Research Article

Enhancement of Dissolution Rate of Acetaminophen Tablet using Solid Dispersions with Polyethylene Glycol 4000 and Polyvinylpyrrolidone K25

Asgarirad H[1], Farmoudeh A[2]*, Mohammadi J[3]

[1] Associate Professor, Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[2] Ph.D. candidate of pharmaceutics, Pharmaceutical Sciences Research Centre, Mazandaran University of Medical Sciences, Sari, Iran.
[3] Student of pharmacy, Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
***Corresponding author's E-mail:** Afarmoudeh@yahoo.com

Received: 27-02-2018; **Revised:** 18-04-2018; **Accepted:** 30-04-2018.

ABSTRACT

Solid dispersions (SDs) have been traditionally used as an effective method for improving the dissolution properties and bioavailability of poorly water-soluble drugs. Here we demonstrate the development and characterization of SD oral tablets, containing the poorly water-soluble drug acetaminophen, prepared using solvent evaporation technique and manufactured from two different polymers, polyethylene glycol 4000 and Polyvinylpyrrolidone K25. The prepared SDs were evaluated by saturation solubility test, differential scanning calorimetry (DSC), X-ray diffraction (X-RD), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). The dissolution efficiency (DE) and the percentage of acetaminophen dissolved (DP) after 15 and 120 min were calculated. After 15 min SD tablets had an enhanced DP and DE compared to the control tablets ($p < 0.05$). similar results were obtained after 120 min ($p < 0.05$). The prepared SDs exhibited a statistically significant increase in the solubility of acetaminophen compared to that of the pure drug ($p < 0.05$). The dissolution rates of SDs were higher than those of the physical mixtures and acetaminophen alone. Better results were obtained with PVP K25 than with PEG 4000. The FTIR spectroscopic test revealed the presence of intermolecular hydrogen bonding between acetaminophen and the polymers in the SD form. These interactions reflect the changes in the crystalline structures of acetaminophen. The thermal analysis and X-RD confirmed the presence of the drug in the amorphous state when it was dispersed in polymers. Therefore, dispersion of the drug in the polymers considerably enhanced the dissolution rate.

Keywords: Solid dispersion; Solubility enhancement; Differential scanning calorimetry; X-ray diffraction; Scanning electron microscopy; Acetaminophen.

INTRODUCTION

Improving the oral bioavailability of poorly water-soluble drugs is a huge challenge in drugs' development. A practical method for improving the dissolution rate of such drugs was developed by Sekiguchi and coworkers [1]. This method was later termed solid dispersion (SD), which generally consisted of two different components, a hydrophilic matrix and a lipophilic drug. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles [2]. Various methods, such as solvent evaporation, melting and kneading are available for the preparation of SD [3, 4]. Polymeric carriers have been the most successful for SDs because they are able to provide amorphous dispersions. This type of SD is homogeneous on a molecular-level [5]. Polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) are commonly used as carriers in the preparation of SDs [6–8]. A high-energy amorphous form of a molecular dispersion could affect the solubility and absorption of the drug [9,10]. Acetaminophen is very slightly soluble in cold water [11]; hence, the preparation of acetaminophen SDs could improve the dissolution characteristics of the drug. This study was designed to evaluate the physicochemical properties of SDs of acetaminophen. In addition, an experiment was conducted for achieving the incorporation of the prepared SDs in oral tablets.

MATERIALS AND METHODS

Materials

Acetaminophen was obtained from Alborz Bulk Company. (Tehran, Iran). PVP K-25, PEG 4000, sodium hydroxide (NaOH) and potassium dihydrogen phosphate were purchased from Merck KGaA (Darmstadt, Germany). All the carriers used were of analytical grade. Fresh deionized water was obtained from Human Ultra-Pure System (Human Corp, Korea).

Preparation of SDs

SDs of acetaminophen in PEG 4000 or PVP K25 was prepared in different ratios (Table 1) by the solvent evaporation method. The drug and the carrier were dissolved in a minimum volume of ethanol and water mixture (1:1). The solvents were removed under vacuum in a rotavapor at 40°C and 50 rpm for 24 h. Subsequently, the resulting residue was freeze-dried to remove the residual water. The dried dispersion was stored in a desiccator for 24 h and, then, pulverized in a mortar and passed through a 160 µm sieve. The concentration of acetaminophen in the dispersion was determined by UV spectrophotometer model v-630 (JASCO) at 250 nm.

Solubility test

Solubility determination of physical mixtures of drug and polymers, solid dispersions, and pure acetaminophen were carried out by adding an excess amount of each sample to conical flasks containing 40 ml of deionized water and subjected to shaking on a rotary shaker for 24 hours at 25°C. Subsequently, the mixture was filtered through a 220-nm membrane filter, and the filtered solution was analyzed to determine the drug content using UV spectroscopy.

Drug release test

Dissolution studies were carried out using United States Pharmacopeia (USP) II apparatus (paddle type). One tablet equivalent to 500 mg of the drug was added to the dissolution medium containing 500 ml of phosphate buffer (pH 6.8). The dissolution medium was maintained at a temperature of 37°C ± 0.5°C, and it was stirred at 50 rpm. At predetermined intervals, aliquots of sample were withdrawn, filtered, and analyzed for drug release by measuring the UV absorbance at 250 nm. The sample withdrawn at each time interval was replaced with the same volume of the fresh medium. To evaluate the dissolution profiles, the dissolution efficiency (DE) of the samples can be calculated as the area under the dissolution curve up to a certain time and expressed as a percentage of the area of the rectangle described by the area of 100% dissolution in the same time [12]. In this study, the DE from 0 to 15 or 120 minutes (expressed as %DE15 and %DE120, respectively) was calculated using the trapezoidal method.

Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out using a differential scanning calorimeter model pyris6 (PerkinElmer, Norwalk, USA). Samples (2 ± 0.2 mg) were sealed in hermetic crimped aluminum pans and heated at a constant rate of 10°C/min over a temperature range of 30°C–300°C, and nitrogen was used as a purge gas. An empty aluminum pan was used as reference material to calibrate the DSC temperature scale and enthalpic response [13].

Infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) studies were performed to determine the interaction between the components using FTIR-One spectrometer (PerkinElmer, Norwalk, USA). The scanning range was 450–4000 cm^{-1}, and the resolution was 1 cm^{-1}.

Scanning electron microscopy (SEM)

The surface morphology of the raw materials and SDs was investigated by a scanning electron microscope model VEGA TESCAN (Brno, the Czech Republic), under an accelerating voltage of 10 kV. Samples were coated with a thin gold layer before investigation.

X-ray diffraction (X-RD) analysis

The diffraction patterns of the raw materials and SDs were obtained using an X-ray diffractometer model D8-Advance (Bruker AXS, Karlsruhe Germany). Measurement conditions included target cu k-alpha, voltage 40 kV, and current 30 mA. The samples were analyzed in the 2θ angle range of 4° to 45° at a scan speed of 1°/min.

Powder mixing and tablet production

Acetaminophen SD tablets were prepared according to the proportions mentioned in Table 3. The raw materials were screened through a 170-mesh sieve prior to mixing. Powdered SD, containing an amount equivalent to 125 mg acetaminophen, was mixed with the other excipients and compressed on a single-punch tablet machine model EKO (Korsch Pressen, Berlin, Germany) equipped with 10-mm diameter flat-faced punches. The tablet weight was adjusted to 500 mg.

Evaluation of the prepared tablets

Physical parameters of the tablets, including weight, drug content, breaking force (hardness), and disintegration time, were evaluated. The drug content was evaluated by the weight variation test based on the USP standards.

Determination of weight variation

A weight variation test is applicable to demonstrate the uniformity of dosage unit for tablets containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit. Ten tablets from each formulation were chosen and then weighed individually, followed by calculation of the mean weight and standard deviation. According to the USP 34, the deviation should not be more than 15% for each tablet to be accepted (USP, 2015).

Determination of tablet hardness

The mean hardness (n = 10) of various tablets was measured with a Erweka hardness tester type TBH 30 MD (Heusenstamm, Germany). The maximum force in newton required to break each tablet was measured (USP, 2015).

Determination of the disintegration time

For analyzing the disintegration time of tablets, six tablets were tested according to the USP standard method using an Erweka type TZ 121 apparatus (Heusenstamm, Germany). The time taken for the complete disintegration of the last tablet at 37°C ± 0.5°C in distilled water was noted (USP, 2015).

Statistics

Results are expressed as mean of three determinations ± standard deviation (S.D.). Statistical analysis was performed using one-way analysis of variance (ANOVA) (SPSS software, version 22.0, SPSS Inc.). Post-hoc comparisons of the means were performed using Tukey's Honestly Significance Difference test. In all tests, a

probability value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Solubility studies

Table 1 shows the effect of increasing concentrations of PEG4000 and PVP K25 on the solubility of acetaminophen. The solubility of acetaminophen in deionized water at 25°C was found to be 12.2 mg/ml. Phase solubility studies showed that the solubility of acetaminophen increased as a function of concentration of polymers. PVP K25 demonstrated a statistically significantly higher solubility than that of PEG4000 ($p < 0.05$).

Kanakam and coworkers analyzed the enhancement of dissolution rate of atorvastatin calcium using SD. Saturation solubility study in phosphate buffer solution (pH 6.8) showed an increase in solubility of both the physical mixture and the SD containing the polymers (PEG4000 or PEG6000), but the increase in drug solubility was much higher in the SD form [14]. Garekani and Sadeghi (2003) reported an increase in aqueous solubility of acetaminophen in the presence of PVP [15].

Drug release

Dissolution data were evaluated according to cumulative percentage drug release. The DE and the percentage of acetaminophen dissolved (DP) after 15 and 120 min are depicted in Table 2. Fig. 1 shows the dissolution profiles of pure acetaminophen, physical mixtures, and SDs in phosphate buffer at 37°C. Drug release profile of all samples revealed two phases, an initial rapid release phase followed by a slower one (Fig. 1a and b). After 15 min, solid dispersions of acetaminophen in PVP K25 or PEG 4000 showed significantly increased DP and DE compared to those of the physical mixtures and the pure drug ($p < 0.05$); in addition, DP_{120} and DE_{120} were higher for SDs than those for the physical mixtures and pure acetaminophen ($p < 0.05$). Dissolution enhancement of SDs was observed by increasing the concentration of carriers. Akiladevi and Shanmugapandiyan (2011) prepared acetaminophen SD by melting method and observed an enhanced release rate with increasing proportions of carriers (PEG 4000 and 6000) [16]. The release profile of the SDs was shown to be improved by drug molecular dispersion in polymers [17], better wettability of the drug caused by drug–carrier hydrogen bonding [18], and inhibition of crystal growth of the drug molecules [19]. Another study showed that PVP K25 could significantly prevent the recrystallization of amorphous ketoconazole [20]. Papageorgiou et al. (2006) showed that nimodipine dispersed in PEG 4000 exhibited faster release compared to that of the physical mixture [21]. The authors concluded that drug amorphization is the primary reason of this behavior.

However, in all formulations, there was an improvement in the dissolution profile of the physical mixture compared to that of the pure drug, but the dissolution rate of SDs was higher than that of the physical mixture and acetaminophen alone (Table 2; Fig. 1a and b).

