doi.org/10.36721/PJPS.2022.35.1.SUP.259-265.1

Ploxomer and β-cyclodextrin; promising tools to improve solubility of dapoxetine through binary and ternary solid dispersion techniques

Muhammad Alamgir*, Muhammad Tayyab Ansari and Muhammad Uzair
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan

Abstract: Present study was aimed to formulate solid dispersions (SD) of Dapoxetine (DAPO), a drug with low water solubility with the help of PVP-30, Ploxomer-180 (P-180) and β-cyclodextrin (CD) by physical mixing to enhance the water solubility and dissolution of drug. Binary and Ternary solid dispersions were prepared with different ratios of drug and polymer and were further evaluated the effects of polymer at individual level as well as when used in combination. The solid dispersions were whitish in color, irregular in shape and have some rough surface when illustrated under SEM. Percentage yield of SDs ranged from 81-95% described the method was structured and significant. Solubility studies were carried out in 0.1N Hcl solution and was observed a remarkable increase in solubility of BSD 8, BSD 12 and TSD 6. Furthermore, the formulations were characterized by FTIR and PXRD. P-180 found an exceptional solubility promoter when used alone and in combination with CD as well. A remarkable enhance in Solubility and dissolution of DAPO was investigated in formulation prepared with ternary SD of Pol-180 and CD.

Keywords: Dapoxetine, solid dispersions, β-cyclodextrin,

INTRODUCTION

With the advancement in drug discovery there were new drug substances discovered recently that experienced the complications of poor water solubility hence dynamically causing hindrances in the bioavailability of those particular drugs. There are number of techniques and polymers available that may lead to get benefits by enhancement in aqueous solubility and dissolution (Chadha, Kapoor & Kumar, 2006). In present days a lot of work has progressed in enhancing the aqueous solubility of newly discovered drugs (Chan, Chung, Cheah, Tan & Quah, 2015). Among various techniques the SD is one of the simplest and important method to enhance the solubility and dissolution of poor water soluble drug substances hence increasing the bioavailability and producing better therapeutic effects (Dalvi, Gerange & Ingale, 2015).

Solid dispersion is a technique where one or more drug substances were dispersed in an inert vehicle where the dispersed moiety is hydrophobic in nature while the vehicle (polymer) represents the hydrophilic characteristics. Solid dispersed matrices may be amorphous or crystalline in nature (Dixit, Singh, & Singh, 2012). A suitable and compatible solid dispersion technique is collected form a variety of available six different types of solid dispersion techniques which were classified on molecular arrangement basis (Emami, Siahi-Shadbad, Adibkia & Barzegar-Jalali, 2018). However many possibilities of enhancing the solubility of drugs are now available such as solid dispersion (Kapoor, Kaur, Kour, Behl, & Kour, 2012). pKa value of DAPO is 8.6 in methanol: water (3:1) and partition co-efficient in n-octanol: water is 0.97. DAPO is light and thermal sensitive drug presented in white or almost white crystalline powder. Serotonin (SSRI) receptors are entangled with ejaculation has confirm by animal and human sexual psychopharmacological studies led towards the role for selective serotonin reuptake inhibitors (SSRIs) in the treatment of premature ejaculation (PE)(Seftel, 2014). DAPO became the drug of choice for the treatment of PE and further studies are progressed for its use in combination with other medication and devices in patients (Fu, Peng & Hu, 2019). Poor aqueous solubility, dissolution and bioavailability dispensed a significant question mark by poorly aqueous soluble drugs (Huang & Dai, 2014). Crystalline Carriers used to form solid dispersions are attributed as first generation. Example: urea, sugars, organic acids. (Sharma *et al*., 2009). Amorphous carriers are used as they are more stable thermodynamically like PVP-30, Ploxomer-180 and β-cyclodextrin as these carriers also possess surface activity or self-emulsifying properties (Jatwani, Rana, Singh, & Aggarwal, 2012).

MATERIALS AND METHODS

DAPO Hydrochloride, was purchased from beijing Mesochem Technology Co., Ltd, beijing china, 100176, Polyvinyl pyrrolidine-30 (PVP-30) and Ploxomer-188 were purchased form Sigma Aldrich, β-cyclodextrin was purchased form Merck Darmstadt Germany, hydrochloric acid (Hcl) from BDH, England, Disodium Hydrogen Phosphate, Sodium dihydrogen phosphate was purchased form Fluka Germany. All other chemicals were of analytical grade.

