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Research article

Preparation and Characterization of Diclofenac Sodium Sustained-Release Solid Dispersion

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ABSTRACT:

Diclofenac sodium is widely used for treatment of arthritis, which has good solubility, rapid absorption, short half-life, and is apt to cause the "peak and trough" phenomenon of plasma concentration. A sustained-release solid dispersion of diclofenac sodium (DS), which is intended to improve the big fluctuation of DS plasma concentration, was prepared with ethyl cellulose (EC) in this work. The formulation and process was investigated by evaluation of drug release behavior, and the solid dispersion was characterized by X-ray diffraction (XRD), differential scanning calorimetry (DSC) and infra-red spectroscopy (IR) as well. With the increase of drug:carrier ratio, the drug release slowed down accordingly. The addition of both hydroxypropylmethyl cellulose (HPMC) and polyethylene glycol (PEG) accelerated the drug release from solid dispersion. The solid dispersion prepared by optimal formulation and process showed good sustained release behavior with an accumulative drug release percentage of 44.11 %, 67.33 %, 78.88% and 82.82% at 1, 4, 8 and 12 h respectively. The spectrum of XRD and DSC indicated that diclofenac sodium may have interaction with carrier material and exist in the solid dispersion as amorphous or molecular form.

KEYWORDS: Diclofenac Sodium; Solid dispersion; Drug release behavior; Characterization.

INTRODUCTION

Many diseases require long-term administration are associated with a series of health problems, such as side effects or toxicities for long-term accumulation of the drug, patients inconvenience when administrate. Generally, the sustained and controlled release drug delivery systems have great potential to address these issues due to the slow and prolonged or even special release behaviour of drug which results in relatively

appropriate steady blood concentration for a long time within the therapeutic window.

Solid dispersion is prepared by highly dispersing drug in different carrier materials as molecular, colloidal, microcrystalline and amorphous form¹.The solid dispersion techniques can be used to enhance the dissolution rate of poorly water-soluble drugs as well as to sustain the drug release by choosing appropriate polymers^{2,3,4-6}. Some carrier materials of solid dispersion can achieve the purpose of fast, sustained, retard or

site-specific release of drug due to their different solubility in water⁷⁻⁹.

Sustained and controlled release solid dispersions generally use insoluble or enteric carrier materials, such as ethyl cellulose (EC), Eudragits, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP) and so on¹⁰⁻¹³. In order to obtain appropriate sustained and controlled release effect, different carrier materials usually used in mixture, or some water-soluble substances may be added, like polyethylene glycol (PEG) and hydroxypropylmethyl cellulose (HPMC). Kumar A. et al. reported that solid dispersions of repaglinide with different carriers, polyvinyl pyrrolidone (PVP) and EC, in different ratios were prepared by suspending method and dissolving methods, which showed extended drug release *in vitro* release studies¹⁴.

Diclofenac sodium (DS) is widely used for treatment of inflammatory and analgesia of rheumatoid arthritis, osteoarthritis and other joint or its periarticular diseases in clinic. DS is water-soluble, shows rapid absorption *in vivo* and short half-life, and is apt to cause the "peak and trough" phenomenon of plasma concentration¹⁵⁻¹⁷. Diclofenac sodium has been reported to be prepared into sustained-release tablets and capsules by using a variety of polymeric materials^{18,19}. However, there is few study about the sustained-release solid dispersion. The purpose of this work was to prepare the sustained-release solid dispersion of DS with water-insoluble polymer ethylcellulose (EC) as the carrier material, which may slow down the drug release rate thus likely to improve the big concentration fluctuation of immediate release preparation. The formulation and process was optimized on the basis of drug release evaluation. The DS solid dispersion was also characterized by X-ray diffraction (XRD), infra-red spectroscopy (IR) and differential scanning calorimetry (DSC).

MATERIALS AND METHODS

MATERIALS

Diclofenac sodium (DS, Anyang Jiuzhou Pharmaceutical Co., Ltd. LOT 20099026); DS sustained release tablets (Sandoz (China) Pharmaceutical Co., Ltd., LOT MM023); Ethylcellulose (EC, The DOW Chemical Co. USA, LOT2B0413T01); The other reagents or materials are analytical grade.

PREPARATION OF SUSTAINED RELEASE SOLID DISPERSION

Sustained release solid dispersions of DS were prepared with EC in different drug carrier ratios by conventional solvent evaporation method. HPMC or PEG was added to adjust drug release rate. Briefly, drug and carrier materials were dissolved in organic solvent and the solvent was removed by heating under stirring. The obtained solid dispersion was vacuum dried and crushed into powder.

DRUG RELEASE OF DS SUSTAINED RELEASE SOLID DISPERSION

The drug release of DS sustained release solid dispersion was measured according to the Method 1 described in Appendix X D of People's Republic of China Pharmacopoeia (Part II, Edition 2010). Briefly, DS solid dispersion was added to 1000 ml phosphate buffer saline (PBS) with a pH value of 6.8, the drug release test was carried out at 37 ± 0.5 °C and 100 r/min. The samples were taken at 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 4.0 h, 5.0 h, 6.0 h, 8.0 h, 10.0 h and 12.0 h respectively, filtered with 0.45µm microporous membrane and the filtrate (diluted when necessary) were analyzed by using ultraviolet spectrophotometry at a wavelength of 276 nm. The absorbance of DS in PBS showed a good linear relationship with concentration in a range of 9 to 27 µg•mL⁻¹. The regression equation was $A=0.0292C-0.013$ ($r^2 = 0.9999$). The accumulative release percentage (Q%) was then calculated and plotted versus time.

