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An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen

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Abstract

A controlled release pellet formulation using a NanoCrystal® colloidal dispersion of ketoprofen was developed. In order to be able to process the aqueous NanoCrystal® colloidal dispersion into a hydrophobic solid dosage form a spray drying procedure was used. The in vitro dissolution profiles of wax based pellets loaded with nanocrystalline ketoprofen are compared with the profiles of wax based pellets loaded with microcrystalline ketoprofen and of a commercial sustained release ketoprofen formulation. Pellets were produced using a melt pelletisation technique. All pellet formulations were composed of a mixture of microcrystalline wax and starch derivatives. The starch derivatives used were waxy maltodextrin and drum dried corn starch. Varying the concentration of drum dried corn starch increased the release rate of ketoprofen but the ketoprofen recovery remained problematic. To increase the dissolution yield surfactants were utilised. The surfactants were either added during the production process of the NanoCrystal® colloidal dispersion (sodium laurylsulphate) or during the pellet manufacturing process (Cremophor® RH 40). Both methods resulted in a sustained but complete release of nanocrystalline ketoprofen from the matrix pellet formulations.

Keywords: Ketoprofen; Sustained release; Nanocrystals; Matrix pellets; Surfactants; Bioavailability

1. Introduction

The advantages of multiple unit dosage forms such as pellets for the administration of oral controlled release dosage forms are well known: (1) they disperse freely in the gastrointestinal tract and so maximise drug absorption, reduce peak plasma fluctuations and minimise side effects; (2) high local concentrations are avoided; (3) flexibility for the development of oral dosage forms as pellets containing different drug substances can be blended and formulated in a single dosage form (Ghebre-Sellassie, 1989). Matrix pellet formulations offer the advantage of a one step production procedure compared to coated pellets. Zhou et al. (1996) already showed the possibilities of micro-

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crystalline wax and starch mixtures for the production of matrix pellets. Nanosuspensions of poorly soluble drugs are generally administered orally or parenterally to increase the bioavailability and the dissolution rate (Liversidge and Conzentino, 1995; Müller and Peters, 1998). The aim of this study was to evaluate the use of a NanoCrystal® colloidal dispersion of ketoprofen for the development of a matrix pellet formulation, based on a melt pelletisation technique. Ketoprofen has a short plasma elimination half-life so extended release preparations can be considered desirable. (Dennis et al., 1990; Habib and Mesue, 1995). The pellet formulation used is based on a mixture of microcrystalline waxes and different starches (Zhou et al., 1996). To prove the advantage of the NanoCrystal® technology the in vitro dissolution profiles of wax based pellets loaded with nanocrystalline ketoprofen are compared with the dissolution profile of wax based pellets loaded with microcrystalline ketoprofen and with a commercially available coated ketoprofen pellet formulation.

2. Materials and methods

2.1. Materials

Microcrystalline ketoprofen was obtained from Spectrum Quality Products (New Brunswick, NJ, USA). The NanoCrystal® colloidal ketoprofen dispersion (containing 20% w/w ketoprofen) was supplied by Elan Pharmaceutical Technologies (King of Prussia, PA, USA). Microcrystalline wax (Lunacera® P) was purchased from Paramelt (Heerhugowaard, The Netherlands), while both waxy maltodextrin (WMD) and drum dried corn starch (DDCS) were provided by Eridania-Beghin Say-Cérestar (Vilvoorde, Belgium). Rofenid® 200 Long Acting (Rhône-Poulenc Rorer, Brussels, Belgium) was used as a reference formulation.

2.2. Spray drying

The NanoCrystal® colloidal ketoprofen dispersion (20% w/w) was spray dried using a mini-spray dryer (Büchi 190, Flawil, Switzerland) delivering the dispersion and drying medium in co-current configuration through a pneumatic feeding system. A nozzle cap of 0.5 mm diameter with intermittent pneumatic clearing of the nozzle was used. Before spray-drying the dispersion was diluted with water (1:2). The inlet temperature of the drying air was set at 75°C (which is substantially lower than the melting point of ketoprofen (94°C)), while the outlet temperature was 49°C. The dispersion feeding rate was 200 ml/h.