**Corresponding author:* e-mail: alamgirrao@yahoo.com

Method for preparation of binary solid dispersions of DAPO

The weighed amount of drug and polymers in described ratios were taken as shown in table1, triturated smoothly and mildly for five minutes using a pestle and mortar. Resultant drug polymer blend was then heated on hot plate magnetic stirrer to melt the blend. After melting the blend put in an ice bath and cooled rapidly with vigorous stirring till solidified (Patel *et al.,* 2012). Solid blend was then dried further in desiccator for 24 hours. Solid blend then mangled and sieved by sieve having mash no. 60 to obtain solid dispersion. Same fusion method was used repeatedly for all formulations in prescribed drug: polymer ratios to obtain solid dispersions. Resultant solid dispersions were stored in a refrigerator for further evaluation and characterization (Nafady, 2014).

Preparation of ternary solid dispersions of DAPO

Prescribed amount of drug and polymers for the preparation of ternary solid dispersion formulations as described in table 1 triturated smoothly and mildly for five minutes using a pestle and mortar. Resultant drug polymer blend was then heated on hot plate magnetic stirrer to melt the blend. After melting the blend put in an ice bath and cooled rapidly with vigorous stirring till solidified (Sharma *et al.,* 2013). Solid blend was then dried further in desiccator for 24 hours. Solid blend then mangled and sieved by sieve having mash no. 60 to obtain solid dispersion. Same fusion method was used repeatedly for all formulations in prescribed drug: polymer ratios to obtain solid dispersions. Resultant solid dispersions were stored in a refrigerator for further evaluation and characterization (Shejul *et al.,* 2019).

Percent practical yield

%age yield was applied to determine the effectiveness and competence of any procedure for the formulation of SD prepared by any technique. Therefore percentage yield was calculated for each and every formulation *(Saeed et al.*, 2018). All the binary and ternary SD formulations prepared with PVP-30, Ploxomer-188 and β-cyclodextrin were weighed accurately and individually on a highly sensitive weighing balance to calculate % age yield by the help of following equation.

$$\text{Percentage yield} = \frac{\text{Mass of recovered nanoparticles}}{\text{Mass of polymers and drug}} \times 100$$

Solubility Studies

Solubility of a drug is its vital characteristic as is concerned directly with bioavailability and effectiveness of that drug. DAPO has low aqueous solubility feature and there are numerous mechanisms are available and in practice to improve it, solid dispersion method is one of them. Aqueous solubility of DAPO was analyzed by taking binary and ternary SD equivalent to 20 mg of drug and were dissolved in 100 ml of water individually and shacked vigoursly on orbital shaker for 24 hours at 150 rpm at 37^{o}C (Saeed *et al*., 2019). Membrane filter of 0.45 µm was used to filter the resultant solution to get a filtrate for further processing. Resultant filtrate was analyzed for drug in UV Spectrophotometer (Shimadzu, Japan) at 291nm (Darcsi *et al*., 2016). Filtrate was analyzed in triplicate manner. Same method was replicated for 0.1N HCl as solvents to find out solubility of DAPO and its solid dispersions.

FTIR, PXRD and SEM

FTIR spectra of DAPO, Ploxomer-188, PVP-30 and β-cyclodextrin and SDs of binary and ternary formulations acquired from ATR-FTIR 7600 spectrometer for 4000-450cm^{-1} (Khalifa, El-Desoky, & Abdel-Galeil, 2018). PXRD patterns of DAPO, Ploxomer-188, PVP-30 and β-cyclodextrin and SDs of binary and ternary formulations were traced by PX-Ray diffractometer (El-Said *et al.*, 2021), JDX-3532, JEOL, Japan with Cu-Kα radiation at 40 kV and 30mA, evaluating at 2Θ range from 5 to 60 with scan step of .05^{o} (Lee *et al.,* 2019).