CHARACTERIZATION OF DS SOLID DISPERSION

In order to figure out the drug-carriers interaction and the physical status of drug in solid dispersion, DS solid dispersion was characterized by XRD, DSC and IR method. The drug powder, carrier materials powder, physical mixture powder of drug and carrier material and DS solid dispersion were measured as samples.

X-ray DIFFRACTION (XRD)

XRD study was conducted by using a Rigaku D/max-III A powder diffractometer. The X-ray powder diffraction patterns were obtained at room temperature using a Cu target tube, and operated at a voltage of 40 kV and a current 100 mA. The scanning angle ranged from 3° to 40°, and the scan speed was 4° per minute.

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Thermal analysis was performed on DSC-STA 409 (NETZSCH, Germany). Samples were accurately weighed and placed in sealed aluminium pans, and thermograms were obtained at a heating rate of 10 °C/min over a temperature range of 25 °C~350 °C. An empty aluminium pan was used as reference.

INFRARED SPECTROSCOPY (IR)

IR spectra were obtained by a EQUINOX 55 infrared spectroscopy (Bruker, Germany) using KBr pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:30). The scanning

spectra were obtained at a resolution of 4 cm⁻¹, from 4,000 to 400 cm⁻¹.

RESULTS FORMULATION AND PROCESS OPTIMIZATION OF DS SOLID DISPERSION EFFECT OF EC TYPE ON DRUG RELEASE

The release profiles of DS solid dispersion prepared by EC of different manufacturers (domestic, Colorcon) and viscosity (7 cps, 20 cps) were shown in Fig.1. Compared with Colorcon EC, the domestic EC exhibited relatively slow drug release. The DS solid dispersion prepared by EC of low viscosity showed faster release than that of high viscosity.

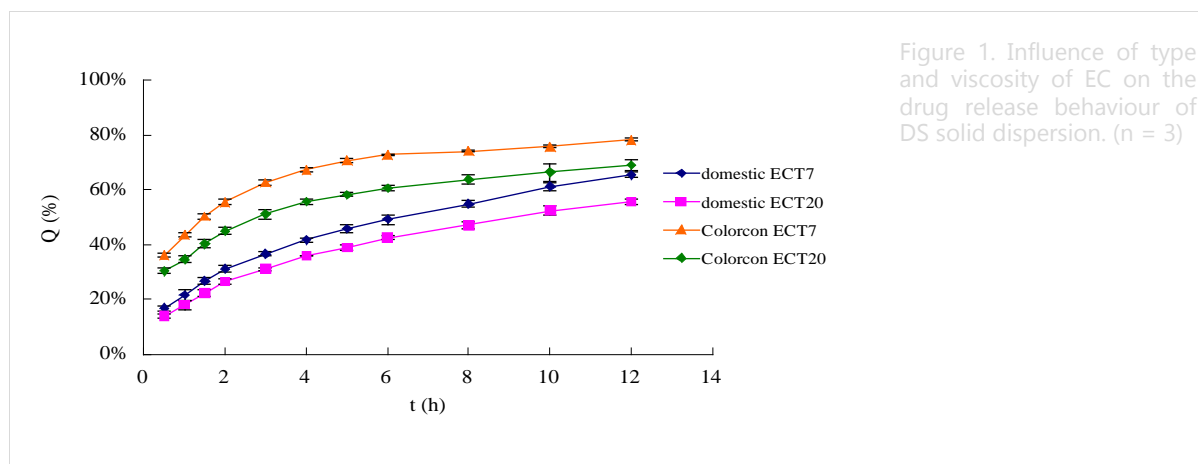


Figure 1. Influence of type and viscosity of EC on the drug release behaviour of DS solid dispersion. (n = 3)

EFFECT OF DRUG-CARRIER RATIO ON DRUG RELEASE

The drug-carrier ratio affected the drug release rate markedly (Fig. 2). The release rate and extent of DS was reduced by decreasing the drug-carrier ratio from 1:3 to 1:19. The release behaviour was

not ideal at high proportion as well as low proportion of the carrier. Appropriate sustained release was achieved when the drug: ratio was in a range of 1:5 to 1:7.