DSC

DSC curves obtained for pure acetaminophen, PEG 4000, PVP K25, SDs (Drug / PEG SD and Drug /PVP SD), and their corresponding physical mixtures are shown in Fig. 2. The DSC curve of pure acetaminophen powder exhibited a single endothermic peak at 169°C–171°C, indicating its crystalline nature [10]. PEG showed a sharp peak at 58°C, whereas scanning of PVP revealed a broad endotherm ranging from 50°C to 130°C, representing the evaporation of water due to the hygroscopic nature of this polymer [22]. Drug-polymer binary mixtures (Drug / PEG PM and Drug / PVP PM) exhibited the same endothermic transitions corresponding to the melting of the polymer and of the drug (Fig. 2A and 2B). As shown in Fig. 2A, acetaminophen in the physical mixture of the drug and PEG exhibited a very broad melting endotherm at a lower temperature compared to that at the melting point of the drug in the crystalline form. Earlier studies suggested that a drug may dissolve in molten PEG during the test which results in the appearance of the drug melting peak at lower temperatures [23,24]. As shown in Fig. 2B, acetaminophen in the physical mixture of the drug and PVP exhibited a sharp melting peak (unlike SD endotherm). This could be because the drug has less time to dissolve in molten PVP as the glass transition temperature of PVP K25 is 155°C (SDS, Merck) and the melting point of acetaminophen is 169°C–171°C. The Absence of the drug melting peak in the DSC thermogram of SDs indicates the destruction of the crystalline phase during melting or dissolution [25].

FTIR spectroscopic analysis

Fig. 3 shows the FTIR spectra of acetaminophen. The characteristic peaks in the spectrum of pure acetaminophen were assigned as follows: 3324 cm^{-1} (O-H stretching), 1657 cm^{-1} (C=O stretching), 1560 cm^{-1} (N-H bending), 1227 cm^{-1} (C-N bending), and 1171 cm^{-1} (C-O stretching) [25,26]. The PVP K25 spectrum showed significant bands at 2957 cm^{-1}(C-H stretching) and a broad peak at 1654 cm^{-1} (C=O stretching). A very broad band at 3460 cm^{-1} was attributed to the presence of water, confirming the broad endotherm detected during the DSC test. The PEG 4000 spectrum showed peaks at 3384 cm^{-1} (O-H stretching), hydrogen bonding at 2887 cm^{-1} (-CH3 stretching), and C-O (ether) stretching at 1110 cm^{-1}. In the acetaminophen/PEG SD spectrum, the hydroxyl peak characteristic for PEG and the carboxyl group characteristic for acetaminophen disappeared. These changes suggest the formation of hydrogen bonds between the drug and the polymer. Similar studies on acetaminophen and ibuprofen SDs containing other types of PEG demonstrated comparable results [27,28]. PVP is capable of forming a hydrogen bond through carbonyl

group on the aromatic ring [29]. In SD of acetaminophen and PVP, the absence of the hydroxyl peak of the drug and a significant decrease in the carbonyl group of PVP refer to the formation of hydrogen bonds between the hydroxyl group of acetaminophen and the carbonyl group in the PVP pyrrole ring.

SEM

The SEM images of acetaminophen powder, PEG 4000, PVP K25, and the SDs are shown in Fig. 4. The untreated acetaminophen crystals are rod like or needle-like (fig. 4A) [30], whereas PEG 4000 and PVP K25 have been reported to be composed of amorphous particles (fig. 4B and 4C) [31]. In contrast, electron micrographs of SDs did not show the original crystal morphology of acetaminophen, and there was a drastic change in the appearance of the polymers (fig. 4D and 4E).

X-RD

The solid-state of acetaminophen, the polymers, and the prepared SDs were analyzed by X-RD (Fig. 5). Pure PEG 4000 produced crystalline peaks at 2θ values of 15.4°, 17.96°, 19.81°, 23.42° and 26.51° [32]. PVP K25 being amorphous did not show any peaks. The powder diffraction patterns of pure acetaminophen showed characteristic high-intensity diffraction peaks at 2θ values of 12°, 13.77°, 15.33°,16.65°, 18.09°, 18.89°, 20.19°, 23.31°, 24.24°, 26.47°, 32.57° and 38.35° that matched the known patterns of acetaminophen [28]. All the principal peaks of acetaminophen were found in the diffraction patterns of SDs but at lower intensity, indicating that the drug was in the amorphous state. These observations are compatible with the above-mentioned findings obtained through the DSC study. Moreover, no peaks other than those that could be assigned to pure acetaminophen and PEG 4000 were detected in the SDs, indicating the absence of chemical interactions in the solid state between the drug and the polymers.

Characterization of the SD tablets

Weight variation values for all the tablets are shown in Table 4, and their drug content was in the acceptable range and close to their theoretical value of 150 mg ($p > 0.05$). All tablets had similar hardness ($p > 0.05$) in the range of 60–80 N, and all tablets disintegrated in 5–8 min in the USP test ($p > 0.05$). Fig. 6 shows the dissolution profiles of tablets containing pure acetaminophen and SDs in phosphate buffer at 37°C. After 15 min, SDs showed significantly increased DP and DE compared to those of the pure drug ($p < 0.05$); in addition, after 120 min DP and DE were higher for acetaminophen SD tablets than those for the pure drug ($p < 0.05$).

CONCLUSION

This study demonstrated the improvement in solubility and dissolution rate of acetaminophen when dispersed in PEG 4000 and PVP K25. Compared with the pure drug, the dissolution rate with the physical mixture was enhanced, but the dissolution rates of SDs were significantly greater than those for the physical mixtures and acetaminophen alone. Physical characterization by DSC and FTIR studies demonstrated that dissolution enhancement of acetaminophen from SDs was caused due to the destruction of the crystalline phase of the dispersed drug. FTIR studies revealed hydrogen bonding of acetaminophen with PVP K25 and PEG 4000, indicating the formation of solid solution resulting in a greater DE than that with PEG 4000 SDs.