DAPO, Ploxomer-188, PVP-30 and β-cyclodextrin and SDs were characterized by SEM to identify the surface topology and nature on Scanning electron microscopy (JSM, 6380L, JEOL/EO, Japan) (Fouad *et al.,* 2016). A small portion of nanoparticles was taken on a gold stub and characterized through field emission scanning electron microscope. The accelerating voltage at which image taken, was set at 5 kV and pressure of 8 mmHg.

In vitro drug release studies

Dissolution apparatus II was used to perform *in vitro* dissolution studies for drug and the selected formulations in 900mL of freshly prepared 0.1N HCl used as dissolution medium at 50 rpm at 37±0.5^{o}C taking each sample equivalent to 20 mg of drug. At defined time intervals like 0, 2.5,5,10, 15, 30,45, 60, 90 and 120 minutes, 5mL of sample was taken and replaced with addition of equal volume of 0.1N HCl dissolution medium (Bozena, *et al*., 2014). Samples were the analysed at 211 nm (Fang *et al*., 2021) in UV spectrophotometer, after filtration from 0.45 mm membrane filter, readings were taken in triplicate manner (Saeed *et al*., 2019).

The rate and extent of drug release from binary and ternary SD was determined by performing dissolution study (Yadav *et al.,* 2013) (Shimadzu, Japan).

Dissolution Efficiency (DE)

Dissolution efficiency is another parameter for determining drug dissolution *in vitro*. This concept was for the first time launched by Khan and Rhodes and can be described as:

$$DE = \frac{\int_{t1}^{t2} y dt}{y100 \times (t2 - t1)} \times 100$$

In this equation, y represented %age of dissolved product. DE represented the area under the dissolution curve between time t_1 and t_2 demonstrated as a %age of the curve at maximum dissolution, for same period of time (Serra *et al.,* 2015).

Statistical Analysis

GhraphPad prism version 7 is used to evaluate mean, standard deviatiuon and %age.

RESULTS

Percentage Yield

%age yield is a salient tool as it gives information about efficiency of the method and also helps to choose an appropriate method for the formulation and development of required products(Bhise, Mathure, Patil & Patankar, 2011). The % age Yield for binary SD ranging from 81% -95%, Similalry the % age Yield for ternary SD ranging from 87% - 95% as showed in fig. 1.

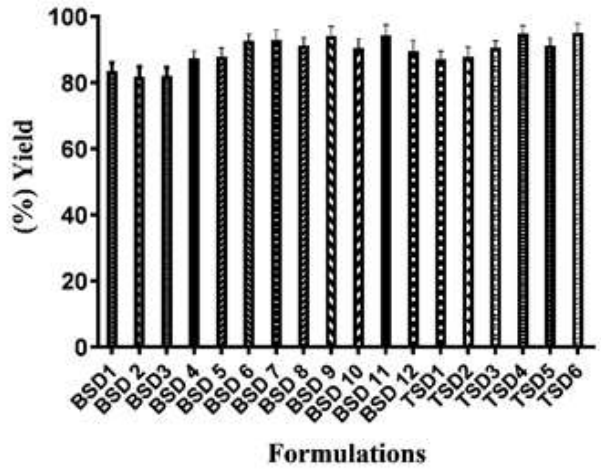

Fig. 1: The %age Yield for binary and ternary solid Dispersions ranged from 81% - 95%

Solubility Studies

Binary and ternary SDs of DAPO were formulated for solubility behavior with the help of water soluble polymers like PVPK30, Ploxomer-188, PVP-30 and β-cyclodextrin (Fouad *et al*., 2016). It was observed that solubility of DAPO enhanced as the ratio of polymer increased moreover solid dispersions of ternary physical mixtures behaviour showed more solubility then solid dispersions of binary physical mixtures. BSD 8 and BSD 12 having drug ploxomer-188 ratio of 1:6 and drug β-cyclodextrin ratio of 1:6 respectively, whereas TSD5 has drug, PVP-30 and poloxomer-188 ratio of 1:1:2 and TSD6 has drug, PVP-30 and β-cyclodextrin ratio of 1:1:2 respectively. While solid dispersions of binary physical mixtures formulated with PVPK30 showed markedly less increase in solubility of DEPO as described in fig. 2.

