International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 10 Issue 7 ǁ July 2022 ǁ PP. 32-37

Development and Characterization of Solid Dispersions for BCS-II Drug Using Cyclodextrins

MadhaviN[1*], Varsha M[2], Shivani[3], Praneeth[4]
[1*,2,3,4]*Department of pharmaceutics, CMR College of Pharmacy, Medchal, Kandlakoya, Hyderabad.*
Corresponding author Emai.ID: nimmathota.madhavi@gmail.com

Abstract: *One of the successfully used technique to increase the solubility and dissolution rates of drugs is the solid dispersions. API is typically spread molecularly in a polymeric matrix in SD's, which are frequently API-polymer system. Solid dispersions have a great deal of attention as an effective way to increase the rate of dissolution and consequently the bioavailability of a variety of hydrophobic drugs.Solid dispersion and physical mixture methods were adapted.The article focusses on improvement of solubility anddissolution of BCS class II drug by using water soluble carriers and mechanism of drug release of both solid dispersion and physical mixtures. Therefore, this research will help you to understand the development of an optimized solid dispersion and physical mixtures.*

Keywords: *Solubility, Dissolution, Carriers, Solid dispersions, physical mixtures, hydrophobic drugs, bioavailability.*

Date of Submission: 18-06-2022 Date of acceptance: 02-07-2022

I. INTRODUCTION

Oral route of drug delivery is most convenient, safe, easy, comfortable and better rote for administering many drugs/drug molecules. The primary objective of certain drugs is to possess enough drug solubility but in most of the BCS class drugs like BCS-II and BCS-IV drugs couldn't offer proper solubility. Hence, if we select such type of drugs to formulate any kind of oral drug delivery system, need to improve its solubility. Now a days many techniques are available to improve solubility but the current research was done on solid dispersion by kneading method based on the feasibility on our institution lab. We have selected clozapine, which is a BCS-II drug and acts as psychiatric drug. Chemically it is a dibenzodiazepine and is very similar to loxapine (originally deemed a typical antipsychotic). It is slightly soluble in water, soluble in acetone, and highly soluble in chloroform (1-4).

Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state. The drugs which are having poor water solubility they often show poor oral bioavailability due to the low levels of absorption. Drugs with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: enhancing solubility and dissolution rate of poorly water-soluble drug and enhancing permeability of poorly permeable drugs. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. In the current research work we have developed dispersions using Hydroxy propyl β-Cyclodextrin (HP β CD) and Sulfobutyl ether β Cyclodextrin (SBE β CD) to increase the solubility. (5-7)

II. MATERIALS AND METHODS

Materials: Clozapine was obtained from college store,Hyderabad.Hydroxy propyl β-Cyclodextrin and Sulfobutyl ether β Cyclodextrinare purchased from Sigma-Aldrich, India.

Methods

Method of preparation of physical mixture and solid dispersion: (8-12)

Physical mixtures were prepared by mixing accurate weight of CLZ with polymer in a ratio of 1:6, 1:8, 1:10, 1:12 and 1:14 for 5 min using glass mortar and pestle. The physical mixture was triturated using a small volume of ethanol-water (1:1) solution to give a thick paste, which was kneaded at three kneading times, 10 and 20 min, and then dried at 45°C in an oven. The dried mass was pulverized, passed through 30 mesh sieve size, stored in a vacuum desiccator (48 h), and passed through 60 mesh sieve size, then weighed, transferred to amber

colored, airtight container, stored at 30±1°C. When ethanol alone was used for kneading, the thick paste got dried immediately. To avoid drying of the solvent during kneading, ethanol was previously mixed with water (1:1) and then used for the kneading process.

Required amount of drug dissolved in suitable solvent (chloroform) and mixed with molten carrier of hydroxy propyl β-cyclodextrin and sulfobutylether β-cyclodextrin. The above prepared solution was evaporated using hot air oven at 105oC for 2 hours and then the mixture was allowed to solidify. Finally, the solid dispersion formation was obtained. Then the prepared dispersion system was filled into zero sized hard gelatin capsules.FTIR spectrum of the sample was recorded with a Bruker FTIR spectrophotometer equipped with Opus software. For interaction studies, samples of appropriate amounts of clozapine, hydroxypropyl-β-cyclodextrin and sulfobutyl ether-β-cyclodextrin were examined. IR spectra of active ingredients and excipients were recorded in the range 400-4000cm^{-1}.Solid dispersions equivalent to 5 mg of CLZ were weighed accurately and dissolved in suitable quantity of methanol. The drug content was analyzed at 360 nm by UV spectrophotometer (Shimadzu, Japan). Each sample was analyzed in triplicate.