2.3. Lyophilisation

About 1000 ml dispersion was homogenised and transferred to Petri dishes. Each Petri dish contains ± 30 ml dispersion. The samples were lyophilised using an Amsco-Finn Aqua GT4 freeze dryer (Amsco, Brussels, Belgium). The dispersion was frozen to 228 K and was kept at this temperature for 30 min. Primary drying was performed by keeping the samples for 12 h. 20 min. at a pressure of 1 mbar and a shelf temperature of 258 K. Secondary drying was carried out by reducing the pressure to 0.1 mbar and increasing the shelf temperature to 298 K. Secondary drying time was 9 h.

2.4. Particle size analysis

Particle size analysis of ketoprofen before and after spray drying was determined by dynamic light scattering (Autosizer 4700, Malvern Instruments, Malvern, UK). Prior to particle sizing, spray dried ketoprofen was resuspended in deionised water at a concentration of 20% w/w. Both the original NanoCrystal® and the redispersed spray dried dispersion were diluted (1:10 000) with deionised water to obtain the appropriate concentration range for DLS-measurement.

2.5. Karl Fischer titration

After spray-drying the moisture content of the spray-dried and the freeze-dried product was determined using a Karl Fischer titration (Mettler DL 35, Mettler Toledo, Lot, Belgium). The moisture content of six randomly selected samples was determined.

2.6. Production of pellets

The matrix pellets were produced in a laboratory scale high shear mixer (Mi-Pro, ProCept, Zelzate, Belgium) equipped with an impeller and chopper whose speed could be adjusted between 0 and 1500 rpm and between 0 and 4200 rpm, respectively. The total product load was 250 g. Ketoprofen (15% w/w, spray dried, nanocrystalline or microcrystalline), starch derivatives (50% w/w) and microcrystalline wax (35% w/w) were weighed and transferred into the mixing bowl. When surfactants (sodium laurylsulphate or Cremophor® RH 40 (Polyoxyl 40 Hydrogenated Castor Oil)) were added during the pelletisation process, the concentration of waxy maltodextrin was reduced in the same amount. Next the mixture was heated using a temperature of the jacketed bowl set 5°C above the melting point of the wax (58–62°C). Meanwhile the mixture was continuously homogenised at an impeller speed of 250 rpm until the wax was completely molten and a dough like mixture was obtained. During this phase of the pelletisation process no chopper was used. When the dough like consistency was formed mixing was continued for an additional 2 min. Next the cooling phase was initiated and the temperature of the jacketed bowl was set at 62°C. Dry ice was added until the mass reached a temperature of 50–52°C. Finally the mass was continuously mixed for 20 min. (impeller: 800 rpm, chopper: 3000 rpm), keeping the temperature constant between 50 and 52°C. The resulting pellets were allowed to cool to room temperature and the fraction between 800–1000 μm was isolated by sieving (sieve tower, Retsch VE 1000, Retsch, Haan, Germany). This size fraction was used for further analysis. During the production of the pellets the temperature of the mixture was continuously monitored using an IR-probe.

2.7. In vitro dissolution testing

Dissolution testing of different pellet formulations was performed in 900 ml buffer (pH 7.5 and 4.6, without enzymes, USP 23) at 37°C ($\pm$ 0.5°C). An automated dissolution tester (Vankel VK 8000, VanKel Industries, NJ, USA) using apparatus 2 (paddle speed 100 rpm) was used in combination with specially designed baskets to prevent the pellets from floating. At different time interval (0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h) 5 ml samples were withdrawn and replaced by new medium (VanKel VK 7000, VanKel Industries, NJ, USA). The samples were spectrophotometrically analysed at 260 nm (Perkin–Elmer UV/VIS λ12, Perkin–Elmer, Norwalk, CT, USA). All dissolution profiles are the mean of six dissolution tests. All dissolution tests were performed under sink conditions. The amount of ketoprofen per dissolution flask was limited to 200 and 30 mg using dissolution medium of pH 7.5 and 4.6, respectively.

To evaluate the influence of the rotational speed of the paddles on the dissolution profile paddle speeds of 50, 100 and 150 rpm were used.

2.8. Porosimetric analysis

The porosity of several pellet formulations was determined before and after dissolution testing using a mercury porosimeter (AutoPore III 9420 System, Micromeritics, Norcross, GA, USA).

