline hydrochloride

1) Solubility

The solubility of Sertraline hydrochloride was checked in different solvents.

2) Melting point

The melting point of Sertraline hydrochloride was found out by capillary method and was compared with the literature value of 246°C - 249°C.

3) Calibration curve for Sertraline HCl

A standard curve was prepared by dissolving 50mg of sertraline hydrochloride in methanol in 100 ml volumetric flask. Then it was diluted and get standard concentrations of 50 to 500 µg/ml. The maximum absorbance was measured at 273 nm.

Preparation of solid dispersions

Kneading method[7]:
The calculated amount of the powdered drug was accurately weighed and then kneads with weighed quantity of CD in a crucible to produce 1:1 and 1:2 ratios of drug and polymer. Drug was added in a small amount of ethanol. After grinding ethanol gets evaporated & powder like complex of drug and CD was obtained. Same procedure is followed by using PVP K-30 as a carrier.

Evaluation of solid dispersions

A) Drug Content[8]

Powder equivalent to 50 mg of Sertraline Hcl was weighed and the weighed amount was dissolved in 50 ml of methanol in different volumetric flasks to obtain a stock solution of 1000 mg/ml. 1 ml was pipette out and diluted with methanol to 10 ml in each case, so as to get 100 mg/ml solutions. The absorbance was noted down after filtering off the solutions at 273 nm. The average weight of drug present in each solid dispersion was calculated and compared with the claimed amount.

B) Dissolution study[8]

Each solid dispersion and plane drug sample equivalent to 50 mg of Sertraline HCl was filled in hard gelatin capsule and subjected to dissolution test. The release rate of Sertraline HCl was determined using USP Dissolution Testing Apparatus I. The dissolution test was performed using 900 ml of 6.8 P^H Phosphate buffer solution, at 37° ± 0.50°C and 50 rpm. 5 ml aliquots were withdrawn at different time intervals of 15, 30, 45, 60, 90 min, the replacement was made each time with 5 ml of fresh dissolution medium. Each sample was filtered through Whattmans filter paper and the absorbance was measured at 273nm using UV-VIS spectrophotometer (SHIMADZU UV-3600). The readings were taken in triplicate.

C) Determination of similarity factor (F2 Values)

F2 value is a simple yet effective measure to determine the similarity between two or

more dissolution profiles. Values between 50 and 100 indicate the similarity, while these below 50 indicate dissimilarity. This tool is effectively used for comparing the improvement in drug release profile of Sertraline Hcl and formed solid dispersions of the same.

RESULTS AND DISCUSSION

Characterization of sertraline hydrochloride

1) Solubility

Solubility of Sertraline HCl in different solvents was depicted in table no. 1.

2) Melting point

Melting point of sertraline HCl was found to be 248^{0}C. The literature value is in the range 246-249^{0}C. Hence, the drug can be stated as pure as it melted sharply at 248^{0}C.

3) Calibration curve of sertraline hydrochloride

Calibration curve of sertraline HCl was prepared in ethanol. It was found that standard calibration curve at 273 nm followed Beer-Lambert's law in the concentration ranging from 50-500 micrograms/ml.

Evaluation of solid dispersions

A) Drug content

The solid dispersions of sertraline HCl was evaluated for its drug content and result obtained showed that it complied with the limit given that not more than one of the individual values thus obtained is outside the limit of 85 to 115%.

B) Dissolution studies[9]

β-Cyclodextrin is oligosaccharide, having cone shape cavity in the structure. When solid dispersion is prepared the drug molecule fits in the cone shape cavity of β-Cyclodextrin and form inclusion complexes. During solubility analysis it cosolubilizes the drug and improves solubility, dissolution rate, and chemical stability. Dissolution data of β-Cyclodextrin solid dispersions is depicted in Table 2, which indicates that the dissolution rate of 1:2 complex is more as compared to 1:1.

The dissolution rate of plain drug and various ratios of solid dispersions prepared were examined in phosphate buffer pH 6.8. From the result it can be noted that dissolution rate of pure drug was extremely low with only about 68 % of drug release during 90 min of dissolution. Where as prepared solid dispersions of drug remarkably improve the dissolution rate of sertraline Hcl (Graph 1).

Comparison of dissolution data of prepared solid dispersions

1) Solid dispersions of CD in different ratios with drug

The dissolution data for the drug and solid dispersion of CD with the ratios 1:1 & 1:2 is depicted in Table no.2 and Figure 2. Solid dispersion of Drug and CD in the ratio 1:2 showed higher dissolution than that of 1:1 ratio i.e. 94.79% and 52.65% respectively in 15 min. Results also suggests that as the concentration of carrier in solid dispersion of drug were increased the dissolution rate is increased. The basic mechanism behind increase in dissolution was as the more amount of carrier is present more drug particles were trapped in helical interstitial space of CD, which give high dissolution of drug hence 1:2 ratio showed better increase in drug release as compared to 1:1 ratio.