Table 1: Solubility test of pure acetaminophen, physical mixtures and solid dispersions after 24 hours. (data shown as mean ± standard deviation, n = 3).

Formulation number	Drug:polymer Ratio	Acetaminophen (mg)	Solubility in 24 h (mg/ml)
F1	PM PEG 5:1	500	13.75 ± 0.09
F2	PM PEG 5:3	500	14.07 ± 0.09
F3	PM PEG 5:5	500	14.63 ± 0.08
F4	SD PEG 5:1	500	14.48 ± 0.13
F5	SD PEG 5:3	500	15.71 ± 0.05
F6	SD PEG 5:5	500	16.53 ± 0.12
F7	PM PVP 5:1	500	16.43 ± 0.03
F8	PM PVP 5:3	500	19.14 ± 0.06
F9	PM PVP 5:5	500	19.77 ± 0.08
F10	SD PVP 5:1	500	17.53 ± 0.04
F11	SD PVP 5:3	500	19.82 ± 0.03
F12	SD PVP 5:5	500	22.14 ± 0.06
F13	Pure acetaminophen	500	12.19 ± 0.05

Table 2: Dissolution characteristics of pure acetaminophen, physical mixtures and solid dispersions after 15 and 120 min in phosphate buffer at 37°C. (Data shown as mean ± standard deviation, n = 3).

Formulation	%DE15	%DE120	%DP15	%DP120
F1	18.41 ± 0.99	63.37 ± 0.65	36.83 ± 1.98	78.85 ± 4.28
F2	21.45 ± 1.88	68.49 ± 0.7	42.9 ± 3.77	84.8 ± 4.52
F3	22.8 ± 1.55	69.28 ± 1.72	45.6 ± 3.1	83.48 ± 2.46
F4	23.32 ± 1.24	71.26 ± 1.08	46.65 ± 2.47	85.45 ± 2.03
F5	25.71 ± 1.83	74.29 ± 0.46	51.43 ± 3.65	86.11 ± 2.58
F6	28.32 ± 2.37	75.98 ± 0.64	56.64 ± 4.75	89.07 ± 2.98
F7	22.26 ± 2.83	69.32 ± 1.77	44.52 ± 5.66	86.15 ± 2.47
F8	25.38 ± 1.58	72.44 ± 2.66	50.76 ± 3.15	88.29 ± 2.7
F9	27.61 ± 1.68	76.57 ± 1.13	55.23 ± 3.35	91.41 ± 3.11
F10	34.49 ± 1.89	79.81 ± 0.66	68.98 ± 3.78	93.75 ± 3.26
F11	38.18 ± 1.32	82.91 ± 0.53	76.36 ± 2.64	92.49 ± 3.09
F12	40.71 ± 1.1	85.3 ± 1.04	81.43 ± 2.21	94.65 ± 1.93
F13	16.9 ± 1.57	57.89 ± 2.01	33.8 ± 3.15	72.81 ± 2.16

Table 3: Ingredients used in preparation of acetaminophen solid dispersion tablets

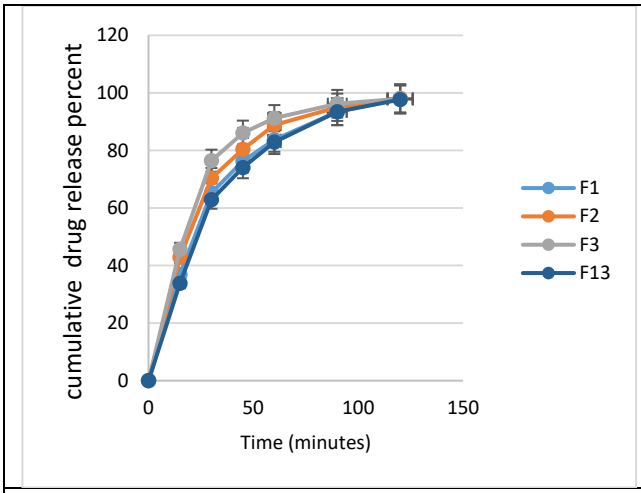
Formulation number	Acetaminophen (mg)	PEG4000 (mg)	PVPK25 (mg)	Maze starch (mg)	Talc (mg)	Magnesium Stearate (mg)	Aerosil (mg)
1	125	125	-	235	5	5	5
2	125	-	125	235	5	5	5
3	125	-	-	360	5	5	5

Table 4: Average weight, hardness and disintegration time of blank and solid dispersion tablets.

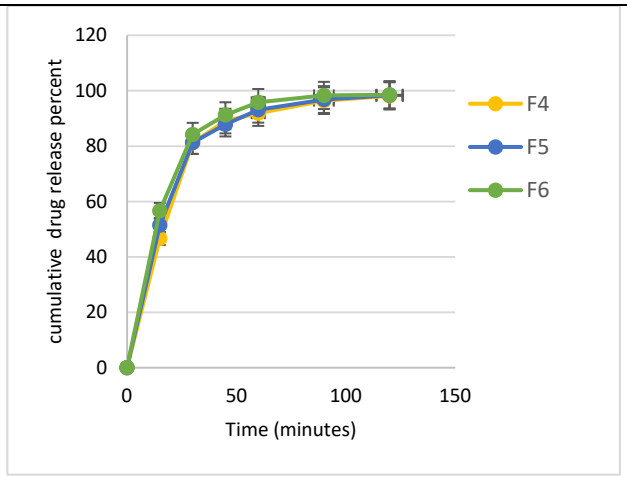
Formulation number	Weight (mg) (n = 10, ± SD)	Hardness (N) (n = 10, ± SD)	disintegration time (min) (n = 6, ± SD)
1	495.16 ± 5.75	71.6 ± 2.31	5.27 ± 0.67
2	496.36 ± 5.6	73.5 ± 2.79	4.51 ± 0.49
3	497.04 ± 6.02	73 ± 2.58	5.46 ± 0.61

Table 5: Dissolution efficiency (DE) and percent acetaminophen dissolved (DP) from tablets containing pure acetaminophen and solid dispersions in phosphate buffer at 37°C. (data shown as mean ± standard deviation, n = 3).

