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Original Article

Enhancement of Avermectin Water-solubility by Addition of Poloxamer 188 and Deep Eutectic Solvent into PEG 6000 Solid Dispersion System

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ABSTRACT

Background: It has been reported previously that AV water-solubility was enhanced great by solid dispersion in PEG6k carrier. **Materials and Methods:** In this study, AV water-solubility was improved primarily by addition of PLX188 into PEG6k carrier, and further by addition of a deep eutectic solvent of CBU (choline chloride, betaine and urea) in the combinatory carrier of PEG6k and PLX188. **Results:** The result showed that the water-solubility of AV-PEG6k-PLX188 solid dispersion was 10.8 times of AV-PEG6k solid dispersion, and the cumulative dissolution rate (within 60 min) of AV-PEG6k-PLX188 solid dispersion was 3.3 times of AV-PEG6k solid dispersions. With the further addition of CBU in the AV-PEG6k-PLX188 system, the water-solubility of AV-PEG6k-PLX188-CBU solid dispersion was increased by 3.4 times, and the cumulative dissolution rate (within 60 min) was increased by 1.6 times. The X-ray powder diffraction measurement indicated that AV existed in the AV-PEG6k-PLX188-CBU solid dispersion as a non-crystalline state. Further, the *in vitro* toxicity against 3rd instar Asiatic migratory locust was measured, which showed that the LC_{50} of the AV-PEG6k-PLX188-CBU solid dispersion (0.88 mg/L) was a third of that of AV emulsifiable concentrate (2.64 mg/L), suggesting a higher bioavailability. **Conclusion:** The finding of this work showed that AV-PEG6k-PLX188-CBU solid dispersion was more effective than AV emulsifiable concentrate, in suppressing or killing locusts.

Keywords: Solid dispersion, Avermectin, Water-solubility, Stability, Bioavailability.

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INTRODUCTION

In solid dispersion, drugs may exist in molecular, amorphous or microcrystalline forms, with reducing particle size and increasing wettability, thereby improving the solubility. Since the first discovery of sulfathiazole-urea solid dispersion[1] in 1961, the solid dispersion had been used frequently to improve dissolution rate of insoluble drugs, among which some high polymers such as polyvinylpyrrolidone, Polyethylene Glycol (PEG), polyvinyl alcohol and poloxamer are used conventionally as the carriers.[2-5] However, there exist defects in cases of high polymer alone used as carrier, such as rapid drug dissolution at initial stage, and nucleation and recrystallization of drugs in the dissolution medium after storage for a certain time.[6-9] Thus, it is meaningful to find alternative carrier, which may improve effectively the dissolution of the drug, prevent the crystallization of the drug from precipitation, increase the stability of the preparation and reduce the toxic and side effects of the drug.

As a green and excellent solvent, deep eutectic solvent[10] firstly discovered by Abbott in 2003, has attracted widespread attention in recent years. Deep eutectic solvent is prepared by melting hydrogen bond receptors (quaternary ammonium salt, quaternary phosphonium salt and choline chloride, etc.) and hydrogen bond donors (urea, amide, carboxylic acid and polyols, etc.) in a certain proportion, with a melting point lower than that of any single component.[11-13] Deep eutectic solvent has noteworthy ionic liquid-like physicochemical properties, such as, good thermal stability, high solubility, negligible vapor pressure, and non-flammability.[14,15] And it shows significant advantages over conventional ionic liquids especially in terms of low-toxicity, biodegradability and ease of preparation. Owing to these significant advantages, deep eutectic solvent has been applied in many fields.

Avermectin (AV) was consisted of eight components, among which B_1b (Figure 1) are the main compounds showing the most effective insect-resistant activity.[16,17] The locusts are one of the

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most destructive pathogenic pests in crops, and AV has a good killing effect on them. However, as AV has weak water-solubility, resulting in poor effects on killing insects. Therefore, it is necessary to find a method to effectively improve the dissolution of AV.