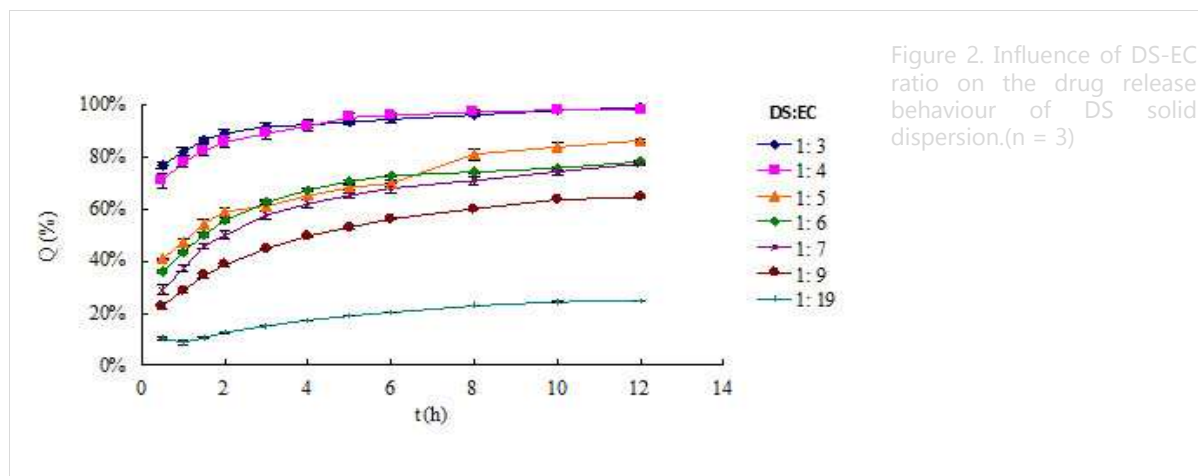
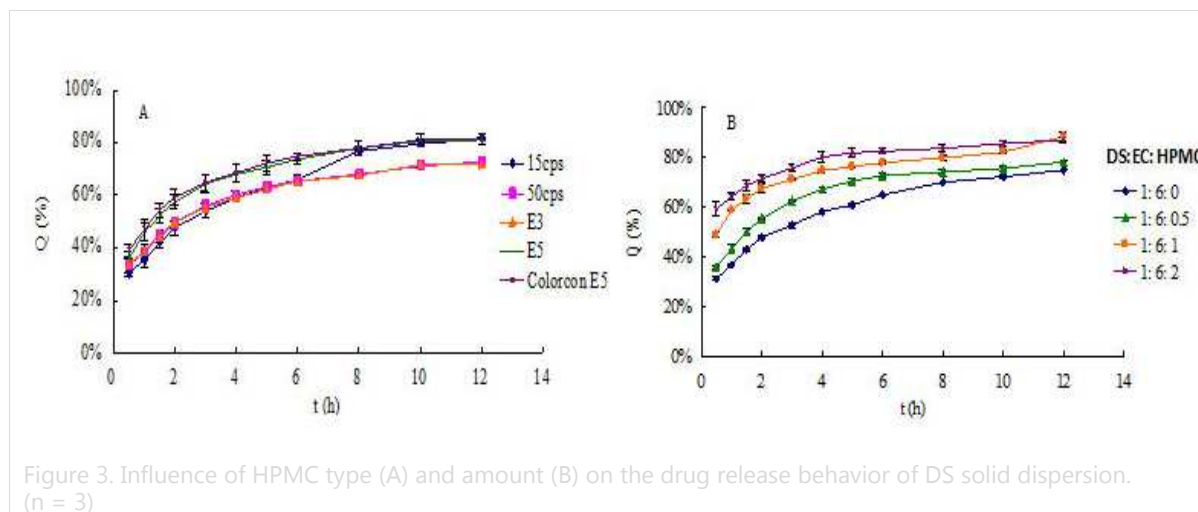


Figure 2. Influence of DS-EC ratio on the drug release behaviour of DS solid dispersion. (n = 3)

EFFECT OF HPMC TYPE AND AMOUNT ON DRUG RELEASE

As it was shown in Fig. 3, the addition of different type of HPMC made the drug release behaviour different. Higher the viscosity of HPMC, slower is the release. HPMC 15 cps was chosen for subsequent experiments due to good sustained

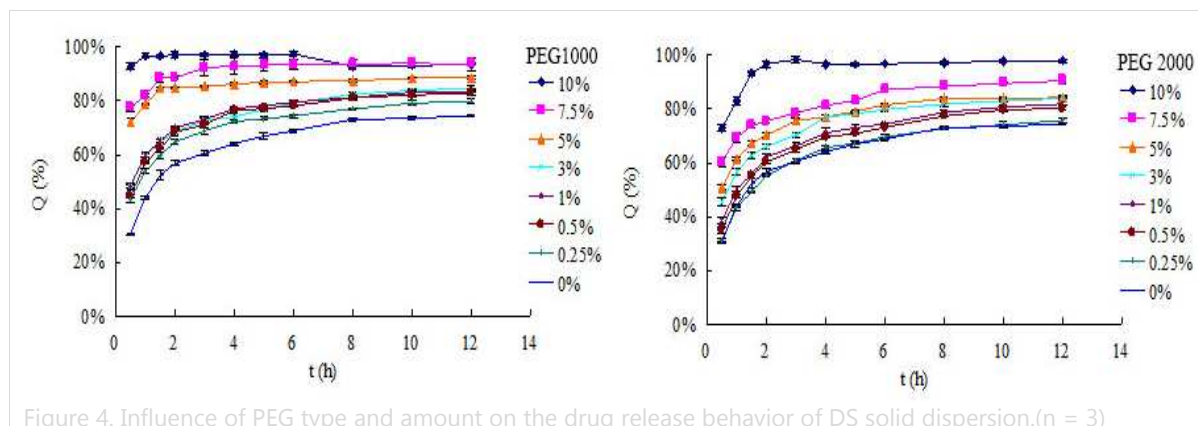
release and final complete drug release. The more amount of HPMC was used, the faster DS released from the solid dispersion. Burst release was observed when too much of HPMC appeared in the solid dispersion.



