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# Matrix pellets based on the combination of waxes, starches and maltodextrins

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**Abstract**

Matrix pellets were produced combining microcrystalline waxes, pregelatinized starches and hydrolysed starches. Ibuprofen, sodium salicylate, benzoic acid, sodium benzoate and chloroquine phosphate were used as model drugs. Using a wax with a melting range between 68 and 72°C and increasing the wax concentration decreased the drug release rate. Pellets containing drum-dried corn starch failed to form matrix pellets. The slowest drug release was obtained for formulations containing waxy maltodextrin, releasing 95% of the incorporated ibuprofen after 48 h in vitro. Increasing the ibuprofen concentration decreased the drug release rate. Drug release was controlled by pore and matrix diffusion. The release of sodium salicylate and sodium benzoate from the wax-starch matrix pellets was characterised by an initial burst release followed by a block of the drug release.

*Keywords:* Matrix pellets; Starch; Maltodextrin; Microcrystalline wax; Melt pelletization

## 1. Introduction

Sustained drug release from pellets is conventionally achieved by polymeric coating. In practice, this time consuming and expensive process sometimes reveals problems of reproducibility of the drug release profile because of a non-constant film quality, variability of the film thickness, cracks in the film or ageing of the polymer coating. Besides, the coating is dependent on the optimization of several parameters during the production process. Therefore, a growing interest in the development of matrix pellet formulations exists. Several studies have shown the possibility to formulate matrix pellets using different types of manufacturing techniques such as extrusion-spheronisation, melt suspension, solvent evaporation and the coacervation technique. Release-retarding agents such as chitosan (Tapia et al., 1993; Goskonda and Upadrashta, 1993) or sodium carboxymethylcellulose (O'Connor and Schwartz, 1985; Ghali et al., 1989a; Goskonda and Upadrashta, 1993; Goskonda et al., 1994b) have been used in pellets made by extrusion-spheronisation to form a hydrophilic layer around the sphere, delaying the in vitro drug release. Others incorporated ethylcellulose (Bianchini et

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al., 1992; Goskonda et al., 1994a), methacrylic acid (Bianchini et al., 1992; Goskonda et al., 1994a; Goskonda et al., 1994b) or pH-adjusting agents (Bianchini et al., 1992; Goskonda et al., 1994a; Goskonda et al., 1994b) in the formulation to obtain a sustained release effect. Pellets made by extrusion-spheronisation and combining microcrystalline cellulose with a hydrophobic component proved to delay drug release (Briquet et al., 1986; Ghali et al., 1989b). Wong et al., 1992 reported on the matrix effect of pellets consisting of cetostearylalcohol and ibuprofen made by a melt suspension technique. Using a coacervation technique, it was possible to slow down the release of ibuprofen (Kurumaddali et al., 1994) and mefenamic acid (Betageri et al., 1995). These techniques are, compared to the melt pelletization technique, multi-step processes or processes that are difficult to control on a larger scale. The melt pelletization technique is a single step-single equipment technique converting fine powders into pellets by means of a molten hydrophobic component which act as a binder in the process. This binder can be a wax, a fat or a fatty acid added as a melt to the preheated powders or as a solid melting due to the friction heat generated during the mixing (McTaggart et al., 1984).

The objective of this study is to develop a versatile matrix pellet formulation based on the combination of a hydrophobic material and a starch derivative using the melt pelletization technique.

## 2. Materials and methods

### 2.1. Materials

Ibuprofen (diam: 25 $\mu$m)(The Boots Co., Nottingham, England), sodium salicylate, benzoic acid, sodium benzoate and chloroquine phosphate were selected as the model drugs. Sodium salicylate, sodium benzoate, benzoic acid and chloroquine phosphate were purchased from Ludeco N.V. (Brussels, Belgium). Lunacera® M (melting range: 68–72°C) and P (melting range: 58–62°C)(Füller GmbH, Lüneburg, Germany), both microcrystalline waxes, were used as hydrophobic materials. Those waxes were combined with pregelatinized starches (*Drum Dried Corn Starch (DDCS); Drum Dried Waxy Corn Starch (DDWCS); Extruded Waxy Corn Starch (EWCS)*) or maltodextrins (*Waxy Maltodextrin (WMD)(D.E. = 10); Potato Maltodextrin (PMD)(D.E. = 3)*). All starch derivatives were supplied by Eridania-Beghin Say-Cerestar (Vilvoorde, Belgium). The pellets were prepared in a jacketed laboratory scale high-shear mixer (Grall 10, Machines Colette, Wommelgem, Belgium).