Improving the solubility of insoluble drugs has kept being one of the major difficulties in pharmaceutical research, with more and more insoluble drugs were discovered in recent years. In this study, AV was molten with heating into the combinatory carrier of a polymer mixture of polyethylene glycol 6000 (PEG6k) and poloxamer 188 (PLX188), and a deep eutectic solvent of choline chloride, betaine and urea (CBU), then the AV-PEG6k-PLX188-CBU solid dispersion was formed upon cooling. As expected, with the addition of deep eutectic solvent in the AV-PEG6k-PLX188-CBU solid dispersion, the dissolving properties were improved greatly.

MATERIALS AND METHODS

Experimental Instruments and Reagents

PEG6k, urea was purchased from Sinopsin Group Chemical Reagent Co. Ltd. PLX188, choline chloride was purchased from Yusuo Chemical Technology Co. Ltd., Shandong. Shandong. AV (containing B_1a 95.1% and B_1b 4.2%) was purchased from Kaijin Medical Technology Co. Ltd., Shanghai. Shanghai. AV emulsifiable concentrate was purchased from Longyou Oriental Anasak Crop Technology Co. Ltd., Zhejiang. Third instar Asiatic migratory locust was obtained from Jiyuan Baiyun Industrial Co. Ltd., Henan. Unless otherwise stated, all other materials were of analytical grade.

AV was determined using Shimadzu LC-20T HPLC system with a C_{18} reverse chromatographic column (250 mm×4.6 mm, 5 um, Shimadzu, Japan). The mobile phase consisted of methanol and water in a ratio of 85:15 at a flow rate of 1.0 mL/min. Analysis was performed at room temperature (25°C) with a total injection volume of 20 µl and the detection wave length of 248 nm.[18,19]

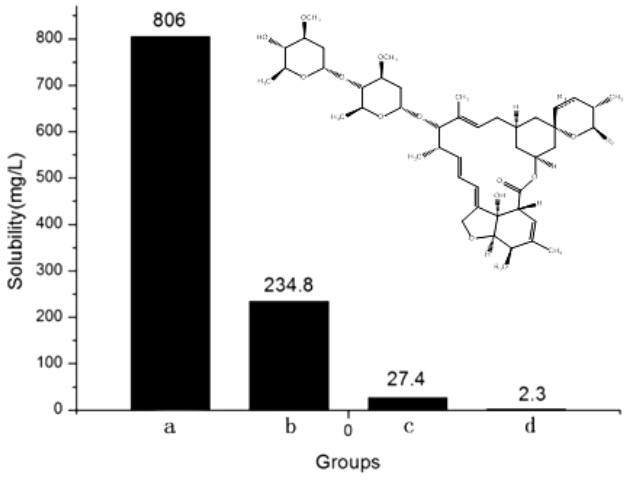

Figure 1: Chemical structure of AV.

AV-PEG6k-PLX188-CBU; b. AV-PEG6k SD; c. physical mixture; d. AV

Preparation of Samples

The deep eutectic solvent (CBU) was prepared by melting choline chloride, betaine and urea in a proper mass ratio at 80°C. Then the combinatory carrier was made by melting and mixing CBU with PEG6k, PLX188 at 80°C. The AV powder was added slowly into the carrier in a mass ratio of 1:19 with stirring at 80°C till it was completely dissolved. Then, the resulting molten mixture was solidified upon cooling in a bath of ice and salt, affording the AV-PEG6k-PLX188-CBU solid dispersion. At final, samples of the AV-PEG6k-PLX188-CBU solid dispersion were made by grinding and sieving through 16-25 mesh. AV-PEG6k-PLX188 solid dispersion was prepared as a control sample through the similar procedure described above, except that CBU was excluded from the system. And the blank solid dispersion was prepared as a control sample through the similar procedure described above, except that AV was excluded from the system. Physical mixture was prepared as comparison sample by mixing each component, with the same content to that of the AV-PEG6k-PLX188-CBU solid dispersion, under grinding till all components was evenly mixed.