EFFECT OF PEG TYPE AND AMOUNT ON DRUG RELEASE

PEG of different molecular weight was used to adjust drug release behaviour of DS solid dispersion as well. As shown in Fig. 4, DS released gradually faster with the increase of PEG amount,

no matter the difference of molecular weight of PEG. PEG 1000 accelerated the drug release more than PEG 2000; however, the solid dispersions prepared by PEG 2000 exhibited better sustained effect than PEG 1000.



EFFECT OF PROCESS ON DRUG RELEASE

The release profiles of DS solid dispersion prepared under different preparing process conditions were shown in Fig. 5, Fig. 6 and Fig. 7. In general, the extension of stirring time increased the release of drug from solid dispersions. Drying

time had almost no effect on drug release. The particle size of solid dispersion had a great influence on the release. The smaller the particle size, the faster and more complete the drug release.

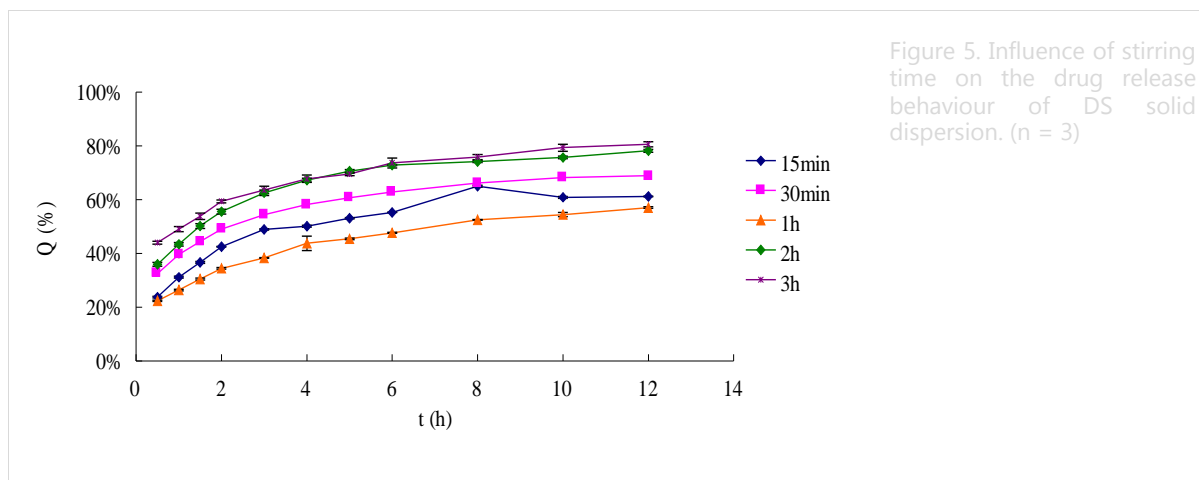


Figure 5. Influence of stirring time on the drug release behaviour of DS solid dispersion. (n = 3)

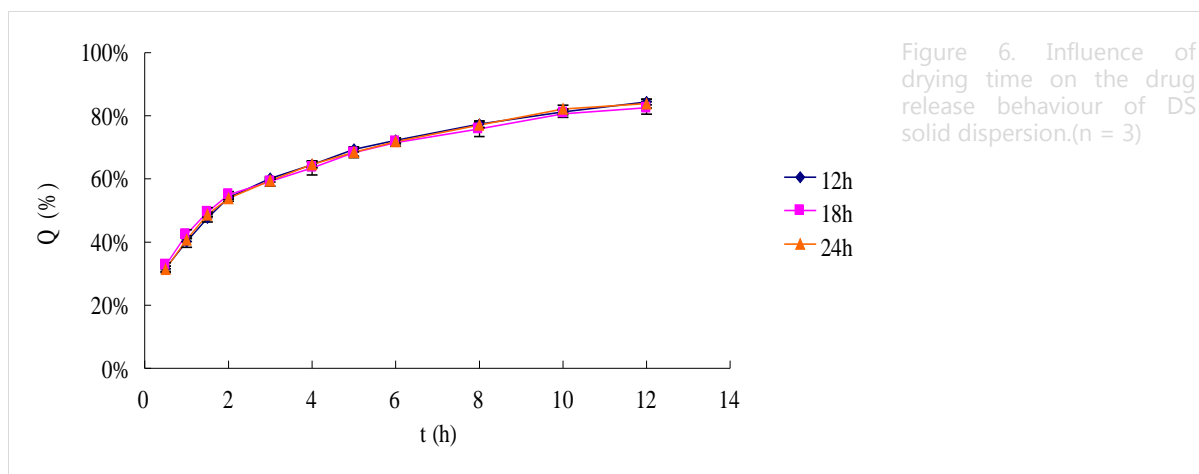


Figure 6. Influence of drying time on the drug release behaviour of DS solid dispersion. (n = 3)

