ELSEVIER

International Journal of Pharmaceutics 108 (1994) 207–212

international journal of pharmaceutics

Enhancement of in vitro drug release by using polyethylene glycol 400 and PEG-40 hydrogenated castor oil in pellets made by extrusion/spheronisation

C. Vervaet, L. Baert, J.P. Remon *

Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium

(Received 2 November 1993; Accepted 20 January 1994)

Abstract

The in vitro release rate of hydrochlorothiazide from Avicel® PH101 pellets was enhanced by the incorporation of polyethylene glycol 400 (PEG 400) and PEG-40 hydrogenated castor oil (Cremophor® RH40) into the formulation. Pellets containing more than 20% (w/w) PEG 400 released greater than 70% of the hydrochlorothiazide during the first 5 min whereas pellets without PEG 400 released only 45% of hydrochlorothiazide after 90 min. X-ray diffraction patterns showed that hydrochlorothiazide was completely dissolved in the PEG 400 present in the formulations. Reducing the amount of PEG 400 in the formulation decreased the release rate of hydrochlorothiazide. The use of PEG-40 hydrogenated castor oil (Cremophor® RH40) in the pellet formulation increased the release rate of hydrochlorothiazide (30% in 5 min) due to solubilisation of the drug in Cremophor® RH40. An increase in the Cremophor® RH40/hydrochlorothiazide ratio increased the in vitro release rate of hydrochlorothiazide. Storage of the PEG 400 pellets under ambient conditions for 6 months did not alter their dissolution profiles. Pellets containing 21% (w/w) Cremophor® RH40 showed a greater release rate after 6 months storage under ambient conditions.

Key words: Hydrochlorothiazide; Pellet; Dissolution rate enhancement; Polyethylene glycol; PEG-40 hydrogenated castor oil

1. Introduction

It is well known that the poor bioavailability of some drugs is related to their low dissolution rate. Several methods have been described in order to increase the in vitro release rate and the bioavailability of poorly water soluble drugs such as reduction of the particle size (Kondo et al. 1993), the use of modified starch (Ntawukulilyayo et al., 1993) and of solid dispersions of high molecular weight polyethylene glycols (Chiba et al., 1991; Law et al., 1992; Varma et al., 1992). The addition of phosphatidylcholine (Law et al., 1992; Fujii et al., 1993), egg albumin (Imai et al.,

* Corresponding author. Tel: +32-9-221-8951; Fax: +32-9-222-8236.

0378-5173/94/$07.00 © 1994 Elsevier Science B.V. All rights reserved
SSDI 0378-5173(94)00049-B

1991), water soluble gelatin (Imai et al., 1989), hydroxypropylcellulose (Yuasa et al., 1993), polyvinylpyrrolidone (Doherty and York, 1989), bile salt (De Smidt et al., 1991) and tensioactives (Kararli and Gupta, 1992) also proved to enhance the dissolution rate of poorly soluble drugs. The aim of this study was to prepare a solid dosage form incorporating a liquid phase in which the drug has completely dissolved. Two known solubilising agents, polyethylene glycol 400 and PEG-40 hydrogenated castor oil (Cremophor® RH 40), were tested as to their ability to enhance the in vitro release rate of hydrochlorothiazide from a pellet formulation prepared by extrusion/spheronisation.

2. Materials and methods

2.1. Materials

Hydrochlorothiazide (HCT) (batch no. 5327 B; Ludeco, Brussels, Belgium) was chosen as the model drug. This diuretic drug is practically insoluble in water (25°C) and has a solubility of 250 mg/l in 0.1 N HCl (25°C). Polyethylene glycol 400 (PEG 400) (α-Pharma, Vichte, Belgium) and PEG-40 hydrogenated castor oil (Cremophor® RH40) (BASF, Ludwigshafen, Germany) were used as solubilising agents. Microcrystalline cellulose (Avicel® PH101) (FMC Wallington, Little Island, Cork, Ireland) was taken as a filler and