X-ray Powder Diffraction Analysis

The AV-PEG6k-PLX188-CBU solid dispersion and the blank carrier were crushed into 1 mm flakes, respectively. The physical mixture of AV and carrier was pulverized into 200 mesh screens to prepare samples. Thermal characteristics of samples were determined by XRD (XPert Pro X-ray powder diffractomer Palmer Naco, Netherland) at scanning range of 5-70°, step length of 0.02° and scanning time of 20 s.

Particle Size Analysis

An appropriate amount of the AV-PEG6k-PLX188-CBU solid dispersion, and AV-PEG6k-PLX188 solid dispersion as blank contrast were added to distilled water, respectively, and the samples were completely disintegrated and dispersed. The resulting liquid was poured into a particle size cup to be detected by a laser particle size analyzer of ZS90 (Malvin, England).

Dissolution Testing

The solubilities of the AV-PEG6k-PLX188-CBU solid dispersion, AV-PEG6k-PLX188 solid dispersion, physical mixture and AV were determined by adding excess samples into 100mL distilled water, respectively. The resulting system was stirred (75 r/min) until the equilibrium was achieved. Appropriate amount of suspension was filtered through polytetrafluoroethylene difluoride 0.45 µm membrane (Millipore), and was determined by HPLC.

Measurement of Cumulative Dissolution Rate

Appropriate amount (5.0 g) of the AV-PEG6k-PLX188-CBU solid dispersions and AV-PEG6k-PLX188 solid dispersions were dissolved into 1000mL dissolution medium of 0.5% ethanol-water (15:85), respectively, and stirred (100 r/min) at 25°C. The amount of 5 mL aliquot was taken for testing at 5, 10, 20, 40, and 60 min, respectively, while equal amount of media was added. The sample was filtered (polytetrafluoroethylene difluoride 0.45 μl m membrane, Millipore) and then detected by HPLC.

The toxicity of the AV-PEG6k-PLX188-CBU solid dispersions against 3rd instar Asiatic migratory locust

The gastric toxicity of solid dispersion was determined by leaf toxicity assay. An appropriate amount of the AV-PEG6k-PLX188-CBU solid dispersion particles was diluted with distilled water into concentrations of 3.72, 1.86, 0.93, 0.47, 0.23 mg/L as experimental group. An appropriate amount of AV emulsifiable concentrate with a concentration of 78 mg/L was diluted into concentrations of 7.80, 3.90, 1.95, 0.98 and 0.49 mg/L as the control sample, and distilled water was taken as the blank control.

Each culture dish was served with a 3rd instar *Asiatic migratory locust* and a piece of prepared poisonous leave disc. 30 samples were tested at each concentration in each group and 15 ones in the blank groups. The samples were moistened and cultured at 25°C. When the poisonous leaf was eaten out, the fresh leaf was put in without medicine till the end of the experiment. After 48 hr, the mortality rate of each group was investigated.

RESULTS AND DISCUSSION

Preparation of the Solid Dispersion

The amount of the individual component in the AV-PEG6k-PLX188-CBU solid dispersion were determined by preliminary screening, and was optimized by orthogonal experiment. The optimal result was listed as followings: PEG6k 55.5% (wt.), PLX188 11.3% (wt.), CBU 25.7% (wt.), AV 5.0% (wt.); and the betaine/urea/choline chloride mass ratio of 1.5:3.29:1 in CBU; stirring for 2 hr.

X-ray Powder Diffraction (XRD) Analysis

As shown in Figure 2, there existed a series of characteristic peaks of AV at 5°-30°, and in the physical mixture, there existed also characteristic peaks of AV with strength weakened. But in the AV-PEG6k-PLX188-CBU solid dispersion, AV peak disappeared, except for weak peaks characteristic of PEG6k at 19.35° and 23.48°, indicating that AV existed mostly in a non-crystalline state, and that CBU and PLX188 appeared in an amorphous state and had good compatibility with PEG6k.