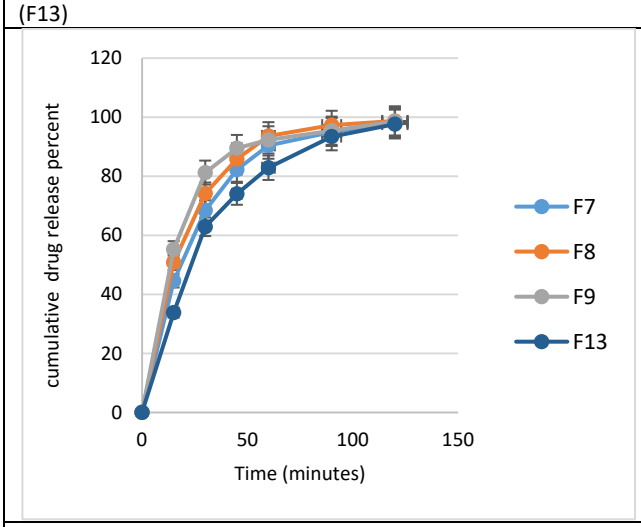
Formulation number	%DE15	%DE120	%DP15	%DP120
1	26.32 ± 1.62	73.83 ± 1.78	52.64 ± 3.23	88.33 ± 2.89
2	40.63 ± 2.6	85.52 ± 1.96	81.26 ± 5.2	95.01 ± 1.62
3	15.07 ± 1.81	57.97 ± 0.74	30.14 ± 3.63	71.78 ± 3.13



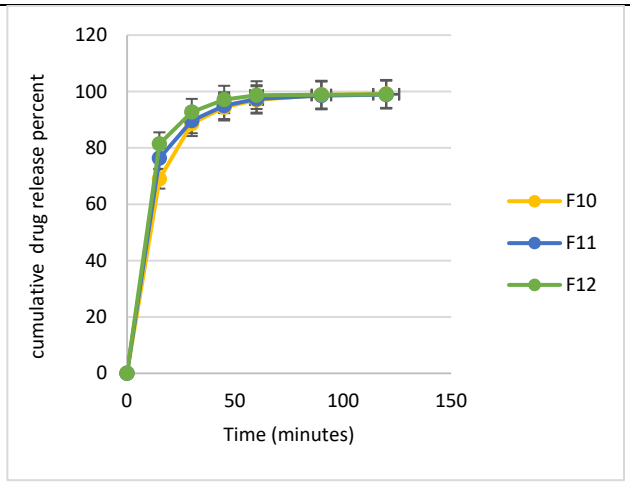
A. Acetaminophen: PEG physical mixture (F1 – F3) and pure drug (F13)



B. Acetaminophen: PEG solid dispersion (F4 – F6)

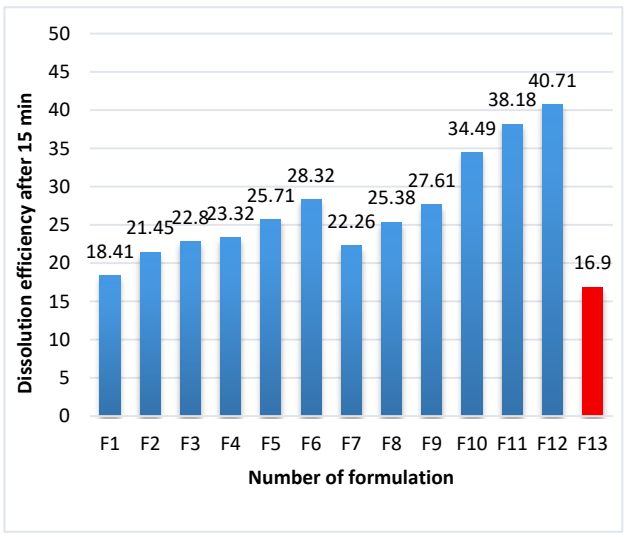


C. Acetaminophen: PVP physical mixture (F7 – F9) and pure drug (F13)

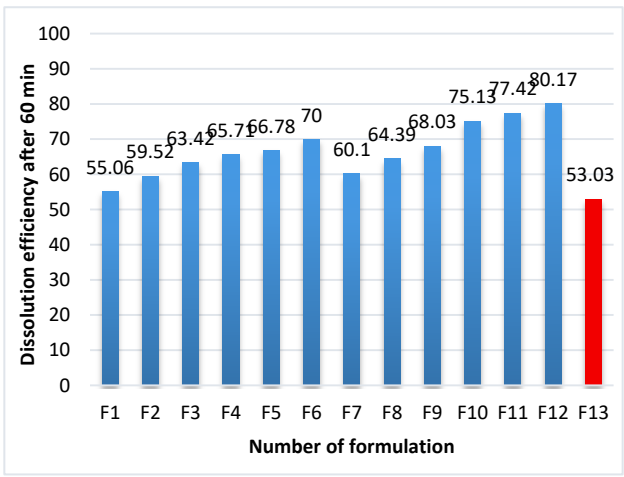


D. Acetaminophen: PVP solid dispersion (F10 – F12)

Figure 1: Dissolution profiles of tablets containing pure acetaminophen, physical mixtures and solid dispersions (data shown as mean ± standard deviation, n = 3).