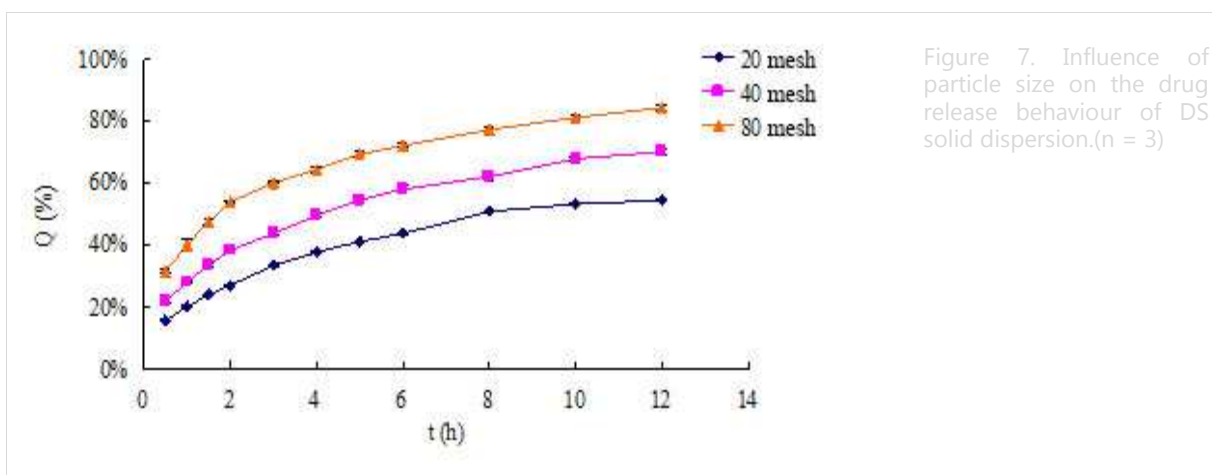


Figure 7. Influence of particle size on the drug release behaviour of DS solid dispersion. (n = 3)

CHARACTERIZATION OF DS SOLID DISPERSION

X-ray DIFFRACTION (XRD) STUDY

XRD study for DS, EC, PEG 2000, DS/EC/PEG 2000 physical mixture and DS/EC/PEG 2000 solid dispersion were shown in Fig. 8. The diffraction

pattern reported that DS was a crystalline compound, with characteristic of peaks observed at 11.29°, 12.65°, 15.22°, 17.19°, 19.94°, 20.58°, 23.51°, 27.14° and 27.91°. There was no obvious diffraction peak in EC, but two very strong diffraction peak presented at 19.20°, 23.36° and

less strong peak at 26.0°, 27.02°, 36.38° and 39.98° in PEG2000. The diffraction peaks of DS still reserved in the physical mixture and no new diffraction peak was observed, which demonstrated no interaction after mixed.

However, all of the diffraction peaks of DS and PEG disappeared in the diffraction pattern of DS solid dispersion, indicating DS might distribute in amorphous or molecular form in the solid dispersion.

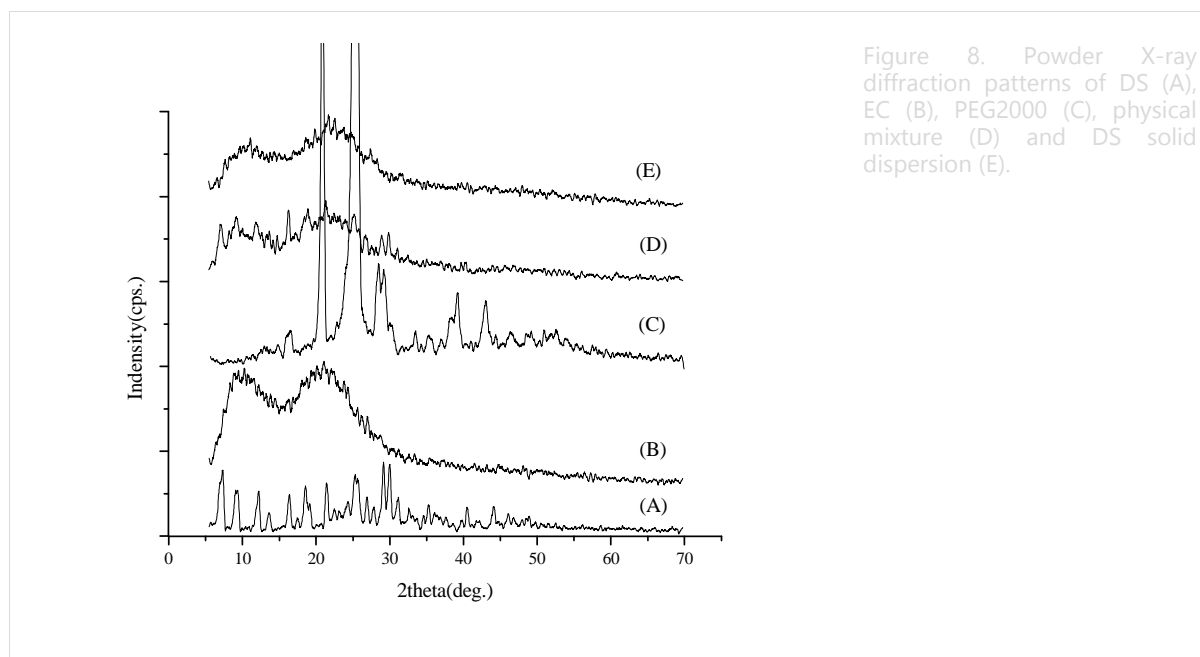


Figure 8. Powder X-ray diffraction patterns of DS (A), EC (B), PEG2000 (C), physical mixture (D) and DS solid dispersion (E).