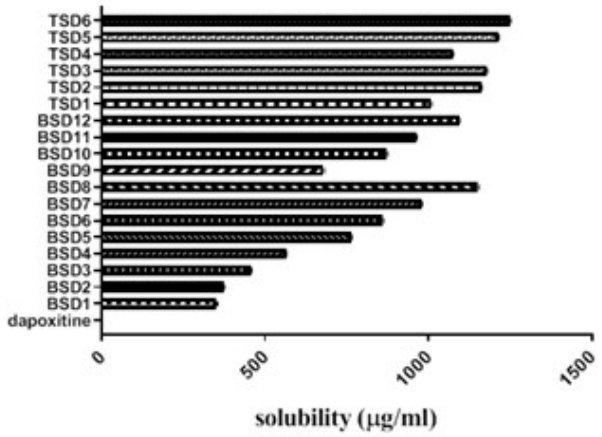

Fig. 2: The solubility of DAPO and binary and ternary solid Dispersions in 0.1N Hcl media at 37°C

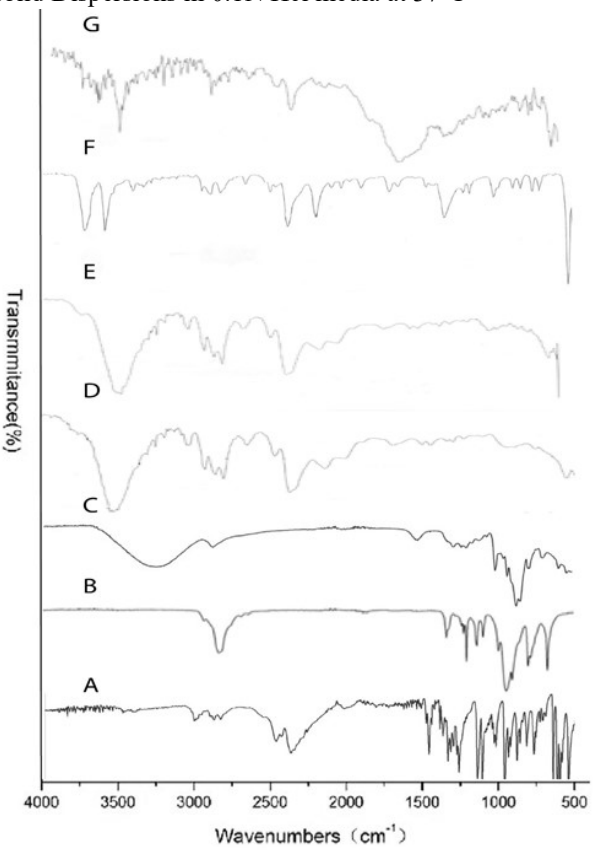

Fig. 3: FTIR spectra of DAPO and selected formulations of Ploxomer-188, PVP-30 and β-cyclodextrin based binary and ternary solid dispersions

FTIR, PXRD, TGA, and SEM

Spectra of DEPO (fig.) shows two vibrational peaks of the C=C bonds at 1454 cm^{-1} and 1631 cm^{-1} which allocated to the skeletal vibrations of DEPO (El-Desoky, Abdel-Galeil, & Khalifa, 2019). It instantiate a broad strong peak at 3049.66cm^{-1} correlated to stretching of C-H aromatic family, a peak at 1268.02 cm^{-1} associated to the C-O-C bonding and a broad peak around 1098 cm^{-1} which could

be related to stretching of C-O. Absorption peaks at 2479.2cm^{-1} and 2562.82cm^{-1} are expressed the symmetric and anti-symmetric stretching of CH3, whereas, the existence of two absorption peaks at 1450 cm^{-1} and 1620 cm^{-1} can be attributed to the stretching of aromatic C=C as shown in fig. 3. Diffractogram of DAPO shows sharp characteristic diffraction peaks appearing at 2θ diffraction angle at 13.1, 16.22, 18.42, 22.91, 25.95, 30.21, 35 and 55 (Lee *et al*., 2019). The sharp peaks were mostly seen in region of 13° to 55° fig. 4. These peaks mentioned that DAPO is in crystalline form. Whereas the XRD spectrum of BSD8 & TSD12 showed a broader and diffused pattern. SEM Photomicrograph of DAPO in fig. 5 exhibited crystals of irregular shapes and sizes with approximately of 400µm diameter. BSD 8, BSD 12, TSD 5 and TSD 6 have shown a noticeable reduction in particle size approx. 200µm mentioning the evidence about drug absorbance and envelopment in the matrix of Ploxomer-188, PVP-30 and β-cyclodextrin (Yadev *et al*., 2011).