2) Solid dispersions of PVP in different ratios with drug

Same results were obtained as that of CD when PVP k-30 was used as carrier. The dissolution data for the drug and solid dispersion of PVP k-30 with the ratios 1:1 & 1:2 is depicted in Table 2 and Figure 3. Solid dispersion of Drug and PVP k-30 in the ratio 1:2 showed higher dissolution than that of 1:1 ratio i.e. 94.14% and 80.53% respectively in 15 min.

3) Solid dispersions of CD & PVP (1:1ratio) with drug

The dissolution data for the drug and solid dispersion of PVP k-30 and CD in ratios 1:1 is depicted in Table 2 and Figure 4. Solid

dispersion of Drug & PVP in the ratio 1:1 showed higher dissolution (80.53%) as compared to the Solid dispersion of Drug & CD in 1:1 ratio (52.63%) after 15 min.

4) Solid dispersions of CD & PVP (1:2ratio) with drug

The dissolution data for the drug and solid dispersion of PVP k-30 and CD in ratios 1:2 is depicted in Table 2 and Figure 5. Solid dispersion of Drug with CD & PVP k-30 in the ratio 1:2 showed nearly same pattern of drug release i.e. 94.79% and 94.14% respectively after 15 min.

C) Determination of similarity factor (F2 Values)

F2 values of Solid dispersions of drug with CD and PVP k-30 in various ratios were depicted in table no. 3. The low F2 values in the Table 3 (below so), indicate significant changes in dissolution pattern of Sertraline hydrochloride as compared to dissolution pattern shown by drug alone. The F2 values also demonstrate effect of CD and PVP k-30 on *In-vitro* drug release pattern of Sertraline hydrochloride. The consistent upper position of curves for all solid dispersions indicates faster release of drug as compared to dissolution pattern shown by drug alone.

Table 1: Solubility of Sertraline Hcl in various solvents

S. No.	Medium	*Solubility(mg/ml)*
1	Water	*3.6*
2	Iso propyl alcohol	*4.5*
3	Ethanol	*15.8*

Table 2: Dissolution data of pure drug and prepared solid dispersions

Time (min)	PURE DRUG	CD (1:1 SD)	CD (1:2 SD)	PVP (1:1 SD)	*PVP (1:2 SD)*
0	0	0	0	0	*0*
15	35.14	52.66	94.79	80.53	*94.14*
30	41.82	100	100	100	*100*
45	63.02	100	100	100	*100*
60	68.56	100	100	100	*100*
90	68.60	100	100	100	*100*

Table 3: Similarity factor (F2 Values) for all ratios of solid dispersions

Sr. No.	Formulations	*F2 value*
01	Sertraline hydrochloride + CD (1:1)	*19*
02	Sertraline hydrochloride + CD (1:2)	*15*
03	Sertraline hydrochloride + PVP k-30(1:1)	*16*
04	Sertraline hydrochloride + PVP k-30(1:2)	*15*