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The DSC thermograms of DS, carrier materials, physical mixture and DS solid dispersion (Fig. 9) showed three low endothermic peaks at 210.0 °C, 257.7°C and 287.5 °C in DS, while no characteristic peak in EC presented. PEG displayed a sharp

endothermic peak at 47.5 °C. In the physical mixture, there was a endothermic peak at 220.0 °C, which was the characteristic peak of DS. However, this peak disappeared and no visible peak displayed in the thermogram of DS solid dispersion.

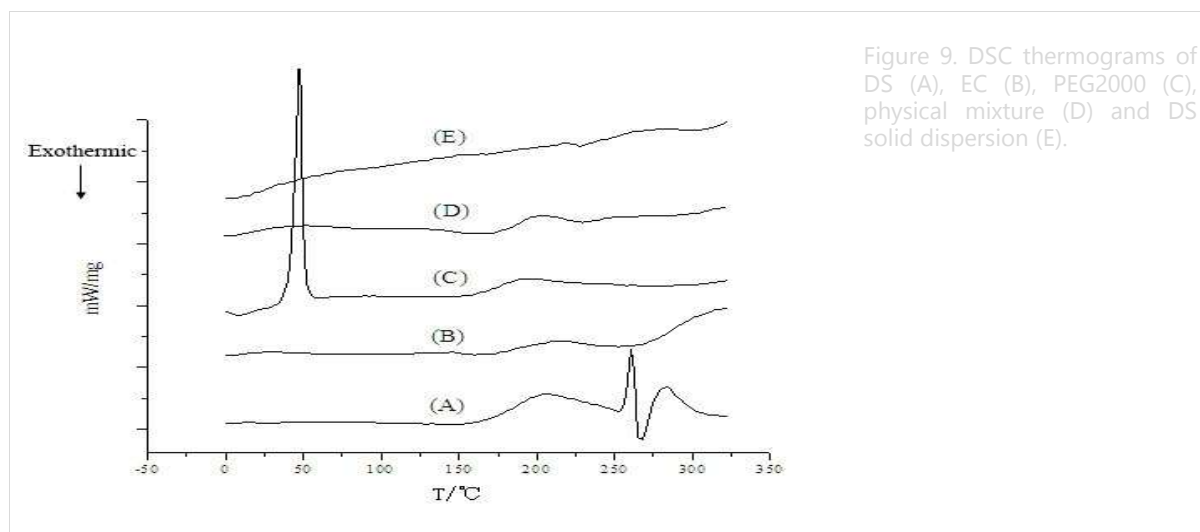


Figure 9. DSC thermograms of DS (A), EC (B), PEG2000 (C), physical mixture (D) and DS solid dispersion (E).

INFRA-RED SPECTROSCOPY (IR)

The IR spectra of DS, carrier materials, physical mixture and DS solid dispersion were illustrated in Fig. 10. The results showed multiple absorption peaks of DS, the wide absorption peak of -NH group at 3100~3500 cm⁻¹, the stretching vibration absorption peak of C=O group at 1575.44 cm⁻¹, benzene ring at 1506.92 cm⁻¹, C-N bond of aromatic -NH group at 1287.49 cm⁻¹, C-Cl bond at 770.49 cm⁻¹ and 747.75 cm⁻¹. EC showed stretching vibration absorption peak of -OH group within 3520-3300 cm⁻¹ and -C-OH group at 1140-1090 cm⁻¹, and the bending vibration absorption

peak of -CH³ at 1381.26cm⁻¹. PEG 2000 displayed the stretching vibration absorption peak of C-O-C group at 1114.48 cm⁻¹, 1060.37 cm⁻¹ and 962.39 cm⁻¹, -CH₂ group at 2888.38 cm⁻¹, C-C-O group at 842.28 cm⁻¹, and the bending vibration absorption peak of -CH₂ group at 1468.74 cm⁻¹, 1344.12 cm⁻¹ and 1242.01 cm⁻¹. The IR spectrum of DS solid dispersion was similar as that of physical mixture, and all the absorption peaks of DS, EC and PEG 2000 appeared without obvious change in peak position and relative intensity. It followed that no chemical interaction occurred when preparing DS solid dispersion.