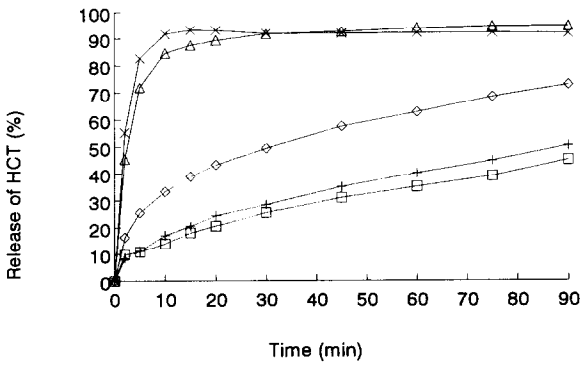

Fig. 1. Dissolution profiles of Avicel PH101 pellets containing 3.5% of hydrochlorothiazide and 2, 11, 21 and 32% polyethylene glycol 400, immediately after preparation. (□) 0%, (+) 2%, (◇) 11%, (△) 21%, (×) 32%

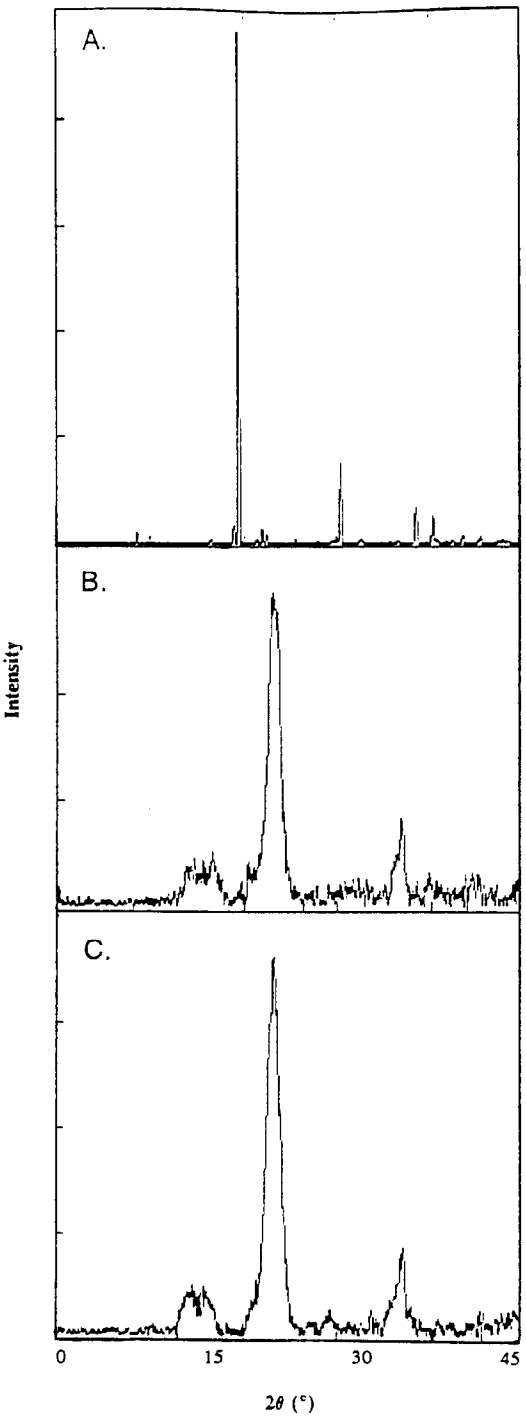

Fig. 2. X-ray diffraction pattern of: (A) pure hydrochlorothiazide; (B) pure Avicel PH101; and (C) Avicel PH101 pellets containing 3.5% hydrochlorothiazide and 32% polyethylene glycol 400.

the pellet forming material. Demineralised water was used as granulation liquid, next to the solubilising agents.

2.2. Methods

2.2.1. Composition of the mixtures

Pellets containing 2, 11, 21 and 32% (w/w) polyethylene glycol 400 and 7, 14 and 21% (w/w) Cremophor® RH40 were prepared. All formulations contained 3.5% (w/w) of hydrochlorothiazide. The remaining part of all formulations consisted of Avicel® PH101. For each composition the amount of water was adjusted in order to achieve proper plasticity of the mass.

A reference formulation was prepared containing 3.5% (w/w) HCT and Avicel® PH101 as a filler, without a solubilising agent.