Particle Size Analysis

A beam passing through the resulting system was observed, indicating that the resulting system was a kind of particle suspension. The Average particle size of the AV-PEG6k-PLX188-CBU solid dispersion was of 122.3 nm, with a uniform particle size distribution, which was 2.8 times smaller than that of the AV-PEG6k-PLX188 solid dispersion (343.2 nm) (Figure 3). In addition, The Average particle size of the AV-PEG6k-PLX188-CBU solid dispersion was 1.4 and 1.6 times smaller than that of the AV aqueous dispersion of single surfactant of SDS and composite surfactant of MERS and SDS (180-196 nm), respectively.[20,21]

The decrease of particle size is one of the mechanisms of solubilization, which is the same to the results reported.[22,23] Further, as a hydrophilic system, the addition of the deep eutectic solvent could improve the wettability of the AV-PEG6k-PLX188-CBU solid dispersion, made AV dispersing in water easily.[24] The tiny particle had increased surface area, and the contact area, so the dissolution rate was improved effectively.[25]

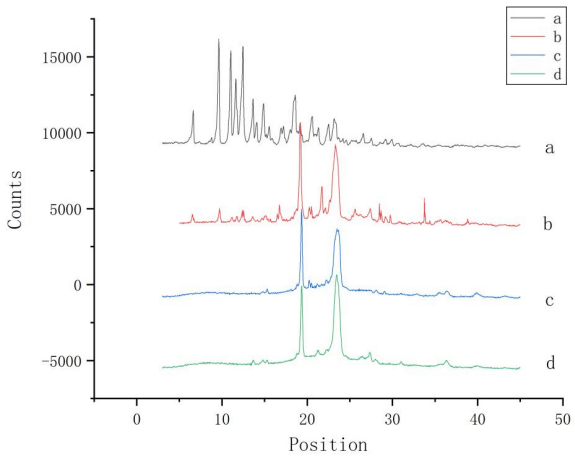

Figure 2: XRD spectrum of AV (a), physical mixture of AV, PEG6k, PLX188 and CBU (b), AV-PEG6k-PLX188-CBU solid dispersion (c), and blank carrier of PEG6k, PLX188 and CBU (d).

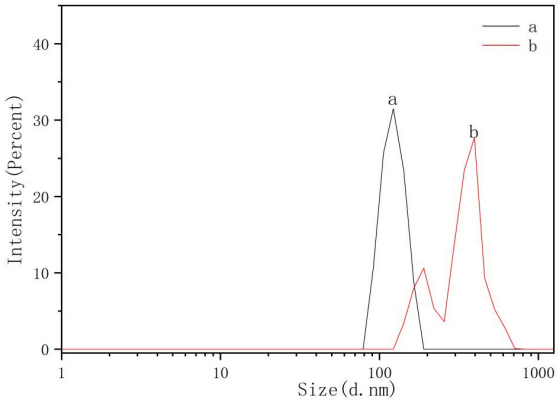

Figure 3: Particle diameter distribution of the AV-PEG6k-PLX188-CBU solid dispersion (a) and AV-PEG6k-PLX188 solid dispersion (b).

Table 1: The comparison of pharmaceutical properties.

		AV	AV-PEG6k	AV-PEG6k-P188	AV-PEG6k-PLX188-CBU
Particle diameter (nm)		/	/	343.2	122.3
Solubility (mg/L)		2.3	21.795	234.8	806.0
Cumulative dissolution rate (%)	5 min	5.3	7.3	53.9	86.3
	60 min	10.3	17.6	58.3	94.6

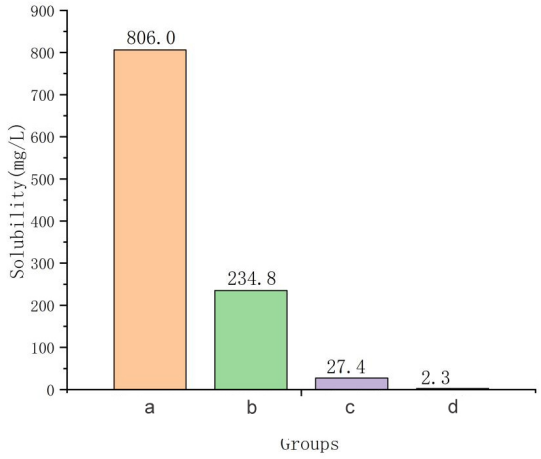

Figure 4: Solubility of the AV-PEG6k-PLX188-CBU solid dispersion (a), AV-PEG6k-PLX188 solid dispersion (b), physical mixture (c) and AV (d).