### 2.2. Composition of the mixtures

#### 2.2.1. Formulation study

The ibuprofen content was 15% (w/w) while the wax concentration varied between 25 and 45% (w/w). The remaining part of the formulation consisted of starch or maltodextrin.

#### 2.2.2. Drug loading study

The influence of drug concentration was studied on pellets containing ibuprofen in concentrations varying from 15 to 70%. The rest of the formulation consisted of WMD and Lunacera® M. The wax/maltodextrin ratio was kept constant at 0.55 for the pellets containing up to 50% ibuprofen. The formulations with 60 and 70% ibuprofen contained 18% Lunacera® M (wax/maltodextrin ratio of 0.82 and 1.5, respectively).

#### 2.2.3. Drug type study

Pellets containing 15% sodium salicylate, 25% benzoic acid, 25% sodium benzoate or 25% chloroquine phosphate were prepared in order to evaluate the application possibility of the wax/starch matrix system to different drugs.

In all cases a 1 kg batch was prepared.

### 2.3. Preparation of the pellets

The drug and the starch derivative were blended in the high shear mixer for 30 s while the temperature of the jacketed bowl was set 5°C above the melting point of the wax. After addition of the molten wax, mixing continued for 2 min (impeller: position I and chopper: position 0) in order to form a homogeneous mix. Following a

cooling phase to ± 53°C, the mass was continuously mixed until pellets were formed. During this mixing step, the speed of the impeller and the chopper was varied in function of the formulation in order to obtain a narrow particle size distribution of the pellets.

### 2.4. Dissolution test

A modified paddle method (USP XXII) was used in which the pellets were kept in a spherical basket positioned at the bottom of the dissolution vessel. After 4 h, the baskets were opened to allow the wetted pellets to sink to the bottom of the dissolution vessel. The dissolution of the pellets containing ibuprofen and benzoic acid was performed in 900 ml of phosphate buffer (pH 7.2), whereas 900 ml of water was used for pellets loaded with sodium salicylate, sodium benzoate and chloroquine phosphate. The temperature of the medium was kept at 37°C ± 0.5°C and the rotational speed of the paddles was set at 100 rpm. Samples of 3 ml were withdrawn at regular time intervals, replaced by fresh medium and spectrophotometrically analyzed at 221 nm for ibuprofen, 223 nm for benzoic acid, 224 nm for sodium benzoate, 295 nm for sodium salicylate and for 343 nm for chloroquine phosphate. All dissolution tests were performed in triplicate.

### 2.5. Swelling test of the pellets

10 pellets of the formulations containing 15% ibuprofen, 40% Lunacera® P and 45% DDWCS or EWCS were kept in phosphate buffer (pH 7.2) at 37°C for 24 h. The swelling capacity of the pellets was determined by calculating the ratio of the longest diameter before and after the test.

### 2.6. Porosimetric analysis

The pore size of the pellets before and after dissolution was determined using mercury porosimetry (AutoPore III 9420 System, Micromeritics Instrum. Corp., Norcross, GA, USA). For the calculation of the porosity of the pellets, the pores larger than 50 $\mu$m have been ignored to eliminate the influence of voids between the pellets.

## 3. Results and discussion

Matrix pellets offer a technical advantage over coated pellets in terms of ease of processing and reduction of production times. A mixture of microcrystalline waxes and pregelatinized starches or maltodextrins prooved to be efficient in matrix pellet formation using a one-step process (Belgian Patent Application n° 09500248).