2.2.2. Preparation of the pellets

Microcrystalline cellulose and hydrochlorothiazide were mixed for 10 min at 60 rpm in a planetary mixer (Kenwood Chef, Hants, U.K.). The granulation liquid was prepared by mixing the dissolution enhancer, PEG 400 or Cremophor® RH40 heated at 45°C, and demineralised water (heated at 45°C in the case of Cremophor® RH40). The Cremophor® RH40/water mixture was cooled to room temperature under continuous stirring. Next, the granulation liquid was added to the powder mixture and granulated for 10 min at 60 rpm in a planetary mixer (Kenwood Chef, Hants, U.K.).

The granulated mass was extruded at 40 rpm using a basket extruder (Caleva Model 10, Caleva Ltd, Sturminster Newton, Dorset, U.K.) through a screen with a thickness of 1 mm and die perforations of 1 mm diameter.

135 g of the extrudate was spheronised for 5 min at 750 rpm in a Caleva Model 15 spheroniser (Caleva Ltd, Sturminster Newton, Dorset, U.K.). The resulting pellets were dried for 12 h in a ventilated oven (Heraus, Obendorf, Germany) at 30°C, after which the dried pellets were sieved using a nest of sieves of 710, 1000 and 1400 μm vibrated on a sieve shaker (Rheostat, Willemshaven, Germany) at maximum vibrational speed.

A second preparation method was used for PEG 400 pellets containing 32% PEG 400 and 3.5% HCT. HCT was first dissolved in the amount of PEG 400 available. This solution was added to the demineralised water and next the complete liquid mixture was added to the microcrystalline cellulose and further processed as in the standard method.

All formulations were stored under ambient conditions during a period of 6 months.

Half of the batch formulated with 21% (w/w) Cremophor® RH40 and 3.5% (w/w) HCT received a thermal treatment for 96 h at 45°C.

2.2.3. Dissolution testing

Dissolution testing was performed on 700 mg pellets (710–1000 μm fraction) containing 25 mg hydrochlorothiazide in 0.1 N HCl (37°C) using the paddle method (USP XXII) at a rotational speed of 100 rpm. Samples of 5 ml were withdrawn at time t_i ($i = 0, 2, 5, 10, 15, 20, 30, 45, 60, 75$ and 90 min) and replaced with an equal amount of test medium. The samples were filtered through a porous metallic filter (pore diameter: 2 μm) and spectrophotometrically analyzed at 273 nm with a Zeiss spectrophotometer (Zeiss PMG-UV, Oberkochen, Germany).

Each formulation was tested four times. The percentage of hydrochlorothiazide released from the formulation at time t_i was calculated and corrected for the amount of HCT withdrawn at time t_{i-1}.

After a 6 month storage period under ambient conditions, the dissolution tests were repeated in order to assess the stability of the pellet formulations.

2.2.4. X-ray diffraction

X-ray diffraction patterns were taken of the formulations containing 11 and 32% (w/w) PEG 400 and of the formulations containing 21% (w/w) Cremophor® RH40 immediately after preparation, after thermal treatment and after 6 months storage under ambient conditions.

3. Results and discussion

Baert and Remon (1993) showed that it was possible to incorporate a liquid substance into microcrystalline pellets. During preliminary experiments the maximum amount of PEG 400 that could be incorporated into the Avicel® PH101 pellets was determined to be 43% (w/w). At this concentration of PEG 400, the pellets stuck to each other whereas below this concentration the pellets retained their typical free-flowing capacity. The limit of Cremophor® RH40 concentration that could be incorporated into the pellets was 21% (w/w). Increasing the concentration of Cremophor® RH40 in the pellets caused the hardness of the pellets to drop below an acceptable level.