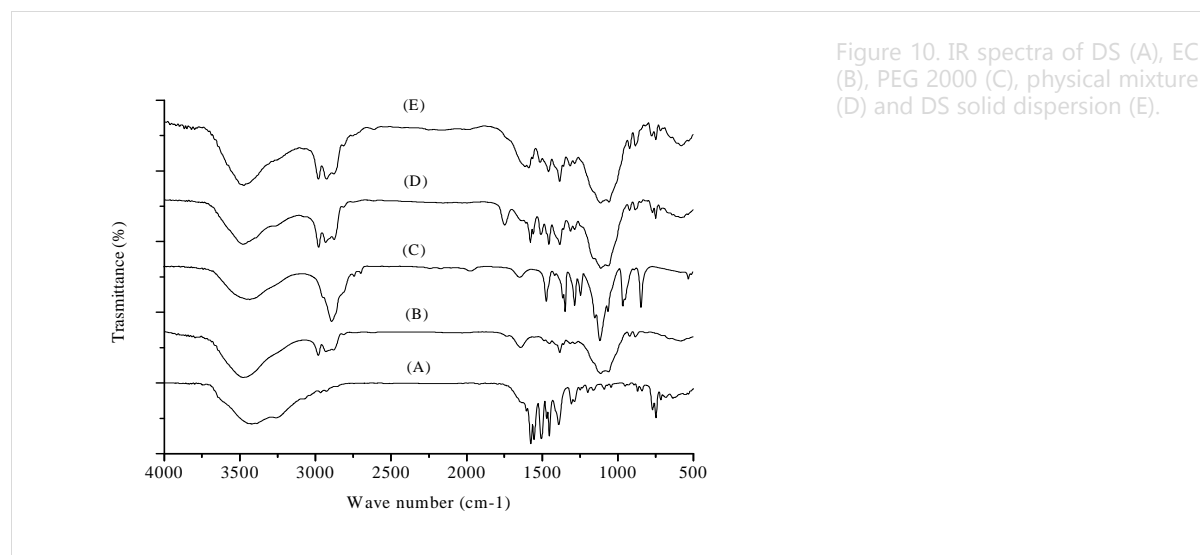


Figure 10. IR spectra of DS (A), EC (B), PEG 2000 (C), physical mixture (D) and DS solid dispersion (E).

COMPARISON OF RELEASE BEHAVIOR BETWEEN SOLID DISPERSION AND COMMERCIAL SUSTAINED-RELEASE TABLET OF DS

The release profiles of solid dispersion and commercially sustained release tablet of DS (Fig.11) showed that DS solid dispersion showed a

relatively faster and complete release when compared with commercially available sustained release tablets. The accumulative drug release percentage (Q%) of DS solid dispersion was about 10% higher than that of commercial sustained release tablet at 12 h. Dissolution similarity factor f₂ between two is 34.78.

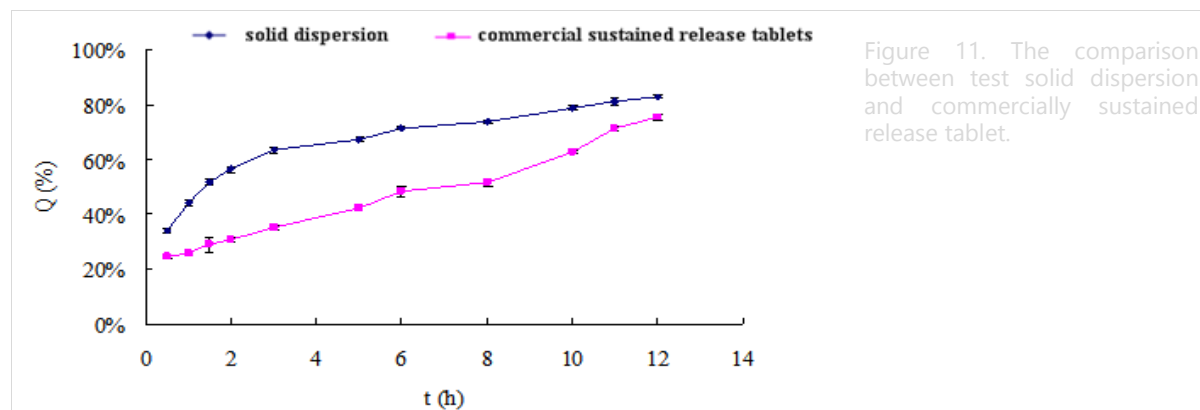


Figure 11. The comparison between test solid dispersion and commercially sustained release tablet.

DISCUSSION

EC is a widely used polymer material in sustained and controlled release preparations. It can be used as coating material and matrix material. In this work, EC was used as a matrix material to make DS dispersed highly to obtain solid dispersion. The prepared DS solid dispersion showed a good sustained release because of the insoluble EC prevent the release of drug. Many formulation and process factors were investigated, and drug-carrier ratio and particle size demonstrated significant influence on DS release. EC T20 brought slower drug dissolving and release in the medium because of its higher viscosity. With the increase of the proportion of carrier material, the network EC matrix turns even denser with smaller gap, the path for drug release is prolonged with more twists and turns, and the thickness of the barrier increased. All this structure change caused the release rate and extent of DS lower.

HPMC and PEG, which has good water solubility, are commonly used as accelerators to adjust the release behaviour of sustained-release solid dispersion. PEG is of low toxicity and soluble in various solvents. The viscosity of PEG increases during solvent evaporation, and can hinder the aggregation between drug. Both HPMC and PEG can accelerate drug release from solid dispersion by dissolved in the medium thus producing many pores and gaps to help water infiltration. Additionally, HPMC and PEG of high viscosity showed accelerate release less than that of low viscosity. It might be related to the highly viscosity of the materials which could produce retardance effect on drug release.