### 3.1. Formulation study

#### 3.1.1. Influence of wax type and wax concentration

The ibuprofen release was dependent on the melting range and on the concentration of the wax used. Pellets formulated with Lunacera® P (melting range 58–62°C) showed a faster release compared to the Lunacera® M-formulations (melting range 68–72°C) (Fig. 1). After 12 h of dissolution testing, the drug release was nearly 100% for the 35% Lunacera® P-pellets whereas the pellets containing 35% Lunacera® M only released 75% of ibuprofen. The same influence of the melting range of a wax on the drug release from pellets formulated with ibuprofen was seen by Adeyeye and Price, 1994. Increasing the amount of wax in the formulation showed a slower release profile (Fig. 1): increasing the Lunacera® P content from 35 to 45% decreased the ibuprofen release from 95 to 75% after 12 h of dissolution testing.

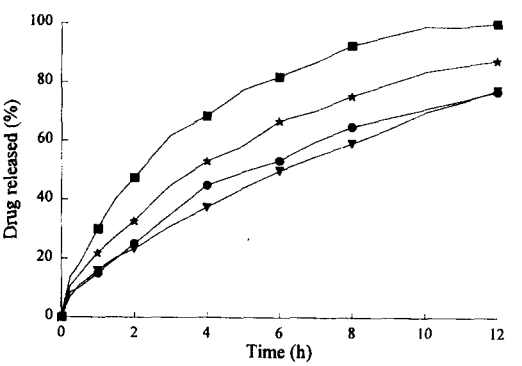


Fig. 1. Dissolution profiles of matrix pellets containing 15% ibuprofen, potato maltodextrin and microcrystalline wax. (■) 35% Lunacera® P, (☆) 40% Lunacera® P, (●) 45% Lunacera® P and (▼) 35% Lunacera® M.

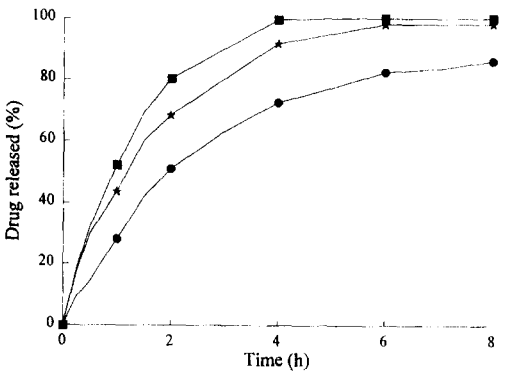


Fig. 2. Dissolution profiles of matrix pellets containing 15% ibuprofen, drum dried waxy corn starch and microcrystalline wax. (■) 40% Lunacera® P, (☆) 45% Lunacera® P and (●) 30% Lunacera® M.

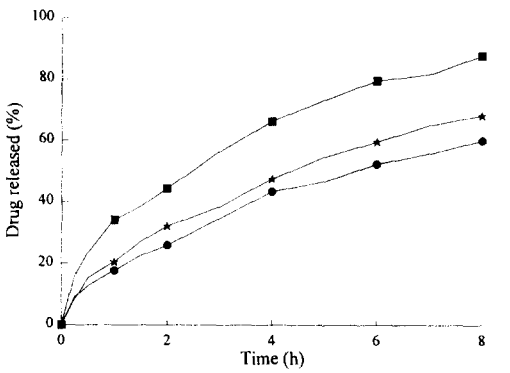


Fig. 3. Dissolution profiles of matrix pellets containing 15% ibuprofen, extruded waxy corn starch and microcrystalline wax. (■) 30% Lunacera® P, (☆) 35% Lunacera® P and (●) 40% Lunacera® P.