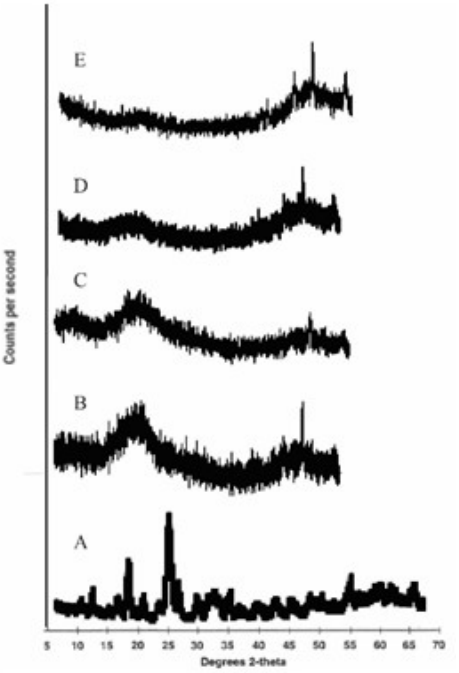

Fig. 4: XRD spectra of DAPO and selected formulations of Ploxomer-188, PVP-30 and β-cyclodextrin based binary and ternary solid dispersions

DISCUSSION

DAPO was a SSRI administered orally prescribed largely for the treatment of depression (Ștefan *et al.,* 2020), also showed remarkable side effects which were pronounced and specifically prescribed to treat for those side effects (Zhao *et al.,* 2019). DAPO became the first prescribed SRRI for the treatment of premature ejaculation (Liu *et al.,* 2021). Following oral administration it faces a serious problem of solubility in gastric fluids led to poor bioavailability of DAPO (Madsen *et al.,* 2016). To enhance the solubility of DAPO ploxomer-188, PVP-30 and β-cyclodextrin were used to prepare solid dispersions by binary and ternary methods (Alshehri *et al*., 2017).

Solubility studies of DAPO, among all the binary SD formulations, represented that BSD8 & BSD12 were foremost formulations having highest solubility. Amidst ternary SD formulations, While TSD5 & TSD6 exhibited maximum solubility increased as compared to other formulations. Furthermore, TSD6 (PVP-30 and β-cyclodextrin, ratio 1:2) exhibited maximum increase in the solubility. Whereas formulations prepared from PVP-30 exhibited least solubility improvement fig.2. Structural variations, physical and chemical interactions for the selected binary and ternary SD samples were analyzed and certified through spectrum of FTIR expressed in fig. 3. It was attested that stretching peak for C=O in 1708 cm^{-1} and banding for CH3 at 1486 cm^{-1}. N-H peak has been confirmed at 3500~3200cm^{-1}, C-H stretching peak in 2957 cm-1 and at 1700cm^{-1} C=O stretching was observed. Banding had been week for C=O and stretching was increased when DAPO compared to binary and ternary SD. So, it was concluded that binary and ternary SDs were similar to structural properties of DAPO. When the results were observed to confirm any dissimilarity for crystal structure between samples, it was measured that binary and ternary SD lost the most of structure and represented a dissimilar property. While characteristic peaks of DAPO were noticed at 1696cm^{-1} indicated C=0 stretching of Acid, 1661cm^{-1} for C=O stretching of ketone, 1593, 1578, 1458cm^{-1} for C=C stretching of aromatic ring, 1437cm^{-1}, 1367cm^{-1} (Pankajkumar *et al*., 2013). Infra-red spectra in range of 865 to 635 cm^{-1} showed existence of aromatic rings (Bozena *et al*., 2014). C-N stretching has been indicating at 1281cm^{-1} (Patel *et al*., 2016).