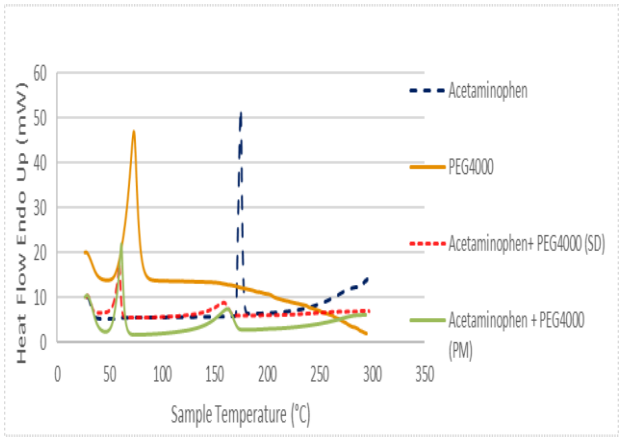


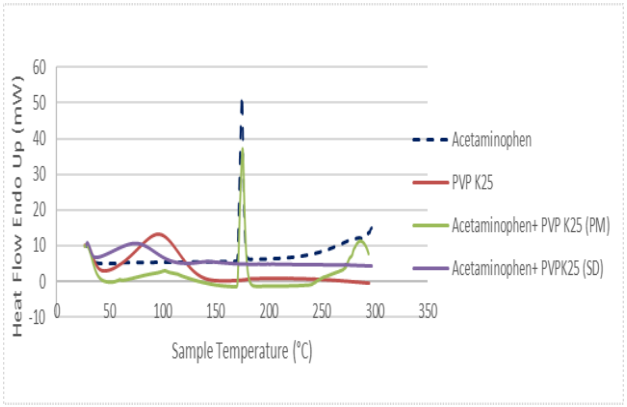
A



B

Figure 2: Dissolution efficiency of pure acetaminophen, physical mixtures and solid dispersions (A) after 15 and (B) 60 min in phosphate buffer at 37°C.





A B

Figure 3: Differential scanning calorimetric curves of (A) acetaminophen, PEG4000, acetaminophen-PEG SD and Physical Mixture. (B) acetaminophen, PVP K25, acetaminophen-PVP SD and Physical Mixture.

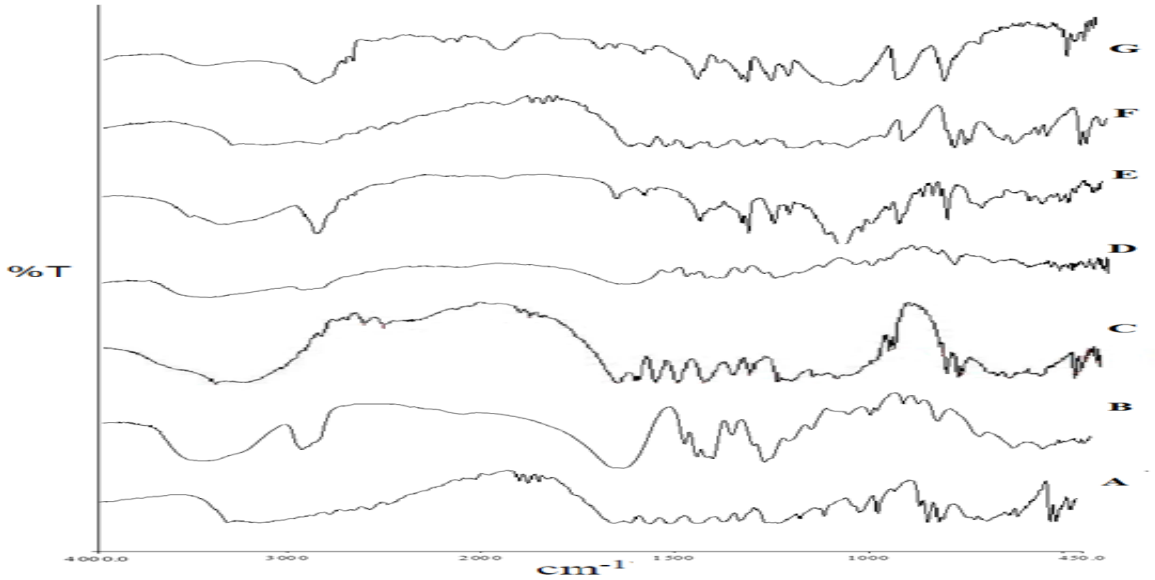
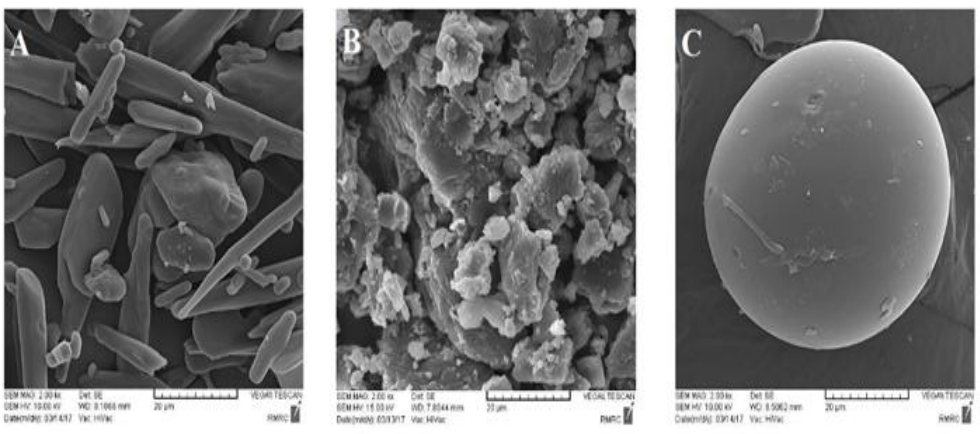