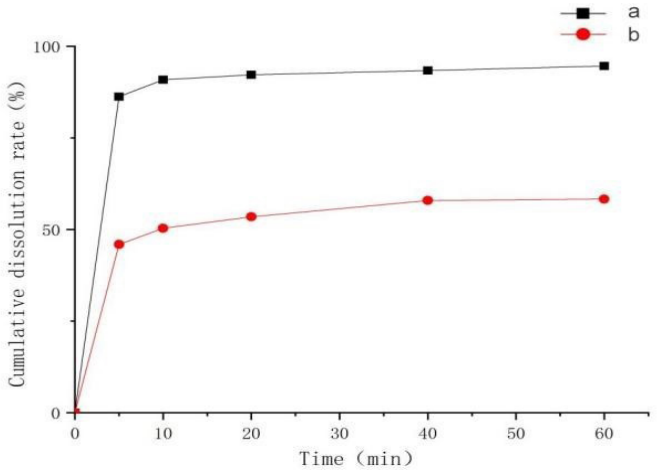

Figure 5: Dissolution curve of the AV-PEG6k-PLX188-CBU solid dispersion (a), AV-PEG-PLX solid dispersion (b).

The bimodal distribution of the AV-PEG6k-PLX188 solid dispersion particle might be due to the unstable dispersion in water, and some dissolved AV turned to spontaneously aggregate, leading to the increase of particle size and the worse uniformity of particles. And this was consistent with the previous observation of drug nucleation and recrystallization in dissolution medium, in case of that polymer alone was used as carrier in solid dispersion system.

Dissolution Testing

As shown in Figure 4, the solubility of AV of the AV-PEG6k-PLX188-CBU solid dispersion was of 806.0 mg/L, 3.4 times that of an AV-PEG6k-PLX188 solid dispersion (234.8 mg/L)[26], 29.4 times that of the physical mixture (27.4 mg/L), and 350 times that of the AV (2.3 mg/L).

It was reported that PEG might induce carbamazepine crystallization and form enriched carrier layer in the dissolution process, resulting in accumulation and precipitation and decreasing the solubility of carbamazepine.[27] The situation of solid dispersion in the combinatory carrier was different from that in PEG alone as carrier. In this study, it was observed that the AV-PEG6k-PLX188-CBU solid dispersion dissolved totally in water, and didn't precipitate from water after storage, thus the solubility of AV in the AV-PEG6k-PLX188-CBU solid dispersion was significantly improved.

Cumulative Dissolution Rate Analysis

As shown in Figure 5, the cumulative dissolution rates of the AV-PEG6k-PLX188-CBU solid dispersion in the dissolution medium were 86.3% within 5 min, and 94.6% within 60 min and the cumulative dissolution rates of AV-PEG6k-PLX188 solid dispersion were 53.9% within 5 min, 58.3% within 60 min. As a comparison reported previously,[26] the cumulative dissolution rate of AV-PEG6k was of 10.3% within 60 min, the cumulative dissolution rate of AV-PEG6k was of 17.6% within 60 min. The AV cumulative dissolution rate was improved by 1.6 times than the solid dispersion of AV-PEG6k-PLX188, 5.4 times than the AV-PEG6k solid dispersion,[26] 9.2 times than the AV.[26]

With the highly hydrophilic deep eutectic solvent was solubilized in water, the structure of the AV-PEG6k-PLX188-CBU solid dispersion was collapsed easily, therefore accelerating the dissolution of AV. Meanwhile, as a surfactant PLX188 could increase the wettability of the solid dispersion, thus increasing the dissolution of AV.[28,29]