The reason for diffused pattern of formulations seems due to irregular molecular arrangement in the crystal lattice. While in binary SD of DAPO with poloxomer-188 and β-cyclodextrin it was noticed that both drug to polymer ratios of 1:6 formulations and same is also with ternary SD of DAPO with PVP-30, poloxomer-188 and β-cyclodextrin having drug polymer ratio of 1:1:2 was amorphous as fig. 5 showed there was no distinctive peak instead of the diffused peaks. DAPO was converted to one phase system with PVP-30 Ploxomer-188 and β-cyclodextrin and changed to amorphous state form crystalline (Salman *et al*., 2015). This change of a drug from crystalline to amorphous state is one of the immense purposes that BSD8, BSD12, TSD5 and TSD6 of DAPO formulated with PVP-30 Ploxomer-188 and β-cyclodextrin expressed a better dissolution profile than other formulations (Anshu *et al*., 2013). Additionally Ploxomer-188 and β-cyclodextrin has high Glass Transition Temperature (Tg), which led to an increase in Tg of drugs with the addition of Ploxomer-188 and β-

Table 1: Formulation of Different Binary and Ternary Solid Dispersions containing DAPO.

SD	Formulations	DRUG (mg)	PVP-30 (mg)	Ploxomer-188 (mg)	β-Cyclodextrin (mg)
Binary	BSD1	100	100		
	BSD 2	100	200		
	BSD 3	100	400		
	BSD 4	100	600		
	BSD 5	100		100	
	BSD 6	100		200	
	BSD 7	100		400	
	BSD 8	100		600	
	BSD 9	100			100
	BSD 10	100			200
	BSD 11	100			400
	BSD 12	100			600
Ternary	TSD 1	100	100	100	
	TSD 2	100	100		100
	TSD 3	100	200	100	
	TSD 4	100	200	-	100
	TSD 5	100	100	200	-
	TSD 6	100	100		200

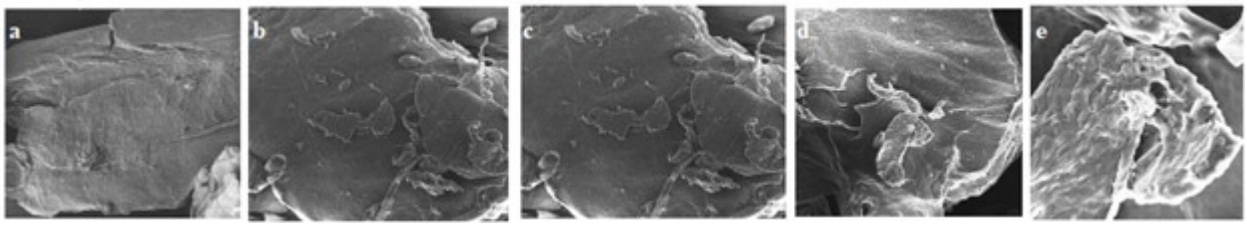

Fig. 5: SEM spectra of DAPO and selected formulations of Ploxomer-188, PVP-30 and β-cyclodextrin based binary and ternary solid dispersions

cyclodextrin this is due to Ploxomer-188 and β-cyclodextrin crystal inhibition properties that also incorporated an anti-plasticizing effects which increased the Tg and changed the steric and specific interactions occurring between drug, PVP-30, Ploxomer-188 and β-cyclodextrin as well (Chadha *et al*., 2006).

It was observed that solid dispersions BSD8, BSD12, TSD 5 & 6 exhibited decrease in particle size paved the way for the use of PVP-30, Ploxomer-188 and β-cyclodextrin polymers combinations expressed in present study, tied in an enhanced dissolution rate of the formulations (Monoela *et al*., 2014)

The change observed in the physical structure of formulation through SEM is one of the main reasons for enhancing the dissolution rate of all solid dispersions. (Dina *et al*., 2014)

CONCLUSION

Solid dispersions of DAPO were formulated by adapting binary and ternary solid dispersion technique. The pure drug and carriers (Ploxomer-188 and β-cyclodextrin) were combined following the mentioned methods in selected ratios. It resulted in an enhanced solubility of drug. These dispersions were used further. The behavior of different ratios was observed by determining their % age yield and solubility. The resultant effect on solubility by different ratios of polymer to drug was studied. Carriers (Ploxomer-188 and β-cyclodextrin) proclaimed a promising effect in enhancement of solubility of drug. Through studies, it was concluded that the purpose of formulating solid dispersions was fulfilled. The changes in behavior of preparations were observed and confirmed by different characterization methods. Bonding interactions among drug and polymers (both binary and ternary polymers) were determined from FTIR studies. The morphological changes in the crystalline structure of DAPO were confirmed through micrographs obtained from SEM. The studies regarding crystallinity and amorphousity were performed using X-diffraction. Studies did not show any interactions between drug and polymers that would decrease the solubility of DAPO. Increase in solubility was noticed with the increase in polymer ratio but some fluctuations were also observed in dispersions with maximum ratios of polymers.

