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Dissolution behaviour and characterization of diazepam-Pullulan coground mixtures

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Summary

The aim of the present study was to investigate the utilization of Pullulan as a water-soluble carrier to improve the in vitro dissolution rate of the poorly water-soluble drug diazepam. The coground mixtures of diazepam with Pullulan were characterized by spectrophotometric (infrared), thermal (DSC), powder X-ray diffractometry and in vitro dissolution techniques. The results indicated the prominent role of amorphization of crystalline drug in enhancing the in vitro dissolution rate. The effect of ageing on dissolution was also studied.

Introduction

The bioavailability of a poorly water-soluble drug is often limited by its dissolution rate, which may be enhanced by prior dispersion of the drug in a water-soluble carrier (Chiou and Riegelman, 1971; Kaplan, 1973). Polyvinylpyrrolidone and polyethylene glycols are the most extensively used carriers (Chiou and Riegelman, 1971; Craig, 1990). Other carriers include lipids (Kim and Jarowski, 1977; Venkataram and Rogers, 1985), freeze-dried milk (Macheras and Reppas, 1986) and various sugars (Ahmed and Madan, 1989, 1991).

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Recently, natural polymers such as polysaccharides and proteins have received much attention as carriers owing to their good biocompatibility and biodegradability (Sawayanagi et al., 1983; Imai et al., 1989). However, the application of high molecular weight polysaccharides as carriers in the pharmaceutical field is limited, probably because of their low aqueous solubility and high viscosity (Shiraishi et al., 1990). Pullulan, a neutral high molecular weight polysaccharide, produced by *Aureobasidium pullulans* from starch, is a biodegradable, biocompatible and non-toxic polymer (Sugimoto, 1978). The aqueous solutions of Pullulan are non-gelling and of relatively low viscosity (Sugimoto, 1978). Pullulan has been used to increase the solubility of indomethacin by the freeze-drying method (Sakamaki and Miyamoto, 1978). In the present study, a simple and effective method, i.e., cogrinding, is proposed for the

preparation of a solid dispersion of diazepam with Pullulan. The coground mixtures of a poorly water-soluble drug, diazepam, with Pullulan PF10 (Mol. Wt 100000) have been prepared and characterized by various techniques.

Materials and Methods

Materials

Pullulan PF10 (Food grade, Mol. Wt 100000) was generously supplied by Hayashibara Biochemical Laboratories, Inc., Japan. Diazepam I.P. was denoted by Cipla Ld, Bombay, India.

All materials were used as supplied.

Methods

Preparation of coground mixtures Diazepam and Pullulan PF10 were blended in various weight ratios (1:1, 1:4, and 1:9 w/w) and then transferred to a laboratory ball mill jar. The jar was half filled with porcelain balls (approx. 1.27 cm diameter). The sealed jar was set in motion on driven rollers for 24 h. For comparison, physical mixtures of drug and Pullulan PF10 were also prepared.

All samples were stored in a desiccator (containing anhydrous calcium chloride) at room temperature until further use.

Solubility studies Solubility studies were carried out in duplicate according to Higuchi and Connors (1965). Excess amount of drug (100 mg) was added to aqueous solutions (100 ml) containing various concentrations of Pullulan PF10 and then vigorously shaken for 7 days. The solutions were filtered and drug concentrations were determined spectrophotometrically at 231 nm.

Spectrophotometric (infrared) studies The infrared spectra of the pure drug and coground mixture were taken using a Hitachi 270-30 infrared spectrophotometer with data processor by the KBr disc method.

Thermal analysis of coground mixtures Thermal analysis was performed using Perkin-Elmer differential scanning calorimeter (Model DSC 7, with TAC 7/DC Thermal Controller). Samples (2–10 mg) were scanned at 10°C/min over the range of 40–250°C under a nitrogen atmosphere using an empty aluminium pan as a reference. The collection and integration of the thermogram was computerized and recording was performed with the help of a chart recorder (PE Graphics Plotter 8).

Powder X-ray diffraction studies Powder X-ray diffraction patterns of pure drug and various mixture systems were recorded on a Philips PW1150 X-ray diffractometer with nickel filtered CuKα radiation, at room temperature. The operating conditions were as follows: voltage, 45 kV; current, 35 mA; time constant, 1 s; diffraction angle, range 9–30° (2θ); scanning speed, 0.015°/s.

Dissolution studies In vitro dissolution studies were carried out in triplicate using USP XXII dissolution apparatus II (paddle) at 37 ± 0.5°C in distilled water. An accurately weighed quantity, equivalent to 40 mg of diazepam, was added to 900 ml distilled water at 100 rpm. 10-ml samples were periodically withdrawn, with replacement, filtered and spectrophotometrically assayed for drug content at 231 nm after appropriate dilution with distilled water. Cumulative corrections were made for the volume of sample solutions previously withdrawn.