The in vitro dissolution profiles of the formulations containing PEG 400 are shown in Fig. 1. Pellets containing 21 and 32% (w/w) PEG 400 released more than 70 and 80% of the active ingredient within the first 5 min, respectively. This indicates a dramatic increase in the in vitro release rate compared to the reference pellets releasing 10 and 45% of HCT after 5 and 90 min, respectively. This observation led to the assumption that the HCT crystals dissolved in PEG 400 during the manufacturing of the pellets. This hypothesis was confirmed for the pellets containing 32% (w/w) PEG 400 prepared using the alternative method where the HCT was allowed to dissolve in PEG 400 before the pellets were prepared. No differences between the in vitro dissolution profiles were observed for pellets prepared by both methods. The typical X-ray diffraction pattern of crystalline HCT in the pellets containing 32% (w/w) PEG 400 could not be detected (Fig. 2). Reducing the percentage of PEG 400 in the formulation to 11 and 2% (w/w) lowered the in vitro drug release rate to 26 and 11% after 5 min, respectively (Fig. 1). The in vitro release rate of HCT from the formulation containing 2% (w/w) PEG 400 was very similar to that of the reference pellets. A solubility test of HCT in PEG 400 at room temperature showed that only a fraction of the amount HCT present could dissolve in the 2% PEG 400 formulation. Although the solubility test showed that all HCT could dissolve in the PEG 400 present in the formulation containing 11% (w/w) PEG 400, the in vitro release rate dropped compared to the formulation containing 21% (w/w) PEG 400. The X-ray diffraction patterns of the pellets containing 11% of PEG 400 showed no difference from those of the pellets containing 32% of PEG 400 (Fig. 2), indicating that all the HCT had dissolved

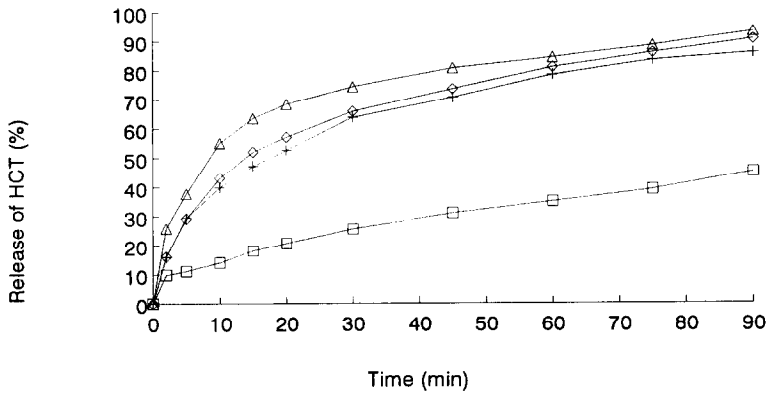

Fig. 3. Dissolution profiles of Avivel PH101 pellets containing 3.5% of hydrochlorothiazide and 0, 7, 14 or 21% Cremophor RH40, immediately after preparation of the pellets. (□) 0%, (+) 7%, (◇) 14%, (△) 21%.

in PEG 400. A possible cause of the lower in vitro release rate with the 11% PEG 400 formulation was the fact that, when the dissolution medium penetrated the pellet, partial precipitation of the dissolved HCT occurred. When 32% PEG 400 was used in the formulation the amount of PEG 400 present allowed the formation of a binary cosolvent-water mixture where all of the HCT was dissolved. When the dissolution medium penetrated the pores of the inert matrix of microcrystalline cellulose (O'Connor and Schwartz, 1993) the dissolved HCT was rapidly solubilized in the dissolution medium. Storage of the PEG 400 pellets under ambient conditions for a period of 6 months did not alter the dissolution profile of HCT.

Fig. 3 shows the dissolution profiles of the pellets containing 7, 14 and 21% (w/w) Cremophor® RH40. An increase in the in vitro release rate of HCT from the Avicel® PH101 pellets was seen although not as pronounced compared to the use of 32% (w/w) PEG 400. The X-ray diffraction pattern of the formulation containing 21% (w/w) of Cremophor® RH40 demonstrated the presence of HCT crystals in the formulation (Fig. 4A), indicating that only part of the HCT was solubilized.