Toxicity of the Solid Dispersion against 3rd-instar locust

Toxicity of the AV-PEG6k-PLX188-CBU solid dispersion against 3rd instar *Asiatic migratory locust* were determined by the method of leaf entrapment, with an AV emulsifiable concentrate was used as a comparison sample. The regression curve was shown in Figure 6. It was calculated that LC_{50} of the AV-PEG6k-PLX188-CBU solid dispersion was 0.88 mg/L, while LC_{50} of AV

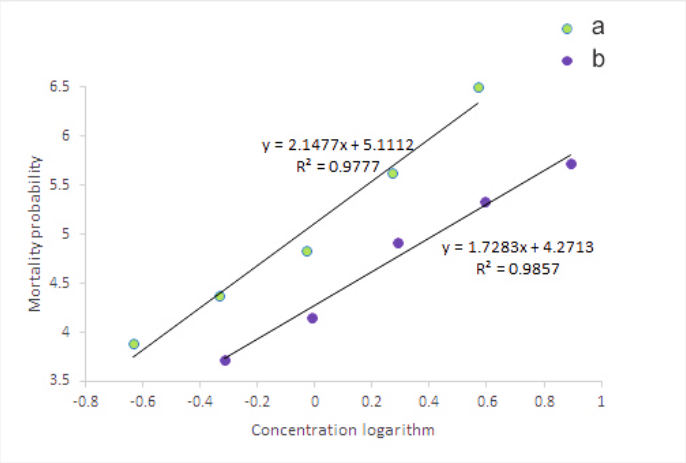

Figure 6: Toxicity regression equation of the AV-PEG6k-PLX188-CBU solid dispersion (a) and AV emulsifiable concentrate (b) against third-instar locusts.

emulsifiable concentrate was of 2.64 mg/L, which meant that the AV-PEG6k-PLX188-CBU solid dispersion was more effective in suppressing or killing locusts than AV emulsifiable concentrate. The possible reason was that the AV-PEG6k-PLX188-CBU solid dispersion increased the solubility of AV, so as to improve its bioavailability, making AV more effective.

CONCLUSION

In this study, AV was molten into a combined carrier of PEG6k, PLX188 and a deep eutectic solvent of CBU, forming the AV-PEG6k-PLX188-CBU solid dispersion upon cooling. The results of XRD showed that AV existed mostly in a non-crystalline state in the solid dispersion. The pharmaceutical properties are measured, and compared with the AV-PEG6k solid dispersion reported previously and AV-PEG6k-P188 solid dispersion in this work, the results of which are summarized in Table 1.

The Average particle size of the AV-PEG6k-PLX188-CBU solid dispersion (122.3 nm) was 2.8 times smaller than that of the AV-PEG6k-PLX188 solid dispersion (343.2 nm). The AV solubility of the AV-PEG6k-PLX188-CBU solid dispersion (806 mg/L) was 3.4 times that of AV-PEG6k solid dispersion (234.8 mg/L), 37.0 times that of AV-PEG6k (21.795 mg/L), and 350 times that of AV (2.3 mg/L). The AV cumulative dissolution (within 60 min in water) rate of the AV-PEG6k-PLX188-CBU dispersion (94.6%) was 1.6 times that of AV-PEG6k-PLX188 solid dispersion (58.3%), 5.4 times of that of the AV-PEG6k solid dispersion[26] (17.6%), and 9.2 times than the AV[26] (10.3%). Finally, LC_{50} of the AV-PEG6k-PLX188-CBU solid dispersion (0.88 mg/L) was 0.33 times of AV emulsifiable concentrate (2.64 mg/L), which meant that the AV-PEG6k-PLX188-CBU solid dispersion was more effective in suppressing or killing locusts than AV emulsifiable concentrate.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AV: Avermectin; **PEG6k:** Polyethylene Glycol 6000; **PLX188:** Poloxamer 188; **CBU:** For Choline chloride, Betaine and Urea; **XRD:** X-ray diffractometry; **HPLC:** High-performance liquid chromatography; **SDS:** 1-dodecanesulfonic acid sodium salt; **MERS:** Maleic rosin-polyoxypropylene-polyoxyethylene ether sulfonate.