2.9. Scanning electron microscopy

SEM photographs (JSM 5600 LV Scanning Electron Microscope, JEOL Europe, Zaventem, Belgium) of different wax based pellet formulations were taken before and after dissolution testing.

2.10. X-ray diffraction

The solubility of ketoprofen in the wax based matrix was determined with X-ray diffraction. A calibration curve ($y = 31.8973x + 3.6755$; y: number of counts, x: %w/w ketoprofen; $r^2 = 0.9998$) was obtained by measuring the X-ray diffraction profiles at $2\theta = 22.8$ (Diffractometer D5000, Cu, Kα, Siemens, Germany) of different physical mixtures containing a constant amount of microcrystalline wax (33% w/w) and varying concentrations of ketoprofen (5, 10, 15 and 25% w/w) and drum dried corn starch. The fraction of crystalline ketoprofen of several formulations was determined.

3. Results and discussion

During this study a commercial aqueous dispersion (NanoCrystal® ketoprofen dispersion) is further processed in order to incorporate it into a hydrophobic matrix pellet formulation. Lyophilisation and spray drying are two techniques available to dry the NanoCrystal® ketoprofen dispersion. Lyophilisation of the dispersion was time consuming and resulted in a residual moisture content of 10% w/w. On the contrary, spray drying yielded a powder with an average ($n = 6$) residual moisture content of 1.32% w/w ($\pm$ 0.12%) and a process yield of 83.8% ($\pm$ 2%). The mean particle size before spray drying and of the redispersed spray dried powder was 230 and 240 nm, respectively, indicating that spray drying hardly affected the particle size of the original nanocrystals.

The in vitro dissolution profiles of matrix pellets composed of a mixture containing microcrystalline wax (35% w/w), ketoprofen (15% w/w nanocrystalline), WMD and different concentrations (5,10, 15 and 20% w/w) of DDCS and of the reference formulation (Rofenid® 200 Long Acting) are shown in Fig. 1. The comparison of the profiles indicated that only the commercial formulation had a sustained and complete drug release. The drug release from the wax based pellets reached after 24 h a plateau varying between 49 and 83% for the formulations containing 5 and 20% w/w DDCS, respectively. Increasing the concentration of drum dried corn starch enhanced the release rate of ketoprofen but the ketoprofen recovery remained problematic. The uncomplete drug release is not due to the dissolution of ketoprofen into the hydrophobic matrix because the X-ray diffraction results prove that only a very small amount (2% $\pm$ 0.4% w/w) dissolved in the matrix during the pelletisation process. To increase the drug release surfactants can be used (Habib and Mesue, 1995). In this study Cremophor® RH 40 and sodium laurylsulphate were used. In Fig. 2 the release profiles of pellet formulations containing 13% w/w DDCS and an increasing concentration of Cremophor® RH 40 (0.01, 0.05, 0.1 and 0.5% w/w) are compared with that of the commercial formulation. Comparison

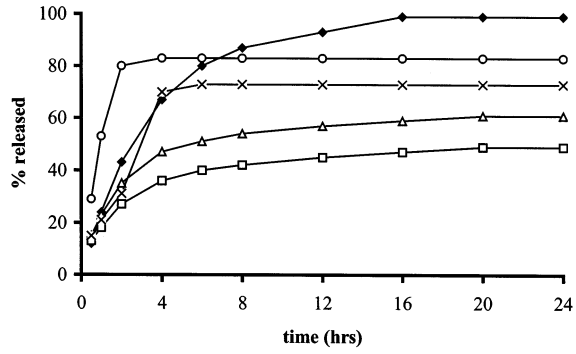


Fig. 1. The influence of drum dried corn starch on the in vitro dissolution profile of pellets composed of spray dried nanocrystalline ketoprofen (15% w/w), microcrystalline wax (35% w/w), waxy maltodextrin and different concentrations of drum dried corn starch. (◆) Reference formulation (Rofenid® 200 Long Acting), (□) 5% DDCS, (△) 10% DDCS, (×) 15% DDCS and (○) 20% DDCS.