The dissolution profiles of pellets containing 21% of Cremophor® RH40 showed an increase in the in vitro release rate after storage under ambient conditions for a time period of 6 months (Fig. 5). The same increase in the in vitro release rate was observed after thermal treatment of the pellets at 45°C for 96 h. This is probably due to an increase in the amount of HCT solubilised in the Cremophor® RH40 as a function of time. This hypothesis was confirmed by X-ray diffraction patterns showing that crystalline HCT could not be detected after a storage period of 6 months under ambient conditions (Fig. 4B) nor after the thermal treatment (Fig. 4C). Although all HCT was solubilised in Cremophor® RH40 the release rate of HCT did not reach that of the pellets formulated with 32% (w/w) PEG 400. HCT solubilisation in Cremophor® RH40 micelles or the slower penetration of the dissolution medium into the microcrystalline/Cremophor® RH40 matrix could be the cause of this lower dissolution rate.

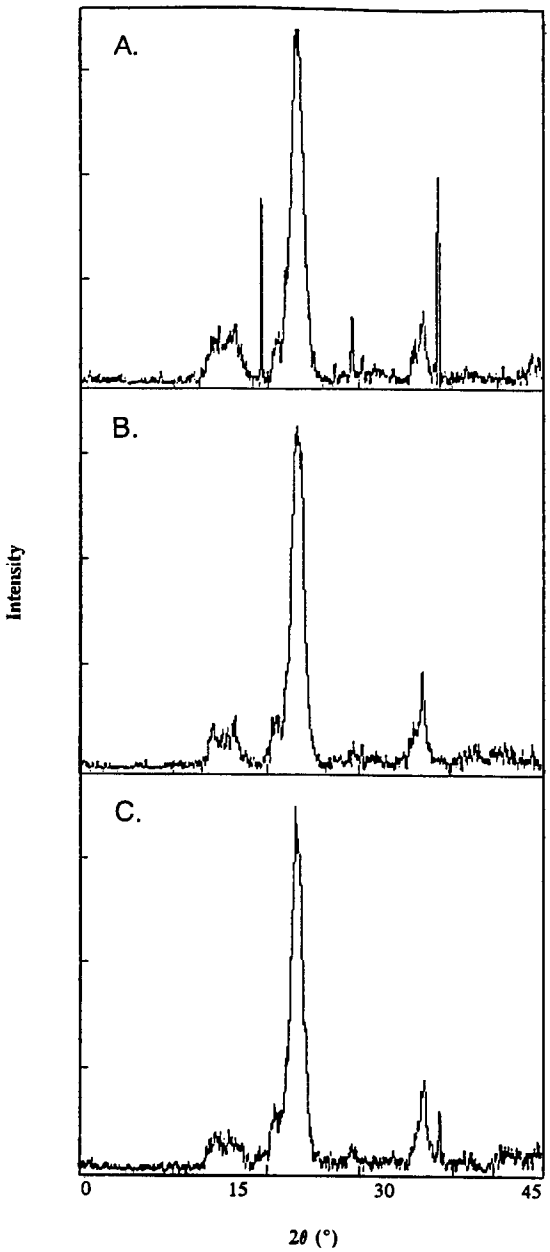

Fig. 4. X-ray diffraction pattern of Avicel PH101 pellets containing 3.5% hydrochlorothiazide and 21% Cremophor RH40: (A) immediately after preparation; (B) after 6 months storage under ambient conditions; and (C) after thermal treatment at 45°C for 96 h.

From these results, it can be concluded that the enhancement of the in vitro release of hydrochlorothiazide from Avicel® PH101 pellets made

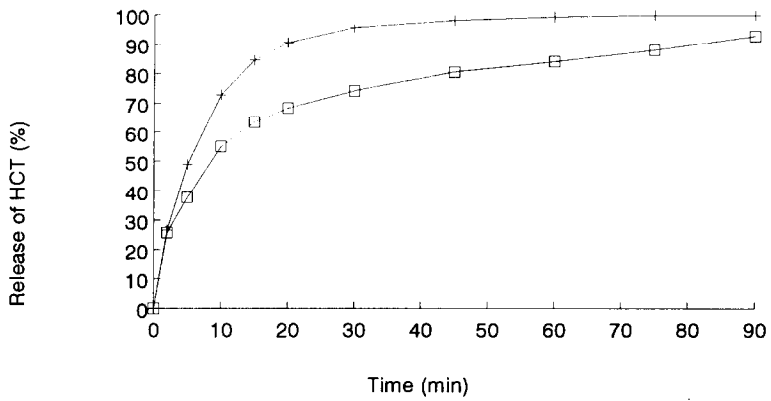

Fig. 5. Dissolution profiles of Avicel PH101 pellets containing 3.5% of hydrochlorothiazide and 21% Cremophor RH40, immediately after preparation and after a 6 month storage period under ambient conditions. (□) After preparation; (+) after 6 months.