### *3.1.2. Influence of the starch derivative*

All formulations containing DDCS and ibuprofen failed to form matrix pellets releasing over 80% of the drug within the first hour of the dissolution testing as the pellets disintegrated into smaller fragments within 15 min. Although these formulations do not have the desired matrix effect, they might present an alternative to microcrystalline cellulose or might be useful when formulating conventional dosage forms requiring taste masking. Incorporating DDWCS in the formulation delayed the ibuprofen release and allowed to adjust the drug release by varying the wax type and the wax concentration (Fig. 2). The slowest drug release was obtained with a formulation containing 30% Lunacera® M ($t_{50\%}$ = 2 h and 85% released after 8 h). When EWCS was used, a waxy corn starch pregelatinized by extrusion, the drug release was function of the type and the concentration of the wax. But a slower drug release was obtained in comparison to the DDWCS pellets (Fig. 3). The $t_{50\%}$ was above 5 h for the formulation containing 40% Lunacera® P. The differences in release characteristics between the formulations containing DDWCS and EWCS are due to the different behaviour of the pregelatinized starches during dissolution. Pellets containing DDWCS showed a swelling ratio of 1.24. The structure of the DDWCS pellets was soft and its surface was ruptured after 24 h of dissolution testing. The EWCS pellets, on the contrary, swelled to a far lesser extent (swelling ratio 1.03) leaving the structure of the pellets intact.

Substituting the pregelatinized starch by WMD had a dramatic influence on the ibuprofen release as the $t_{50\%}$ value was about 12 h for pellets containing 30% Lunacera® M (Fig. 4), releasing 95% of the total drug amount after 48 h. The use of a potato maltodextrin allowed to adjust the drug release profile as with WMD but the matrix effect was less pronounced ($t_{50\%}$ = 6 h and 100% release after 24 h for pellet containing 35% Lunacera® M) (Fig. 1). Increasing the wax concentration could theoretically allow to formulate

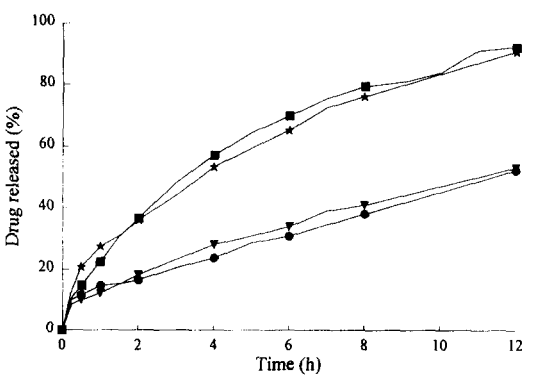


Fig. 4. Dissolution profiles of matrix pellets containing 15% ibuprofen, waxy maltodextrin and microcrystalline wax. (■) 35% Lunacera® P, (☆) 40% Lunacera® P, (●) 45% Lunacera® P and (▼) 30% Lunacera® M.

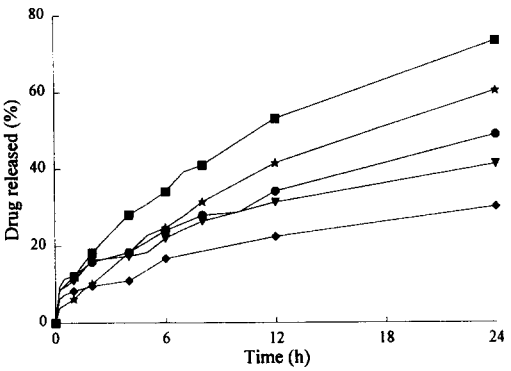


Fig. 5. Dissolution profiles of matrix pellets containing ibuprofen, waxy maltodextrin and Lunacera® M. The wax/maltodextrin ratio is 0.55 for the formulations containing up to 50% ibuprofen. The wax/maltodextrin ratio is 0.82 and 1.5 for formulations containing 60 and 70% ibuprofen, respectively. (■) 15% ibuprofen, (☆) 25% ibuprofen, (●) 50% ibuprofen, (▼) 60% ibuprofen and (◆) 70% ibuprofen.

pellets with an even more pronounced matrix effect but processing parameters were the limiting factors.

These results show that the wax/starch system offered a flexible matrix system allowing to produce pellets with the desired release profile depending on the wax type and concentration, on the starch concentration and on the swelling rate of the starches.