The prepared solid dispersions and physical mixtures were filled into zero sized hard gelatin capsules for getting suitable drug release of drug product. The prepared test products with two different carrier systems were subjected to *in vitro* dissolution. Dissolution test was carried out using USP type 1basket method. The stirring rate was 50 rpm, phosphate buffer 6.8 used as dissolution medium and the temperature maintained at 37±1°C. The time intervals for sample collection was at 15 min, 30 min, 45 min, 60 min, 75 min, 90 min and the samples of 5 ml were withdrawn, filtered and replace with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and the samples were analysed by using UV visible spectrophotometer at a wavelength of 360nm.The mean of at least three determinations was used to calculate the drug release. The same procedure was followed for physical mixture and solid dispersion.

Solid dispersions:

There are several carriers which have been reported for the preparation of solid dispersions, in that for current research work we have selected the carriers as Hydroxy propyl β-Cyclodextrin (HP-β-CD) and Sulfobutyl ether β Cyclodextrin (SBE-β-CD).

Physical mixture:

Drug and carriers (Hydroxy propyl β-Cyclodextrin, Sulfobutyl ether β Cyclodextrin) in different ratios are mixed uniformly at a particular speed. The mixture is filled into the hard gelatin capsule.

Table 1: Formulation composition ofsolid dispersions using HP-β-CD andSBE-β-CD

Formulation code	Drug: Polymer ratio	Formulation code	Drug: Polymer ratio
SD HP- β-CD 1	1:6	SD SBE- β-CD 1	1:6
SD HP- β-CD 2	1:8	SD SBE- β-CD 2	1:8
SD HP- β-CD 3	1:10	SD SBE- β-CD 3	1:10
SD HP- β-CD 4	1:12	SD SBE- β-CD 4	1:12
SD HP- β-CD 5	1:14	SD SBE- β-CD 5	1:14

Table 2: Formulation composition ofphysical mixtures using HP-β-CD andSBE-β-CD

Formulation code	Drug: Polymer ratio	Formulation code	Drug: Polymer ratio
PM HP- β-CD 1	1:6	PM SBE- β-CD 1	1:6
PM HP- β-CD 2	1:8	PM SBE- β-CD 2	1:8
PM HP- β-CD 3	1:10	PM SBE- β-CD 3	1:10
PM HP- β-CD 4	1:12	PM SBE- β-CD 4	1:12
PM HP- β-CD 5	1:14	PM SBE- β-CD 5	1:14

III. Results and discussion:

Clozapine solid dispersions and physical mixtures were prepared and evaluated. Calibration curve was constructed in pH 6.8 phosphate buffer solution. The method obeyed Beer's law in the concentration range of 1-5µg/mL. The degree of linear relationship correlation coefficient (r) was calculated and found to be 0.999, it indicates a positive correlation between the concentration of CLZ and the corresponding absorbance values. FTIR studies were conducted to know the drug-excipient compatibility and the results shown there is a compatibility among the optimized physical mixtures and solid dispersions.