of the different profiles indicated that all wax based pellet formulations with Cremophor® RH 40 showed a complete drug release. The formulation containing 0.01% w/w Cremophor® RH 40 showed an in vitro dissolution profile similar to the commercial formulation. However the addition of small amounts of Cremophor® RH 40 or another tensioactive agent such as sodium lauryl-

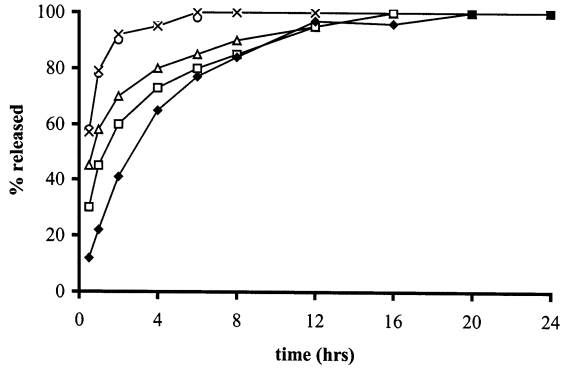


Fig. 2. The influence of different concentrations of Cremophor® RH 40 on the in vitro dissolution profile of matrix pellet formulations containing nanocrystalline ketoprofen (15% w/w), microcrystalline wax (35% w/w), waxy maltodextrin and drum dried corn starch compared to that of a commercial formulation Rofenid® 200 Long Acting. (◆) Reference, (□) 0.01% Cremophor® RH 40, (△) 0.05% Cremophor® RH 40, (×) 0.1% Cremophor® RH 40 and (○) 0.5% Cremophor® RH 40.

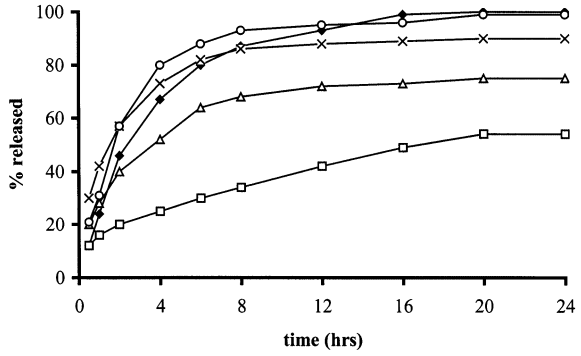


Fig. 3. The influence of different concentrations of drum dried corn starch on the in vitro dissolution profile of wax based (35% w/w) pellets loaded with spray dried nanocrystalline ketoprofen (15% w/w) containing 0.15% w/w sodium laurylsulphate. (◆) Reference, (□) 0% DDCS, (△) 4% DDCS, (×) 5% DDCS and (○) 6.5% DDCS.

sulphate seemed difficult during the pellet forming process due to problems of homogenisation during production. The alternative was the production of a sodium laurylsulphate stabilised ketoprofen NanoCrystal® dispersion before spray drying. Fig. 3. shows the mean dissolution profiles of wax pellet formulations loaded with the spray dried NanoCrystal® dispersion containing 0.15% w/w sodium laurylsulphate and different concentrations DDCS (0, 4, 5 and 6.5% w/w). The dissolution profiles of the wax pellet formulations are compared with those of the reference formulation. Comparison of the profiles indicated that the formulations containing 6.5 and 5% w/w drum dried corn starch had a profile similar to the commercial formulation. The formulations containing 6.5, 5, 4 and 0% w/w DDCS released after 24 h 100, 90, 75 and 54% of the total drug amount, respectively. Fig. 4 shows the dissolution profiles of pellets loaded with a spray dried NanoCrystal® or microcrystalline ketoprofen dispersion stabilised with 0.15% w/w sodium laurylsulphate. The dissolution profile of ketoprofen from the matrix pellets was independent of pH between 4.6 and 7.5 when nanocrystals were used in the formulation. After 12 h 100% ketoprofen was released from the nanocrystalline ketoprofen pellets, while about 95 and 75% was released when microcrystalline ketoprofen was used at a pH of 7.5 and 4.6, respectively. For the same amount of ketoprofen the total surface area for nanocrystals is larger than for microcrystals which makes the release of ketoprofen from a formulation containing nanocrystals faster than for a formulation containing microcrystals. The influence of surfactants on the solubility (Luner et al., 1996) is mostly important at low pH where ketoprofen (pKa 4.4) is mainly unionised. In this case coprocessing of nanocrystals and sodium laurylsulphate makes the dissolution rate of ketoprofen independent of pH. Lowering the pH of the dissolution medium decreases the solubility of ketoprofen (pH 7.5: 11 g/l, pH 4.6: 400 mg/l) but also influences the dissolution rate of the formulation containing microcrystals. The release kinetics and release mechanisms were determined for different wax based formulations by a non linear regression of the drug release data up to 80% using the following equation: $C/C_{max} = kt^n$.