by extrusion/spheronisation using a cosolvent such as PEG 400 and a solubilising agent like Cremophor® RH40 is a very promising technique. Further investigations should be conducted to evaluate the formulations in vivo and their application to other drugs.

Acknowledgments

This study was financially supported by the N.F.W.O. (Brussels, Belgium). The authors wish to thank FMC Corporation for the generous supply of Avicel® PH101.

References

Baert, L. and Remon, J.P., *Belgian Patent Application 09300407* (1993).

Chiba, Y., Kohri, N., Iseki, K. and Miyazaki, K., Improvement of dissolution and bioavailability for mebendazole, an agent for human echinococcosis, by preparing solid dispersion with polyethylene glycol. *Chem. Pharm. Bull.*, 39 (1991) 2158–2160.

De Smidt, J.H., Offringa, J.C.A and Crommelin, D.J.A., Dissolution rate of griseofulvin in bile salt solutions. *J. Pharm. Sci.*, 80 (1991) 399–401.

Doherty, C. and York, P., The in vitro-pH-dissolution dependence and in vivo bioavailability of frusemide-PVP solid dispersions. *J. Pharm. Pharmacol.*, 41 (1989) 73–78.

Fujii, M., Hioki, M., Nishi, M., Henmi, T., Nakao, M., Shiozawa, K. and Matsumoto, M., Preparation of the solid dispersion of indomethacin with phosphatidylcholine by heating method. *Chem. Pharm. Bull.*, 41 (1993) 1275–1278.

Imai, T., Nishiyama, T., Ueno, M. and Otagiri, M., Enhancement of the dissolution rates of poorly water-soluble drugs by water-soluble gelatin. *Chem. Pharm. Bull.*, 37 (1989) 2251–2252.

Imai, T., Nohdomi, K., Acarturk, F. and Otagiri, M., Enhancement of dissolution and absorption of mefenamic acid by egg albumin. *J. Pharm. Sci.*, 80 (1991) 484–487.

Kararli, T.T. and Gupta, V.W., Solubilization and dissolution properties of a leukotriene-D_4 antagonist in micellar solutions. *J. Pharm. Sci.*, 81 (1992) 483–485.

Kondo, N., Iwao, T., Masuda, H., Yamanouchi, K., Ishihara, Y., Yamada, N., Haga, T., Ogawa, Y. and Yokoyama, K., Improved oral absorption of a poorly water-soluble drug, HO-221, by wet-bead milling producing particles in submicron region. *Chem. Pharm. Bull.*, 41 (1993) 737–740.

Law, S.L., Lo, W.Y., Lin, F.M. and Chaing, C.H., Dissolution and absorption of nifedipine in polyethylene glycol solid dispersion containing phosphatidylcholine. *Int. J. Pharm.*, 84 (1992) 161–166.

Ntawukulilyayo, J.D., Bouckaert, S. and Remon, J.P., Low substituted *N*-octenylsuccinate starch as a dissolution rate enhancer in solid dosage forms. *Int. J. Pharm.*, 91 (1993) 23–27.

O'Connor, R.E. and Schwartz, J.B., Drug release mechanism from a microcrystalline cellulose pellet system. *Pharm. Res.*, 10 (1993) 356–361.

Varma, M.M. and Jayaswal, S.B., In vitro and in vivo evaluation of fast release solid dispersions of glibencamide. *Ind. Drugs*, 29 (1992) 608–611.

Yuasa, H., Takahashi, H., Ozeki, T., Kanaya, Y. and Ueno, M., Application of the solid dispersion method to the controlled release of medicine: III. Control of the release rate of slightly water soluble medicine from solid dispersion granules *Chem. Pharm. Bull.*, 41 (1993) 397–399.