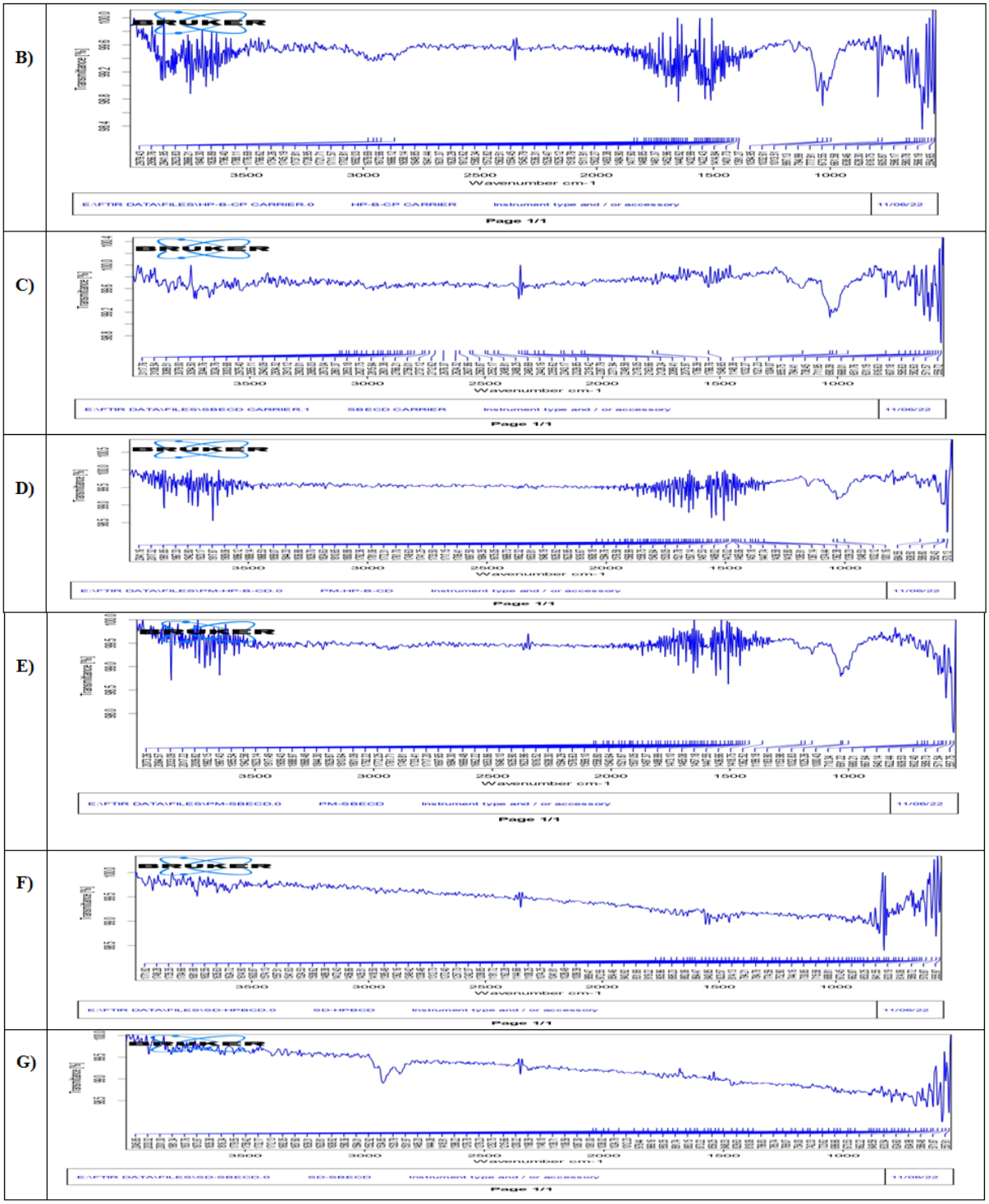

Figure 1.FTIR spectrum of A) Drug B) β-CD C) SBCD D) Optimized Physical mixture withβ-CD E) Optimized Physical mixture with SBCD F) Optimized solid dispersion with β-CD G) Optimized solid dispersion with SBCD

From FTIR spectrum, CLZ produces a characteristic peak at 3149cm^{-1}, which represents the free N-H stretching of the diazepine ring and at 2921cm^{-1}, 2789 cm^{-1} and aliphatic C-H stretching was observed at 2791cm^{-1}. The spectrum frequencies for β-CD, C-H stretching at 2941cm^{-1}, ketone group stretching from 1414 cm^{-1} to 1440 cm^{-1} and carboxylic stretching at 2666 cm^{-1} was observed. These groups are responsible for symmetric and antisymmetric stretching. For SBCD, medium C-H stretching at 3089cm^{-1}, carboxylic acid stretching found at 2488cm^{-1} it is representing bending vibration of acid group respectively. The optimized formulations of physical mixturesand solid dispersions with β-CD and SBCD were shown the same functional

groups as observed with original drug and excipients. Hence, the prepared dispersion mixtures are compatible with excipients, which have been used for formulation.