SUMMARY

AV was molten into a combined carrier of polyethylene glycol 6000, poloxamer 188 and a deep eutectic solvent of choline chloride, betaine and urea, forming a solid dispersion upon cooling. AV water-solubility was improved primarily by addition of PLX188 into PEG6k carrier, and further by addition of a deep eutectic solvent of CBU (choline chloride, betaine and urea) in the combinatory carrier of PEG6k and PLX188. The results of XRD showed that AV existed mostly in a non-crystalline state in the solid dispersion. The result of toxicity evaluation showed that AV-PEG6k-PLX188-CBU solid dispersion was more effective than AV emulsifiable concentrate, in suppressing or killing locusts.

REFERENCES

1. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull. 1961;9(11):866-72. doi: 10.1248/cpb.9.866.
2. Palazi E, KarAVas E, Barmpalexis P, Kostoglou M, Nanaki S, Christodoulou E, *et al*. Melt extrusion process for adjusting drug release of poorly water soluble drug felodipine using different polymer matrices. Eur J Pharm Sci. 2018;114:332-45. doi: 10.1016/j.ejps.2018.01.004, PMID 29305982.
3. Yousaf AM, Malik UR, Shahzad Y, Mahmood T, Hussain T. Silymarin-laden PVP-PEG polymeric composite for enhanced aqueous solubility and dissolution rate: Preparation and *in vitro* characterization. J Pharm Anal. 2019;9(1):34-9. doi: 10.1016/j.jpha.2018.09.003, PMID 30740255.
4. Matos RL, Lu T, Prosapio V, Mc Conville C, Leeke G, Ingram A. J CO2 UTIL. 2019;30:48-62.
5. Knopp MM, Olesen NE, Holm P, Langguth P, Holm R, Rades T. Influence of polymer molecular weight on drug-polymer solubility: A comparison between experimentally determined solubility in PVP and prediction derived from solubility in monomer. J Pharm Sci. 2015;104(9):2905-12. doi: 10.1002/jps.24410, PMID 25740567.
6. Satoh T, Hidaka F, Miyake K, Yoshiyama N, Takeda K, Matsuura T, *et al*. Surfactant-free solid dispersion of fat-soluble flavour in an amorphous sugar matrix. Food Chem. 2016;197(B):1136-42. doi: 10.1016/j.foodchem.2015.11.097, PMID 26675850.
7. Everaerts M, Der Mooter GV. Iran. J Pharm. 2019;566:77-88.
8. Der Mooter GV. Drug Discov Today Technol. 2012;9:79-85.
9. Shi NQ, Wang SR, Zhang Y, Huo JS, Wang LN, Cai JH, *et al*. Hot melt extrusion technology for improved dissolution, solubility and "spring-parachute" processes of amorphous self-micellizing solid dispersions containing BCS II drugs indomethacin and fenofibrate: Profiles and mechanisms. Eur J Pharm Sci. 2019;130:78-90. doi: 10.1016/j.ejps.2019.01.019, PMID 30684657.
10. Abbott AP, Capper G, Vies DA. Chem Commun. 2003;9:70-1.