Methods of preparing the dispersions were greatly involved in solubility. However, each method and ratio

lead to a gradual increase in solubility of DAPO. In binary dispersions, BSD 8 & 12 shown more enhanced solubility than others. While ultimately, in ternary solid dispersions TSD 5 & 6 shown a remarkable improvement in solubility of DAPO.

REFERENCES

Alshehri S, Shakeel F, Ibrahim M, Elzayat E, Altamimi M, Shazly G and Alshetaili AJPO (2017). Influence of the microwave technology on solid dispersions of mefenamic acid and flufenamic acid. *PLoS One,* **12**(7): e0182011.

Bhise S, Mathure D, Patil MV and Patankar RD (2011). Solubility enhancement of antihypertensive agent by solid dispersion technique. *Int. J. Pharm Life Sic,* **2**(8): 970-975.

Chadha R, Kapoor V and Kumar A (2006). Analytical techniques used to characterize drug-polyvinyl-pyrrolidone systems in solid and liquid states-An overview. *J. Sci. Ind. Res.,* **65**(6): 459-469

Chan SY, Chung YY, Cheah XZ, Tan EYL and Quah J (2015). The characterization and dissolution performances of spray dried solid dispersion of ketoprofen in hydrophilic carriers. *Asian J. Pharm. Sci,* **10**(5): 372-385.

Dalvi P, Gerange A and Ingale P (2015). Solid dispersion: Strategy to enhance solubility. *J. Drug Deliv. Therp,* **5**(2): 20-28.

Darcsi A, Szakacs Z, Zsila F, Toth G, Racz A and Beni S (2016). NMR, CD and UV spectroscopic studies reveal uncommon binding modes of dapoxetine to native cyclodextrins. *RSC Advances,* **6**(104): 102315-102328.

Dixit A, Singh R and Singh S (2012). Solid dispersion-a strategy for improving the solubility of poorly soluble drugs. *Int. J. Resh. Pharma. and Biomed. Sci.,* **3**(2): 13.

El-Desoky H, Abdel-Galeil M and Khalifa A (2019). Mesoporous SiO2 (SBA-15) modified graphite electrode as highly sensitive sensor for ultra trace level determination of Dapoxetine hydrochloride drug in human plasma. *J. Ele. Chem,* **846**: doi.org/10.1016/j.jelechem.2019.05.039

El-Said IA, Aboelwafa AA and ElGazayerly ON (2021). Optimization of taste-masked dapoxetine oral thin films using factorial design: *in vitro* and *in vivo* evaluation. *Pharm. Dev. Technol.,* **26**(5): 522-538.

Emami S, Siahi-Shadbad M, Adibkia K and Barzegar-Jalali M (2018). Recent advances in improving oral drug bioavailability by cocrystals. *BioImpacts: BI,* **8**(4): 305.

Fang R, Liu Y, Ma L, Yu X, Jin YJMS and CE (2021). Facile preparation of solid dispersions by dissolving drugs in N-vinyl-2-pyrrolidone and photopolymerization. **124**: 112063.

Fouad SA, Shamma RN, Basalious EB, El-Nabarawi MA and Tayel SA (2016). Novel instantly-soluble transmucosal matrix (ISTM) using dual mechanism solubilizer for sublingual and nasal delivery of dapoxetine hydrochloride: *In-vitro* / *in-vivo* evaluation. *Int. J. of Pharm,* **505**(1-2): 212-222.

Fu M, Peng X and Hu YJA (2019). Effect of premature ejaculation desensitisation therapy combined with dapoxetine hydrochloride on the treatment of primary premature ejaculation. **51**(4): e13135.

Huang Y and Dai Wgjapsb (2014). Fundamental aspects of solid dispersion technology for poorly soluble drugs. **4**(1): 18-25.