Effect of ageing The effect of ageing on the dissolution profile of the coground mixture showing an optimum dissolution in the freshly prepared form was studied. The coground mixture of diazepam:Pullulan PF10 (1:4) was stored in a desiccator (containing anhydrous calcium chloride) at room temperature and the in vitro dissolution profile of the samples were studied at regular intervals over a period of 6 months.

Results and Discussion

Solubility studies

Fig. 1 shows the equilibrium phase solubility diagram obtained for diazepam with various concentrations of Pullulan PF10 in distilled water at 25°C. The solubility of diazepam in the presence of Pullulan PF10 increased almost linearly with increasing amounts of the polymer and thus, the solubility curve could be classified as being of Higuchi type A (Higuchi and Connors, 1965).

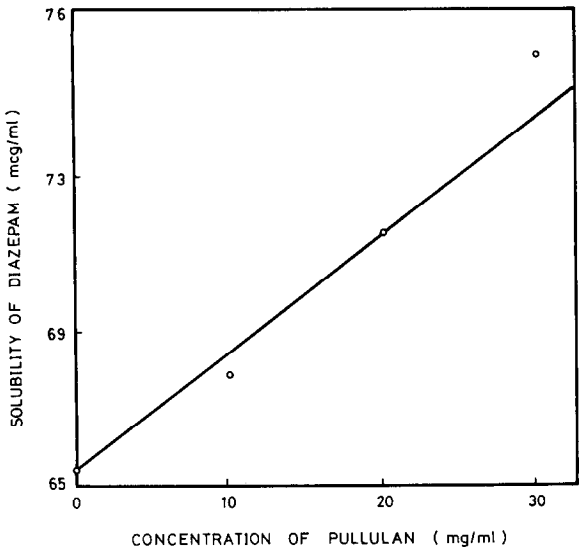

Fig. 1. Solubility studies of diazepam-Pullulan system in water at 25°C.

Spectrophotometric (infrared) studies

Infrared spectra of coground mixtures of drug with polymer showed absorption bands for NH (3390 cm^{-1}), C=O (1680 cm^{-1}) and aromatic group (1560, 1480 cm^{-1}) which are the characteristic peaks of diazepam. It could therefore be concluded that there was no chemical interaction between diazepam and Pullulan PF10.

Thermal analysis of coground mixtures

The DSC thermograms of the diazepam : Pullulan PF10 (1 : 4) coground mixture, physical mixture (1 : 4), diazepam and Pullulan PF10 are presented in Fig. 2. Pullulan exhibited a broad and small endothermic peak owing to its amorphous form. In the case of diazepam, the physical mixture and the coground mixture, an endothermic peak due to the melting of diazepam was observed at around 133°C. However, on grinding with Pullulan PF10, the drug melting endotherm showed a decrease in intensity. It was smaller, broader and shifted to a lower peak temperature, indicating an increase in amorphousness of the drug. The thermograms showed no evidence of the formation of a solid complex or any chemical interaction between Pullulan and diazepam. It could thus be postulated that Pullulan probably influenced the solubility of diazepam by amorphization of the drug. The alteration of surface properties such as the particle size and affinity between solid drug and water could also contribute to the improvement in solubility of the drug.

Powder X-ray diffraction studies

The crystallinity of diazepam in the coground mixture was compared with that of physical mixture and ground diazepam by means of powder X-ray diffractometry. Fig. 3 shows the X-ray diffraction patterns of drug, ground drug, polymer, physical and coground mixtures. The diffraction peaks of diazepam in the coground mixture were broader and smaller than those in the physical mixture and ground drug, indicating that cogrinding of the drug with Pullulan PF10 improved amorphization of the drug. These data can be explained by considering that the drug powder is dispersed as separate crystals in the coground mixture and cogrinding appears to cause a decrease in the crystallinity and microcrystal size.

Dissolution studies

Fig. 4 shows in vitro dissolution profiles of diazepam from its physical and coground mix-

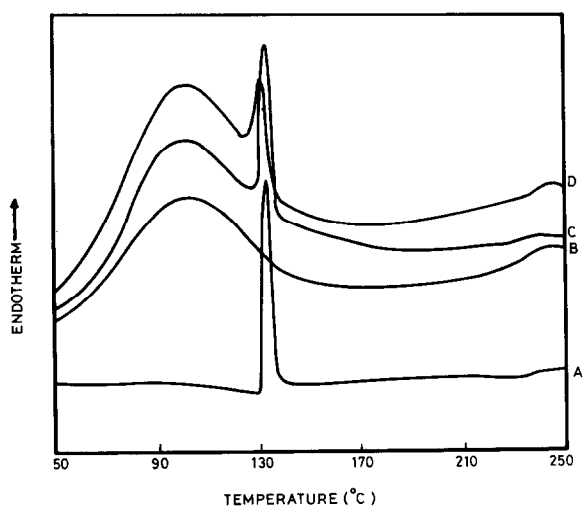

Fig. 2. DSC studies. (A) Diazepam; (B) Pullulan; (C) diazepam : Pullulan, 1 : 4 (physical mixture); (D) diazepam : Pullulan, 1 : 4 (coground mixture).