Figure 4: FTIR spectra of pure materials, solid dispersions, inclusion complexes and corresponding physical mixtures. (A) pure acetaminophen, (B) PVP K25, (C) physical mixture of acetaminophen/PVP, (D) solid dispersion of acetaminophen/PVP K25, (E) PEG 4000, (F) physical mixture of acetaminophen /PEG, (G) solid dispersion of acetaminophen /PEG.



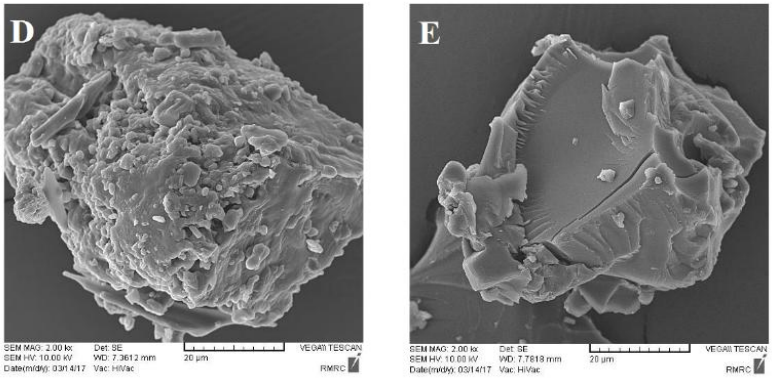


Figure 5: SEM images of (A) acetaminophen powder; (B) PEG 4000; (C) PVP K25; (D) drug / PEG 4000 solid dispersion (1:1); (E) drug / PVP K25 solid dispersion (1:1)

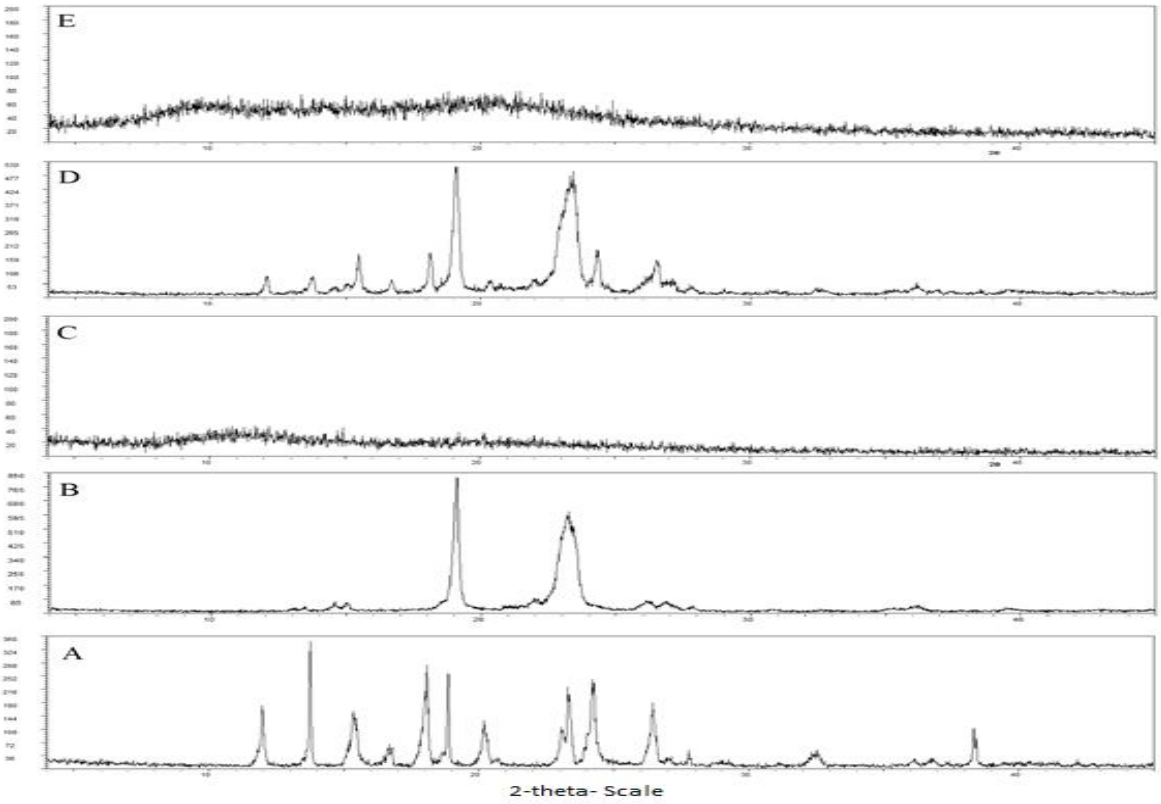


Figure 6: Powder X-ray Diffractograms of (A) acetaminophen powder; (B) PEG 4000; (C) PVP K25; (D) drug / PEG 4000 solid dispersion (1:1); (E) drug / PVP K25 solid dispersion (1:1)

REFERENCES

1. Patel, Rakesh P., et al. "Physicochemical characterization and dissolution study of solid dispersions of furosemide with polyethylene glycol 6000 and polyvinylpyrrolidone K30." Dissolution Technol 15.3, 2008, 17-25.