Jatwani S, Rana AC, Singh G and Aggarwal G (2012). An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. *Int. J Pharm. Sci. Res.* **3**(4): 942.

Kapoor B, Kaur R, Kour S, Behl H and Kour S (2012). Solid dispersion: an evolutionary approach for solubility enhancement of poorly water soluble drugs. *Int. J. Recent Adv. Pharm. Res.,* **2**(2): 1-16.

Khalifa A, El-Desoky H and Abdel-Galeil M (2018). Graphene-based sensor for voltammetric quantification of dapoxetine hydrochloride: A drug for premature ejaculation in formulation and human plasma. *J. Ele. Soc,* **165**(3): H128-H140.

Lee GW, Cho HH, Jeon SH, Choi MJ, Kim D, Kim HS and Khang G (2019). Improved rapid action of dapoxetine hydrochloride & L-arginine solid dispersion using film formulation. *Macromol. Res.,* **27**(4): 354-359.

Liu J, Li Z, Yan K, Ju G and Qiu Wjcpidd (2021). Pharmacokinetics and safety of dapoxetine hydrochloride in healthy Chinese men: Impact of dose and high fat meal. *Clin. Pharmacol. Drug Dev.,* **10**(10): 1216-1224.

Madsen CM, Boyd B, Rades T and Mullertz AJEJOPS (2016). Supersaturation of zafirlukast in fasted and fed state intestinal media with and without precipitation inhibitors. *Eur. J. Pharm. Sci.,* **91**: 31-39.

Nafady M (2014). Enhancement of ketoprofen and ibuprofen solubility and dissolution by lyophilized milk. *Int. J. Pharm Sci. Rev. Res.,* **2014**(24): 2.

Patel P, Prajapati S, Patel N, Patel N and Patel C (2012). Solid dispersion: A method of improving bioavailability and taste masking. *Inventi Rapid: Pharm. Tech.,* **2012**(4):

Saeed MA, Ansari MT and Ch BAJPJOPS (2019). Enhancement of solubility and dissolution profile of artesunate by employing solid dispersion approach: An in-vitro evaluation. *Pak. J. Pharm. Sci.,* **32**(1 Suppl.): 353-361.

Seftel ADJTJOU (2014). Efficacy and safety of dapoxetine in men with premature ejaculation and concomitant erectile dysfunction treated with a phosphodiesterase type 5 inhibitor: Randomized, placebo-controlled, phase III study. *J. Sex. Med.,* **10**(9): 2312-2325.

Serra CHDR, Chang KH, Dezani TM, Porta V and Storpirtis S (2015). Dissolution efficiency and

bioequivalence study using urine data from healthy volunteers: A comparison between two tablet formulations of cephalexin. *Braz. J. Pharma. Sci,* **51**(2): 383-392.

Sharma A, Jain CP and Tanwar YS (2013). Preparation and characterization of solid dispersions of carvedilol with poloxamer 188. *J. Chil. Chem. Soc,* **58**(1): 1553-1557.

Shejul MB, Godge R, Kakad S and Siddheshwar S (2019). Solid dispersion as strategy to improve the solubility of poorly water soluble drugs and their utilization and consideration during formulation development. *J. Drug Del. Therp.,* **9**(3-s): 874-880.

Singh D, Bedi N and Tiwary AKJJOPI (2018). Enhancing solubility of poorly aqueous soluble drugs: Critical appraisal of techniques. *J. Pharm. Investig.,* **48:** 509-526.

Ștefan MG, Kiss B, Gutleb AC and Loghin FJAOT (2020). Redox metabolism modulation as a mechanism in SSRI toxicity and pharmacological effects. *Arch, Toxicol.* **94**(5): 1417-1441.

Yadav PS, Kumar V, Singh UP, Bhat HR and Mazumder B (2013). Physicochemical characterization and *in vitro* dissolution studies of solid dispersions of ketoprofen with PVP K30 and d-mannitol. *Saudi Pharm. J,* **21**(1): 77-84.

Zhao GJ, Guo Q, Li YF and Zhang YGJSH (2019). Efficacy and safety of dapoxetine for premature ejaculation: An updated systematic review and meta-analysis. *Sex Health,* **16**(4): 301-313.