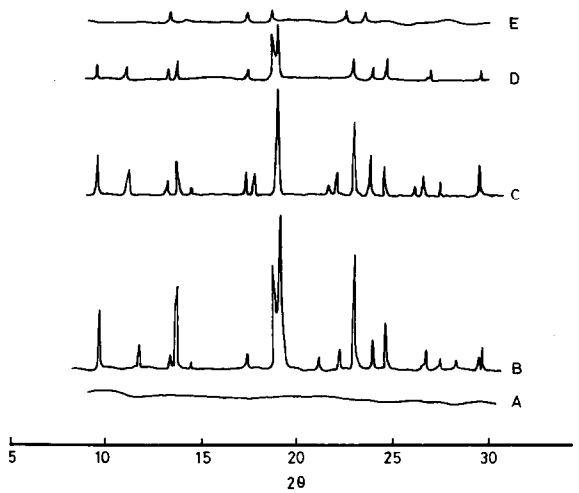

Fig. 3. Powder X-ray diffraction studies. (A) Pullulan; (B) diazepam; (C) diazepam (ground); (D) diazepam:Pullulan, 1:4 (physical mixture); (E) diazepam:pullulan, 1:4 (coground mixture).

tures, in water at 37°C. The coground mixtures were evaluated at three different ratios (1:1, 1:4 and 1:9 w/w, diazepam:Pullulan PF10). All the coground mixtures exhibited a significantly higher dissolution rate than that of diazepam, ground diazepam or physical mixture. The dissolution of coground mixture (1:4) was faster than that of 1:1 ratio. Further increase in polymer content (in the case of 1:9) showed no significant improvement. The improved dissolution rate of diazepam on grinding with Pullulan could predominantly be due to more amorphous formation of the drug in the coground mixture which could be easily explained from powder X-ray diffraction patterns (Fig. 3). In addition to amorphization, other factors, for example, increased surface area, improved wettability and reduced aggregation could also have contributed to some extent to the enhancement in dissolution rate of diazepam from coground mixtures.

The dissolution of the physical mixture of diazepam and Pullulan PF10 was slightly greater than that of diazepam alone probably because of rapid dissolution of Pullulan PF10 which would allow water solutes to surround and dissolve diazepam and reduced aggregation of diazepam particles.

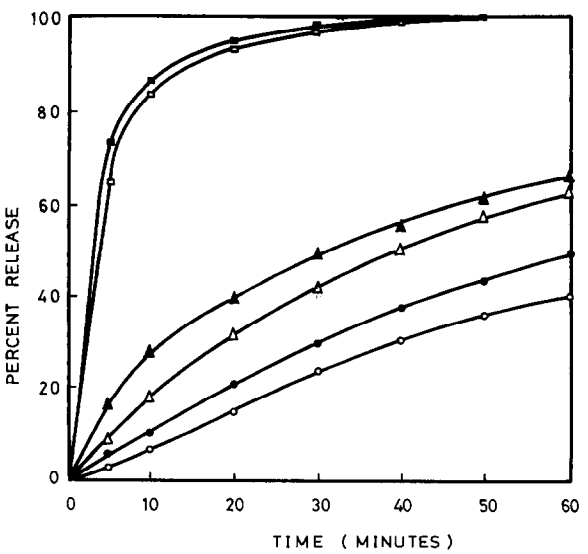

Fig. 4. In vitro dissolution studies. (○———○) Diazepam; (●———●) diazepam (ground); (△———△) diazepam:Pullulan, 1:4 (physical mixture); (▲———▲) diazepam:Pullulan, 1:1 (coground); (□———□) diazepam:Pullulan, 1:4 (coground); (■———■) diazepam:Pullulan, 1:9 (coground).

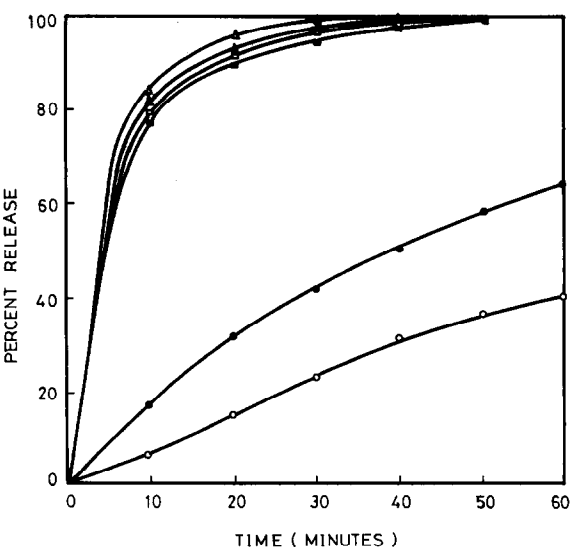

Fig. 5. Effect of ageing on dissolution of diazepam:Pullulan (1:4) coground mixture. (○———○) Diazepam; (●———●) physical mixture; (△———△) freshly prepared; (▲———▲) 2 months; (□———□) 4 months; (■———■) 6 months.