The particle size decides the surface area of DS solid dispersion contacting with release medium. Smaller the particle size, larger the surface area. Larger surface area leads to faster and more complete drug release.

XRD, DSC and IR are often used to figure out whether there is an interaction between drug and carrier materials and to illustrate their basic physical and chemical properties as well. By comparing the spectra and thermograms of drug, carrier materials, physical mixture and solid dispersion, we knew DS and PEG 2000 are in crystal form and EC is an amorphous material. It indicated an interaction between DS and EC, and DS dispersed in EC as amorphous or molecular form because of the inhibitory action of EC to crystal formation of DS.

The DS solid dispersion prepared in this work was not only achieved a better sustained effect but also a complete release. The accumulative release of DS from solid dispersion reached 44.11%, 67.33%, 78.88% and 82.82% at 1, 4, 8 and 12 h respectively. Compared with the commercial sustained release tablet, the prepared DS solid dispersion showed a slightly fast release and complete release, and the dissolution similarity factor f_2 between them was 34.78.

CONCLUSION

In this study, soluble DS is prepared into solid dispersion with water-insoluble polymer ethylcellulose through solvent evaporation method. The DS solid dispersion produced good sustained and complete release of drug up to 12 h. The sustained release of DS might lower down the blood concentration fluctuation, which needs further investigation *in vivo*.

REFERENCES

- 1.Cui FD. Pharmaceutics. 6th edition [M]. Beijing: People's Health Publishing House, 2009, 375-380.
- 2.Lovrecich M, Nobile F, Rubessa F, Zingone G. Effect of ageing on the release of indomethacin from solid dispersion with eudragits. Int. J. Pharm, 1996;131(2): 247-255.
- 3.Karnachi AA, DeHon RA, Khan MA. Compression of indomethacin coprecipitates with polymer mixtures:effect of preparation methodology. Drug Dev. Ind. Pharm, 1995; 21(12): 1473-1483.
- 4.Sadeghi F, Afrasiabi GH, Sadr A. Influence of polymer viscosity and plasticizer addition on ethylcellulose matrix characteristics prepared from solid dispersion system. STP Pharma. Sci, 2003;13: 105-110.
- 5.Hernandez JI, Ghalj ES, Malave A, Marti A. Controlled release matrix of acetaminophen ethylcellulose solid dispersion. Drug Dev. Ind. Pharm, 2008;20(7): 1253-1265.
- 6.Goracinova K, Klisarova LJ, Simov A. Physical characterization and dissolution properties of verapamil HCl coprecipitates. Drug Dev. Ind. Pharm, 1995; 21(3): 383-391.
- 7.Desai J, Alexander K, Riga A. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. Int. J. Pharm, 2006;308 (1-2): 115-123.
- 8.Serajuddin AT. Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs. J. Pharm. Sci 1999; 88(10): 1058 -1066.
- 9.Ozeki T, Yuasa H, Kanaya Y. Application of the solid dispersion method to the controlled release of medicine.IX. Int. J. Pharm 1997;155(2): 209-217.

10. Chiou WL, Rielman S. Pharmaceutical application of solid dispersion system. *J. Pharm.Sci* 1971;60(9): 1281-1302.
11. Kaur J, Aggarwal G, Singh G, Rana AC. Improvement of drug solubility using solid dispersion. *Int. J. Pharm. Pharm. Sci* 2012; 4(2): 47-53.
12. Pinnamaneni S, Das NG, Das SK. Formulation approaches for orally administered poorly soluble drugs. *Pharmazie* 2002; 57(5): 291-300.
13. Desi Reddy RB, Sivanarayana P, Madhu Mounica T, Prathibha N, Sandhya G, Alekhya P. Solid dispersion- An approach to enhance the dissolution rate of amlodipine. *Int. J. Pharm* 2013; 3(1): 170-172.
14. Kumar A, Grawal R, Sharma P, Puri D, Bhandari A. Extended Release System of Hypoglycemic Agent Containing Solid Dispersions: Strategies and Mechanisms. *International Scholarly and Scientific Research & Innovation* 2014;8(3): 162-166.
15. Qian ZY. *Pharmacology*. Third Edition. Beijing: Chinese Medical Science and Technology Publishing House 2009;335.
16. Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Diclofenac sodium: A review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. *Drugs*, 1980, 20(1): 24-48.
17. Small RE. Drug reviews: Diclofenac sodium. *Clin. Pharm* 1989; 8: 545.
18. Sahoo J, Murthy PN, Biswal S, Sahoo SK, Mahapatra AK. Comparative study of propranolol hydrochloride release from matrix tablets with Kollidon®SR or hydroxy propyl methyl cellulose. *AAPS Pharm. SciTech* 2008; 9(2): 577-582.
19. Saha RN, Sanjeev C, Sahoo J. A comparative study of controlled release matrix tablets of diclofenac sodium, ciprofloxacin hydrochloride, and theophylline. *Drug Deliv* 2001;8(3): 149-154.

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