Table 3. Percentage drug content of solid dispersions using HP- β-CD and SD SBE- β-CD

Formulation code	Drug content (%)	Formulation code	Drug content (%)
SD HP- β-CD 1	82±0.03	SD SBE- β-CD 1	90±0.02
SD HP- β-CD 2	79±0.05	SD SBE- β-CD 2	85±0.05
SD HP- β-CD 3	75±0.07	SD SBE- β-CD 3	81±0.07
SD HP- β-CD 4	70±0.09	SD SBE- β-CD 4	78±0.08
SD HP- β-CD 5	68±0. 08	SD SBE- β-CD 5	74±0.09

Each value represents mean values ± SD (n=3)

Physical mixing code	Drug content (%)	Physical mixing code	Drug content (%)
PM HP- β-CD 1	75±0.02	PM SBE- β-CD 1	79±0.01
PM HP- β-CD 2	71±0.05	PM SBE- β-CD 2	75±0.03
PM HP- β-CD 3	67±0.06	PM SBE- β-CD 3	69±0.05
PM HP- β-CD 4	63±0.07	PM SBE- β-CD 4	65±0.07
PM HP- β-CD 5	59±0.08	PM SBE- β-CD 5	60±0.09

Table 4. Percentage drug content of physical mixtures using HP- β-CD and SD SBE- β-CD

Each value represents mean values ± SD (n=3)

The physical mixture was prepared to compare this formulation with that of solid dispersion prepared by kneading method. The dissolution profile of physical mixing and solid dispersion showed that, the % drug release of physical mixture is more when compared to pure drug and is less when compared to solid dispersion. The drug content of the prepared solid dispersions with HP-β-CD was found in the range of 82±0.03 to 68±0%. The drug content of the prepared solid dispersions with SBE-β-CD was found in the range of 90±0.02 to 74±0.09% respectively. The drug content of the prepared physical mixtures with HP-β-CD was found in the range of 75±0.02 to 59±0.08%. The drug content of the prepared solid dispersions with SBE-β-CD was found in the range of 79±0.01 to 60±0.09%. The maximum percentage of drug content was found as 90 % in SD SBE- β-CD 1 formulation. The maximum percentage of drug content was found as 79 % in PM SBE- β-CD 1 formulation. The drug content values indicating that the dispersion and physical mixture is showing more uniformity with SBE- β-CD than HP- β-CD. The amount of drug in solid dispersions and physical mixtures was calculated and the values are shown in Table. 3 and Table. 4 respectively.

***In vitro* dissolution studies of physical mixtures and solid dispersions:**

These studies were performed to know the % drug release of the formulations and to compare the rate of dissolution of solid dispersions with physical mixtures. The samples were analysed spectrophotometrically at 360nm and the solid dispersion drug release results were shown in the Figure 2.Among, all the prepared solid dispersions, 1:6 ratio of solid dispersion with carriers of HP- β-CD and 1:8 ratio of SBE- β-CD showed greater solubility respectively. When we try to prepare SD and with higher carrier ratio, it use to get hardening of the mixture with improper solubility. In case of physical mixture PM SBE- β-CD 2 (1:8) and HP- β-CD 1 (1:6) batches were shown highest drug release respectively