11. Pätzold M, Siebenhaller S, Kara S, Liese A, Syldatk C, Holtmann D. Deep eutectic solvents as efficient solvents in biocatalysis. Trends Biotechnol. 2019;37(9):943-59. doi: 10.1016/j.tibtech.2019.03.007, PMID 31000203.
12. Saha SK, Dey S, Chakraborty R. J Mol Liq. 2019;11:9-56.
13. Malaeke H, Housaindokht MR, Monhemi H, Izadyar M. Deep eutectic solvent as an efficient molecular liquid for lignin solubilization and wood delignification. J Mol Liq. 2018;263:193-9. doi: 10.1016/j.molliq.2018.05.001.
14. Smith EL, Abbott AP, Ryder KS. Deep eutectic solvents (DESs) and their applications. Chem Rev. 2014;114(21):11060-82. doi: 10.1021/cr300162p, PMID 25300631.
15. Francisco M, Van den Bruinhorst AVD, Kroon MC. Low-transition-temperature mixtures (LTTMs): A new generation of designer solvents. Angew Chem Int Ed Engl. 2013;52(11):3074-85. doi: 10.1002/anie.201207548, PMID 23401138.
16. Burg RW, Miller BM, Baker EE, Birnbaum J, Currie SA, Hartman R, *et al*. Avermectins, new family of potent anthelmintic agents: Producing organism and fermentation. Antimicrob Agents Chemother. 1979;15(3):361-7. doi: 10.1128/AAC.15.3.361, PMID 464561.
17. Awasthi A, Razzak M, Al-Kassas R, Harvey J, Garg S. An overview on chemical derivatization and stability aspects of selected avermectin derivatives. Chem Pharm Bull (Tokyo). 2012;60(8):931-44. doi: 10.1248/cpb.c12-00258, PMID 22863694.
18. Wang YS, Hu QW, Zheng XC, Zhang JF, Zheng YG. A spectrophotometric screening method for avermectin oxidizing microorganisms. J Microbiol Methods. 2017;135:93-5. doi: 10.1016/j.mimet.2017.02.007, PMID 28215961.
19. Lemos MA, Matos CA, De Resende MF, Prado RB, Donagemma RA, Netto AD. Development, validation, and application of a method for selected avermectin determination in rural waters using high performance liquid chromatography and fluorescence detection. Ecotoxicol Environ Saf. 2016;133:424-32. doi: 10.1016/j.ecoenv.2016.07.038, PMID 27513222.
20. Jiang GX, Shen GQ, Zhu HL. Sci Technol. Bull. 2012;28(5):125-9.
21. Cui B, Wang C, Zhao X, Yao J, Zeng Z, Wang Y, *et al*. Characterization and evaluation of avermectin solid nanodispersion prepared by microprecipitation and lyophilisation techniques. PLOS ONE. 2018;13(1):e0191742. doi: 10.1371/journal.pone.0191742, PMID 29360866.
22. Lin C. Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions. International Journal of Pharmaceutics. 1996;127(2):261-72. doi: 10.1016/0378-5173(95)04245-8.
23. Eloy JO, Marchetti JM. Solid dispersions containing ursolic acid in poloxamer 407 and PEG 6000: A comparative study of fusion and solvent methods. Powder Technol. 2014;253:98-106. doi: 10.1016/j.powtec.2013.11.017.
24. Lu Y, Tang N, Lian R, Qi JP, Wu W. Understanding the relationship between wettability and dissolution of solid dispersion. Int J Pharm. 2014;465(1-2):25-31. doi: 10.1016/j.ijpharm.2014.02.004, PMID 24524825.
25. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88(10):1058-66. doi: 10.1021/js980403l, PMID 10514356.
26. Cao LH, Wang LS, Yang H. Hubei Agric Sci. Chinese version. 2016;5:1163-11671171.
27. Zerrouk N, Chemtob C, Arnaud P, Toscani S, Dugue J. *In vitro* and *in vivo* evaluation of carbamazepine-PEG 6000 solid dispersions. Int J Pharm. 2001;225(1-2):49-62. doi: 10.1016/S0378-5173(01)00741-4, PMID 11489554.
28. Ali W, Williams AC, Rawlinson CF. Int J Pharm. Int J Pharm. 2010;391:162-8.
29. Kolašinac N, Kachrimanis K, Homšek I, Grujić B, Đurić Z, Ibrić S. Solubility enhancement of desloratadine by solid dispersion in poloxamers. Int J Pharm. 2012;436(1-2):161-70. doi: 10.1016/j.ijpharm.2012.06.060, PMID 22772487.

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