### 3.2. Drug loading study

Pellets with Lunacera® M and WMD were prepared with an increasing ibuprofen concentration. The ratio wax/maltodextrin was kept constant at 0.55 for formulations containing a maximum of 50% of drug. As a minimum amount of 18% wax was required to form pellets, the ratio could not be kept constant for the pellets prepared with 60 and 70% of ibuprofen, respectively. Fig. 5 shows the drug release profiles for WMD pellets and indicates that the ibuprofen release decreased with an increasing drug concentration. The decrease of ibuprofen release at higher drug concentrations is due to a decrease in starch content (from 55 to 12% (w/w) for the formulations containing 15 and 70% of ibuprofen, respectively). This results in a reduction of the hydrophilic pathways for the water molecules to have access to the drug crystals inside the pellet. The same phenomenon was observed by Adeyeye and Price, 1994 and indicates that the pore diffusion played a role in the drug release mechanism. This was confirmed by a shift in the pore size analysis before and after drug release as the pore size distribution shifted to larger pores after dissolution for all samples tested (Table 1). The drug release mechanism will probably be due to a combination of pore and matrix diffusion as the part of the ibuprofen that dissolved in the wax during pellet production can diffuse through the wax, while the remaining part is suspended in the wax and will be dissolved in the water penetrating through the pores.

### 3.3. Drug type study

The wax/starch matrix system was also applied to other types of drugs, ibuprofen was substituted by sodium salicylate, benzoic acid, sodium benzoate and chloroquine phosphate. All formulations containing sodium salicylate exhibited an initial burst release followed by a block of the drug release. A formulation containing WMD and 35% Lunacera® M released 25 and 28% of sodium salicylate after 4 and 24 h, respectively.

Table 1

| Formulation (w/w/w) | Porosity Before dissolution | After dissolution |
|---|---|---|
| Ibuprofen/PMD/Lunacera P (15/50/35) | 21.3 | 52.7 |
| Ibuprofen/PMD/Lunacera M (15/50/35) | 29.5 | 54.3 |
| Ibuprofen/DDWCS/Lunacera P (15/40/45) | 9.5 | 56.9 |
| Ibuprofen/WMD/Lunacera M (50/32/18) | 8.8 | 33.4 |
| Ibuprofen/WMD/Lunacera M (70/12/18) | 7.4 | 14.5 |

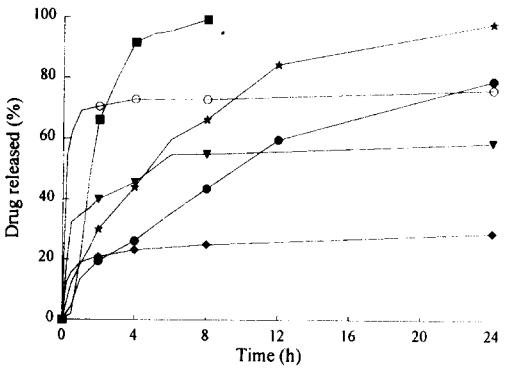


Fig. 6. Dissolution profiles of matrix pellets containing 27% Lunacera® M, 48% WMD and (■) 25% chloroquine phosphate, (☆) 25% benzoic acid, (●) 25% ibuprofen, (▼) 25% sodium benzoate. Dissolution profiles of matrix pellets containing 15% sodium salicylate, 35% Lunacera® M, (●) 50% DDCS and (◆) 50% WMD.

The extend of the burst effect was a function of the type and the concentration of the wax and the starch product. Even the DDCS pellets did not completely release the sodium salicylate although the pellets disintegrated into smaller fragments (Fig. 6). The same phenomenon was seen when using formulations containing 25% (w/w) benzoic acid or sodium benzoate; a progressive release of the lipophilic benzoic acid but a block of the sodium benzoate release after an initial burst release (Fig. 6). The reason for this block in release remained unclear. A possible cause could be an interaction between the carboxylate function of the salicylate and the benzoate molecule and the starch product. Substituting the anionic sodium salicylate by the cationic chloroquine phosphate gave a formulation which gradually released all chloroquine phosphate (Fig. 6).

Research is ongoing in relation to the robustness of the system and the bioavailability of the pellets.

## 4. Conclusion

The combination of microcrystalline waxes and pregelatinized starches or maltodextrins is a flexible system for the production of matrix pellets, even with a high drug concentration. Drug release could be modelled by varying the type and the concentration of the wax and the starch.

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