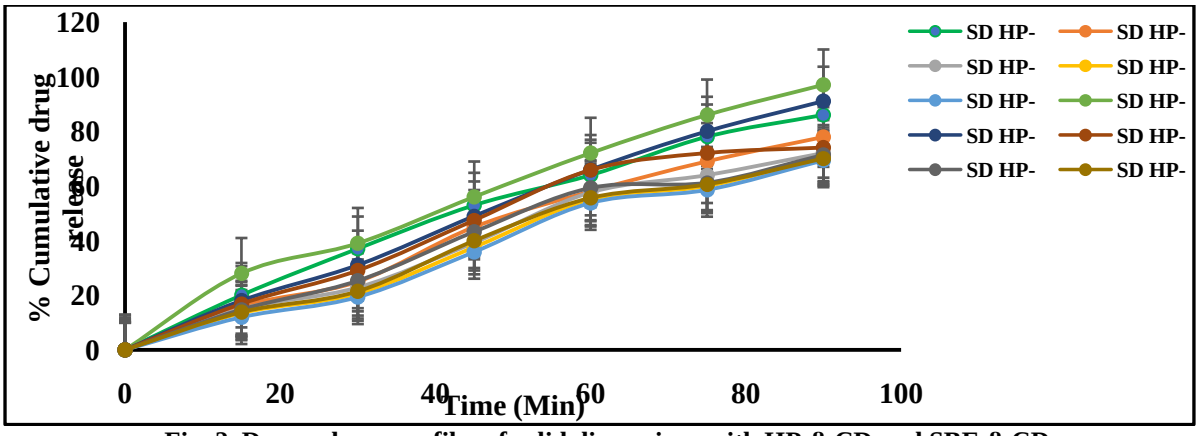

Fig. 2. Drug release profiles of solid dispersions with HP-β-CD and SBE-β-CD

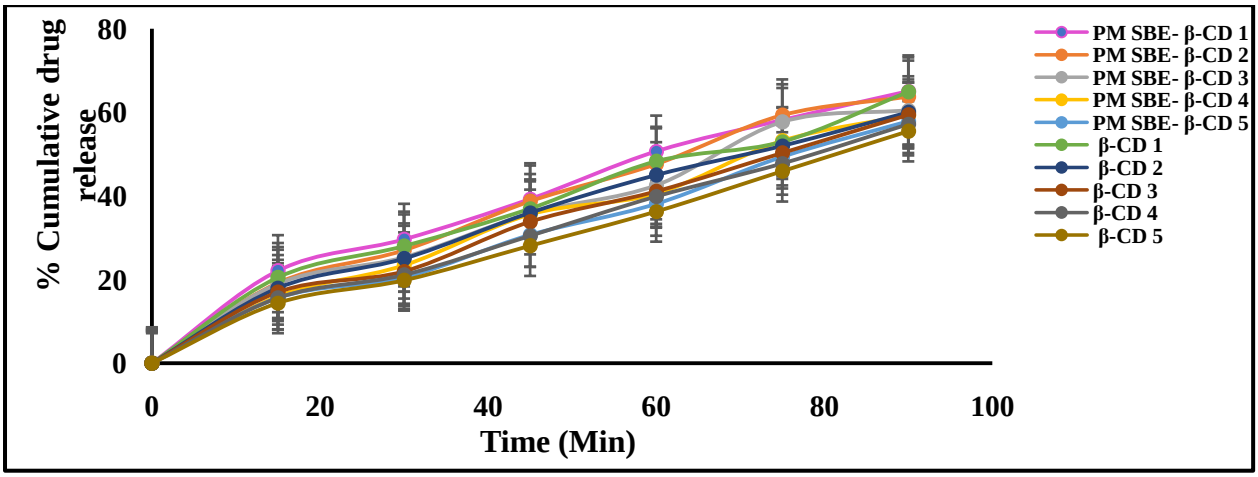

Fig.3. Drug release profiles of physical mixtures with HP-β-CD and SBE-β-CD

***In vitro* drug release kinetics**

It was found that all the prepared HP-β-CD solid dispersions are follows non-Fickian diffusion as indicated by the 'n' values of their peppas plots (0.716-0.981). plots of the log fraction of CZP released vs log time was found to be linear. SD formulations correlation coefficient values for SD HP- β-CD 1 to SD HP- β-CD 5were found to be in the range of 0.9475 to 0.9997. the zero -order rate constant values were found to be in the range of 0.9830 to 0.9950 respectively. Based on the highest 'r' value it was concluded that all the prepared SD dispersions with HP-β-CD were followed zero order kinetics**.**

It was found that all the prepared SBE -β-CD solid dispersions are follows non-Fickian diffusion as indicated by the 'n' values of their peppas plots (0.716-0.981). plots of the log fraction of CZP released vs log time was found to be linear. SD formulations correlation coefficient values for SD HP- β-CD 1 to SD HP- β-CD 5were found to be in the range of 0.720 to 0.9978. the zero -order rate constant values were found to be in the range of 0.9596 to 0.9962 respectively. Based on the highest 'r' value it was concluded that all the prepared SD dispersions with SBE -β-CD were followed zero order kinetics**.**