Effect of ageing

Since the diazepam : Pullulan PF10 coground mixture (1 : 4) showed an optimum dissolution profile at the freshly prepared stage, it was subjected to dissolution test at regular time intervals for a period of 6 months during storage in a desiccator containing anhydrous calcium chloride. From the dissolution behaviour of the coground mixture at different ages (Fig. 5), it appears that there was no change in release profile after 2 months. However, a slight decrease in dissolution rate was observed after 4 months. This could be attributed to the slow conversion of the metastable form of the drug. However, there was an appreciable superiority in dissolution rate of coground mixture of all ages over the corresponding physical mixture.

Conclusion

Coground mixtures of diazepam with Pullulan PF10 showed a remarkably rapid dissolution rate compared to pure drug and physical mixture. The infrared spectra and DSC thermograms showed no evidence of physical or chemical interaction between diazepam and Pullulan PF10. DSC and X-ray diffractometry indicated the presence of a more amorphous form of the drug in coground mixtures. Thus, the enhanced dissolution of diazepam from coground mixtures could be mainly attributed to amorphization of the drug. However, a contributory role of improved wettability, reduced aggregation and increased surface area cannot be completely ruled out as factors in the improvement in dissolution rate. Ageing was found to affect in vitro dissolution slightly, however, the results were superior to those with the physical mixture and drug alone. Thus, this method could be considered as a very promising technique to improve the dissolution rate of poorly water-soluble drugs.

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References

Ahmed, S.U. and Madan, P.L., Influence of selected water soluble carbohydrates on the dissolution profile of prednisolone. *Drug. Dev. Ind. Pharm.*, 15 (1989) 1243–1261.

Ahmed, S.U. and Madan, P.L., Evaluation of the in vitro release profile of digoxin from drug-carbohydrate coprecipitates. *Drug Dev. Ind. Pharm.*, 17 (1991) 831–842.

Chiou, W.L. and Riegelman, S., Pharmacuetical applications of solid dispersion system. *J. Pharm. Sci.*, 60 (1971) 1281–1302.

Craig, D.Q.M., Polyethylene glycols and drug release. *Drug. Dev. Ind. Pharm.*, 16 (1990) 2501–2526.

Higuchi, T. and Connors, K.A., Phase solubility techniques. *Adv. Anal. Chem. Instrum.*, 4 (1965) 117.

Imai, T., Saito, Y., Matsumoto, H., Satoh, T. and Otagiri, M., Influence of egg albumin on dissolution of several drugs. *Int. J. Pharm.*, 53 (1989) 7–12.

Kaplan, S.A., Biopharmaceutics in the preformulation stages of drug development, In Swarbrick, J. (Ed.), *Dosage Form Design and Bioavailability*, Lea & Febiger, Philadelphia, 1973, p. 20.

Kim, K.H. and Jarowski, C.I., Surface tension lowering and dissolution rate of hydrocortisone from solutions of selected *N*-acyl esters of cholesterol. *J. Pharm. Sci.*, 66 (1977) 1536–1540.

Macheras, P.E. and Reppas, C.I., Studies on drug-milk freeze dried formulations. I: Bioavailability of sulfamethizole and documarol formulations. *J. Pharm. Sci.*, 75 (1986) 692–696.

Sakamaki, Y. and Miyamoto, M., Submorphous drug preparations. *Jap. Pat.* 78 12,417, 1978.

Sawayanagi, Y., Nambu, N. and Nagai, T., Dissolution properties and bioavailability of phenytoin from ground mixtures with chitin or chitosan. *Chem. Pharm. Bull.*, 31 (1983) 2064–2068.

Shiraishi, S., Arahira, M., Imai, T. and Otagiri, M., Enhancement of dissolution rates of several drugs by low-molecular chitosan and alginate. *Chem. Pharm. Bull.*, 38 (1990) 185–187.

Sugimoto, K., Pullulan: production and applications. *Fermentation Ind.*, 36 (1978) 98–108.

Venkataram, S. and Rogers, J.A., Controlled release of griseofulvin from coprecipitates with phospholipids. *Drug. Dev. Ind. Pharm.*, 11 (1985) 223–238.