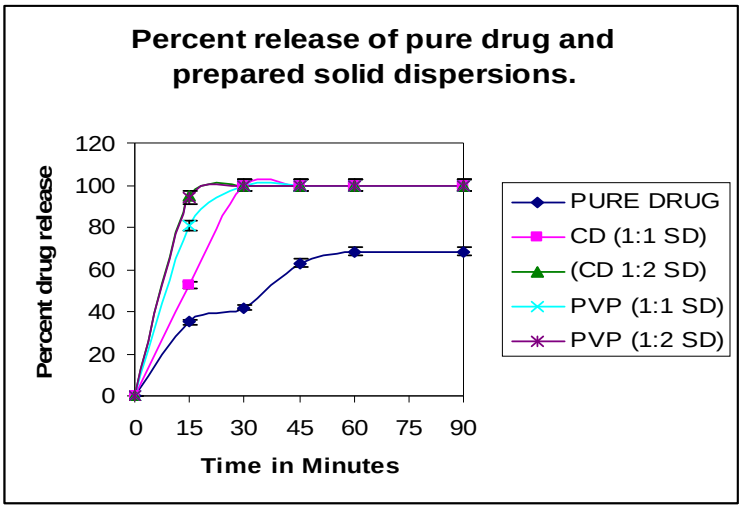

Fig. 1: Percent drug release of plain drug and its solid dispersions

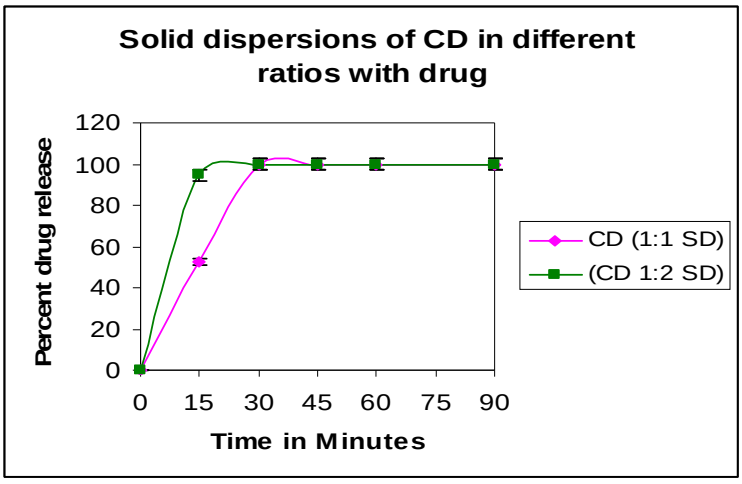

Fig. 2: Percent drug release of Solid dispersions of drug with CD

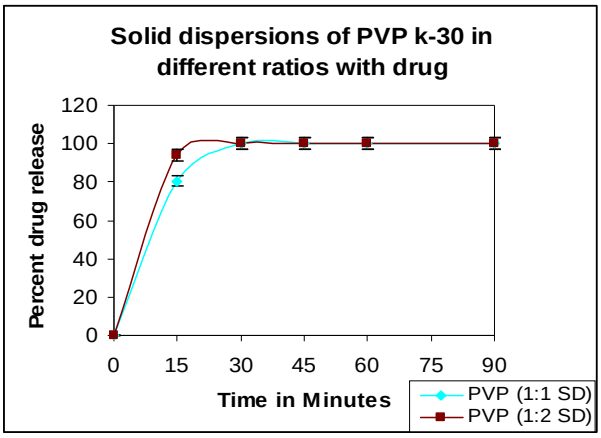

Fig. 3: Percent drug release of Solid dispersions of drug with PVP k-30

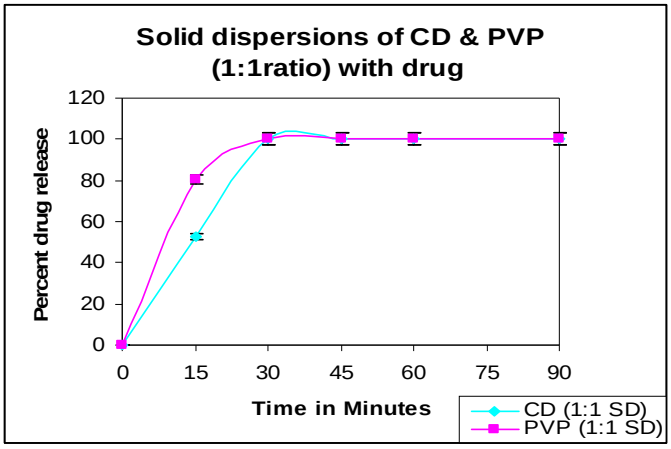

Fig. 4: Percent drug release of Solid dispersions of CD & PVP (1:1ratio) with drug

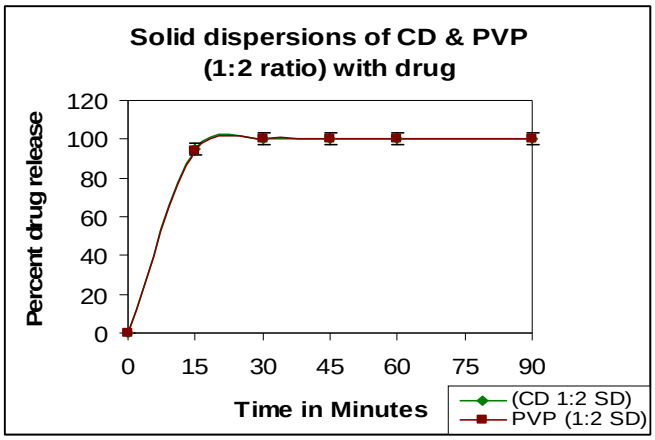

Fig. 5: Percent drug release of Solid dispersions of CD & PVP (1:2ratio) with drug

CONCLUSION

The difficulties in solubility of sertraline hydrochloride prompted present study to develop the solid dispersion of sertraline hydrochloride. From obtained results it can be noted that as the amount of carrier in formulation increases the release of drug also increases. Thus in present investigation positive results with reference to improvement in solubility of Sertraline hydrochloride were successfully achieved by using PVP and β-cyclodextrin as a carriers.

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