C/C_{max} is the fraction of drug released up to time t, k is the kinetic constant and n is the diffusional exponent indicating the mechanism of drug release. For swellable spherical matrices

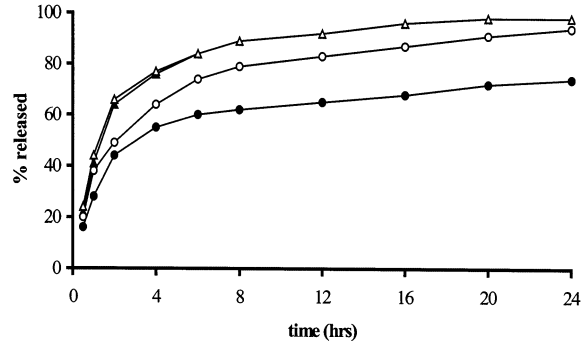
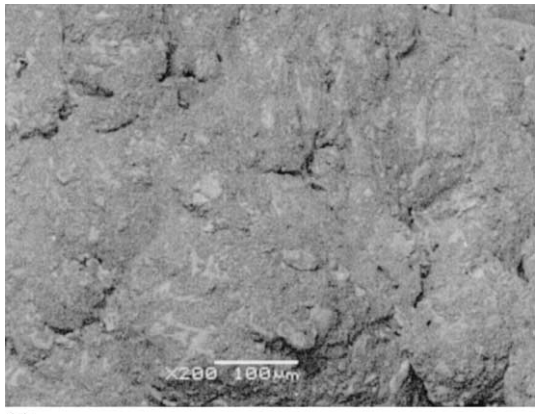


Fig. 4. The influence of the pH of the dissolution medium on the in vitro dissolution profile. All pellet formulations contain 15% w/w ketoprofen, 35% w/w wax, 6.5% w/w drum dried corn starch and waxy maltodextrin. The pellet formulations were loaded with spray dried nanocrystalline or microcrystalline ketoprofen stabilised with 0.15% w/w sodium laurylsulphate. (△) nanocrystalline ketoprofen pH 7.5, (▲) nanocrystalline ketoprofen pH 4.6, (○) microcrystalline ketoprofen pH 7.5, (●) microcrystalline ketoprofen pH 4.6.



(a)

(b)

Fig. 5. (a) SEM photograph (× 200) of a pellet formulation before a dissolution test. (b) SEM photograph (× 140) of a pellet formulation after a dissolution test.

a value of $n = 0.43$ stands for a Fickian diffusion, while a value between 0.43 and 0.85 indicates an anomalous (non-Fickian) transport (Ritger and Peppas, 1987). For all wax-based formulations a n-value around 0.5 was calculated indicating a non-Fickian diffusion release mechanism. SEM photographs of a pellet formulation before (Fig. 5a) and after (Fig. 5b) a dissolution test revealed that during dissolution testing additional pores have been formed. The data of the porosity determination indicated that the porosity before the dissolution test is around 10% for all wax based samples and increased to approximately 50% for all samples after dissolution testing. All these factors indicated that pore diffusion is probably the main mechanism governing the drug release. Release due to erosion was minimal as the release rate was not influenced when the rotational speed of the paddles was increased from 50 to 150 rpm. Moreover, the pellets remained visually intact during dissolution testing. As a conclusion it can be said that ketoprofen can be formulated into matrix pellets using a spray dried NanoCrystal® dispersion. A complete drug release was obtained when a tensioactive agent was added to the formulation. To prove the advantages of nanocrystals a bioavailability study in dogs is on-going in order to study the in vivo drug release profile of the nanocrystalline ketoprofen matrix pellets in comparison with a microcrystalline ketoprofen and the reference formulation.

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