It was found that all the prepared HP-β-CD physical mixtures are follows non-Fickian diffusion as indicated by the 'n' values of their peppas plots (0.643-0.742). plots of the log fraction of CZP released vs log time was found to be linear. SD formulations correlation coefficient values for PM HP- β-CD 1 to PM HP- β-CD 5were found to be in the range of 0.8435 to 0.9936. the zero -order rate constant values were found to be in the range of 0.9733 to 0.9905respectively. Based on the highest 'r' value it was concluded that all the prepared PM dispersions with HP-β-CD were followed zero order kinetics**.**

It was found that all the prepared SBE-β-CDphysical mixtures are follows non-Fickian diffusion as indicated by the 'n' values of their peppas plots (0.625-0.749). plots of the log fraction of CZP released vs log time was found to be linear. SD formulations correlation coefficient values for SD HP- β-CD 1 to SD HP- β-CD 5were found to be in the range of 0.9670 to 0.9945. the zero -order rate constant values were found to be in the range of 0.9681 to 0.9957 respectively. Based on the highest 'r' value it was concluded that all the prepared SD dispersions with HP-β-CD were followed zero order kinetics**.**

IV. Conclusion

To improve the solubility, the present research focused mainly on solid dispersions and physical mixtures and those were developed successfully for BCS class-II drug. Water soluble carriers like HP β-CD and SBβ-CD were used to improve the drug solubility. From the drug excipient compatibility studies, we observe that there are no interactions between the pure drug and optimized formulation, which indicates there are no physical changes.The maximum percentage of drug content was obtained from SD SBE- β-CD 1(182±0.03%) and (PM HP- β-CD 1)75±0.02%.Solid dispersions were developed using kneading method by observing the dissolution studies kneading method shown good results for solid dispersions (1:6 ratio) formulation and for physical mixtures (1:8 ratio) shown better results respectively.

References

[1]. Aggarwal S, Gupta GD, Chaudhary S. Solid dispersion as an eminent strategic approach in solubility enhancement of poorly soluble drugs. Int J Pharm Sci Res. 2010; 1(8):1–13.
[2]. Velaga SP, Ghaderi R, Carlfors J. Preparation and characterization of hydrocortisone particles using a supercritical fluid extraction system. Int J Pharm. 2002; 231(2):155–166.
[3]. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutical classification system. New scientific approaches to international regulatory standards. Eur JPharm Sci. 2000; 50(1):3–20.

[4]. Jain C.P., Sharma A,Solid dispersion: A promising technique to enhance solubility of poorly water-soluble drug. Int. J of Drug Delivery. 2011; 3: 149-170.
[5]. Dhirendra K, Lewis S, Udupa N. Solid Dispersions: A Review. *Pak J Pharm Sci*. 2009; 22(2):234–246.
[6]. Giliyar C, Fikstad DT, Tyavanagimatt S. Challenges and opportunities in oral delivery of poorly water-soluble drugs. Pharm Dev Technol. 2006; 6:57–63.
[7]. Shah H, Shah V, Bhutani S, et al. Dissolution improvement of nebivolol hydrochloride using solid dispersion adsorbate technique. Asian J Pharm. 2015; 21(2):49–55.
[8]. Dixit AK, Singh RP. solid dispersion: A strategy for improving the solubility of poorly soluble drugs. IJRPBS. 2012; 3(2); 960-966.
[9]. Liebenberg W, Villiers MM, Wurster DE, et al. The effect of polymorphism on powder compaction and dissolution properties of chemically equivalent oxytetracycline hydrochloride powders. Drug Dev Ind Pharm. 1999; 25(9):1027–1033.
[10]. Pandya RB, Mehta TA, Gohel MC. Solid dispersion adsorbate-a novel technique for dissolution enhancement of febuxostat. Int J Pharm Sci Res. 2015; 6(10):4236–4242.
[11]. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. EurJ Pharm Sci. 2006; 29(3-4):278–287.
[12]. Patrick JM, Tonglei L, Lynne ST. Estimation of Drug–Polymer Miscibility and Solubility in Amorphous Solid Dispersions Using Experimentally Determined Interaction Parameters. Pharm Res. 2009; 26(1):133–139.