2. Chiou, Win Loung, and Sidney Riegelman. "Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin." Journal of pharmaceutical sciences 58.12, 1969, 1505-1510.

3. Beneš, Michal, et al. "Methods for the preparation of amorphous solid dispersions–A comparative study." Journal of Drug Delivery Science and Technology 38, 2017, 125-134.

4. Kim, Dong Shik, et al. "Comparison of solvent wetted and kneaded l-sulpiride loaded solid dispersions: Powder characterization and in vivo evaluation." International journal of pharmaceutics 511.1, 2016, 351-358.

5. Van Drooge, D. J., et al. "Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques." International journal of pharmaceutics 310.1-2, 2006, 220-229.

6. Ng, Choon Lian, et al. "Solubilization and formulation of chrysosplenol C in solid dispersion with hydrophilic carriers." International journal of pharmaceutics 512.1, 2016, 314-321.

7. Lee, Hyo-Jung, et al. "Controlled-release oral dosage forms containing nimodipine solid dispersion and hydrophilic carriers." Journal of Drug Delivery Science and Technology 37, 2017, 28-37.

8. Vasconcelos, Teófilo, et al. "Amorphous solid dispersions: rational selection of a manufacturing process." Advanced drug delivery reviews 100, 2016, 85-101.

9. Sinha, Shilpi, et al. "Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir." Aaps Pharmscitech 11.2, 2010, 518-527.

10. Kalepu, Sandeep, and Vijaykumar Nekkanti. "Insoluble drug delivery strategies: review of recent advances and business prospects." Acta Pharmaceutica Sinica B 5.5, 2015, 442-453.

11. O'Neil, Maryadele J., ed. The Merck index: an encyclopedia of chemicals, drugs, and biologicals. RSC Publishing, 2013.

12. Khan, K. A. "The concept of dissolution efficiency." Journal of pharmacy and pharmacology 27.1, 1975, 48-49.

13. Liu, Longxiao, and Xiaocui Wang. "Improved dissolution of oleanolic acid with ternary solid dispersions." AAPS PharmSciTech 8.4, 2007, 267-271.

14. Kanakam, Vijaya Bhaskar. "Enhancement of dissolution rate of atorvastatin calcium using solid dispersions by dropping method." Int J Pharm Tech Res 3.2, 2011, 652-9.

15. Afrasiabi Garekani, H., F. A. T. E. M. E. H. Sadeghi, and A. Ghazi. "Increasing the aqueous solubility of acetaminophen in the presence of polyvinylpyrrolidone and investigation of the mechanisms involved." Drug development and industrial pharmacy 29.2, 2003, 173-179.

16. Akiladevi, D., et al. "Preparation and evaluation of paracetamol by solid dispersion technique." Int J Pharm Pharm Sci 3.1, 2011, 188-191.

17. Ford, James L. "The current status of solid dispersions." Pharmaceutica Acta Helvetiae 61.3, 1986, 69-88.

18. Tantishaiyakul, V., N. Kaewnopparat, and S. Ingkatawornwong. "Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30." International journal of pharmaceutics 143.1, 1996, 59-66.

19. Betageri, G. V., and K. R. Makarla. "Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques." International journal of pharmaceutics 126.1-2, 1995, 155-160.

20. Van den Mooter, Guy, et al. "Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25." European journal of pharmaceutical sciences 12.3, 2001, 261-269.

21. Papageorgiou, George Z., et al. "Effect of physical state and particle size distribution on dissolution enhancement of nimodipine/PEG solid dispersions prepared by melt mixing and solvent evaporation." The AAPS journal 8.4, 2006, E623-E631.

22. Van den Mooter, Guy, et al. "Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30." International Journal of Pharmaceutics 164.1-2, 1998, 67-80.

23. Craig, D. Q. M. "Polyethyelene glycols and drug release." Drug Development and Industrial Pharmacy 16.17, 1990, 2501-2526.

24. Lloyd, G. R., D. Q. M. Craig, and A. Smith. "An investigation into the melting behavior of binary mixes and solid dispersions of paracetamol and PEG 4000." Journal of pharmaceutical sciences 86.9, 1997, 991-996.

25. Trivedi, Mahendra Kumar, et al. "Effect of biofield treatment on spectral properties of paracetamol and piroxicam." (2015).

26. Bashpa, P., et al. "Polymorphism of paracetamol: A comparative study on commercial paracetamo l samples." Int J Chem Studies 1, 2014, 25-29.

27. Khan, Sheraz, et al. "Systems biology approach to study permeability of paracetamol and its solid dispersion." International journal of pharmaceutics 417.1-2, 2011, 272-279.

28. Khanmohammadi, M., et al. "Qualitative discrimination between paracetamol tablets made by near infrared spectroscopy and chemometrics with regard to polymorphism." Journal of Structural Chemistry 51.4, 2010, 663-669.

29. SEKIZAKI, Haruo, et al. "Solid-state interaction of ibuprofen with polyvinylpyrrolidone." Chemical and pharmaceutical bulletin 43.6, 1995, 988-993.

30. Rossmann, Matthias, et al. "Manipulating the size, the morphology and the polymorphism of acetaminophen using supercritical antisolvent (SAS) precipitation." The Journal of Supercritical Fluids 82, 2013, 230-237.

31. Xie, Yongmei, et al. "Preparation of esomeprazole zinc solid dispersion and study on its pharmacokinetics." International journal of pharmaceutics 360.1-2, 2008, 53-57.

32. Ansari, Muhammad Tayyab, et al. "Physicochemical characterizations of artemether solid dispersions with hydrophilic carriers by freeze dried and melt methods." Archives of pharmacal research 33.6, 2010, 901-910.

Source of Support: Nil, **Conflict of Interest:** None.