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PROLONGED RELEASE MATRIX PELLETS PREPARED BY MELT PELLETIZATION
II. HYDROPHOBIC SUBSTANCES AS MELTABLE BINDERS

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ABSTRACT

12 meltable substances were studied with respect to their ability to form prolonged release pellets in a melt pelletization process using a laboratory scale high shear mixer. It was found that few substances were able to pelletize a formulation with 12.5% m/m paracetamol and 87.5% m/m calcium hydrogen phosphate. Favourable technical features of glyceryl monostearate were combined with release prolonging features of more hydrophobic substances. Pellets prepared with combinations of glyceryl monostearate and microcrystalline wax demonstrated the slowest release. The release of drug could be varied within wide limits by varying the composition of the binder phase.

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INTRODUCTION

Polyethyleneglycols (PEG's) have been used as binders for melt pelletization in a high shear mixer, but they are considered unfit for prolonged release formulations because of their hydrophilic nature. Coating of PEG-based pellets with a release controlling membrane may be problematic because of the possible interaction between the PEG and the polymer film [1]. A number of hydrophobic meltable substances has been used in the field of prolonged release formulation of oral solid dosage forms, matrix tablets in particular. Fatty acids, fatty alcohols, natural waxes, and glycerides have been used, primarily [2].

So far, no systematic investigations on the applicability of such substances as binders in a melt pelletization process have been reported, only preparation of *granules* has been reported earlier [3,4]. The purpose of the present work was to study a number of meltable substances in order to assess the possibility of making pellets with prolonged release properties by a simple melt pelletization process in a high shear mixer. Solvents and release controlling film coating should not be applied.

The substances investigated as binders were selected on the basis of the following criteria. Primarily, melting should occur in the interval from 45 °C - 100 °C, because lower melting points were anticipated to cause stability problems during storage and higher melting points were considered inexpedient from a manufacturing point of view. Next, water solubility should be very low in order to prevent rapid release of the drug substance. Finally, the substance should be chemically inert, non toxic, cheap, and preferably supplied as powder or flakes.

MATERIALS

Calcium hydrogen phosphate and paracetamol were used in the qualities previously described [5,6]. The mean particle size by volume was 11 μm and 19 μm, respectively. The melting intervals of the investigated meltable substances are listed in Table 1.

METHODS

Density:

Densities in the solid state were determined with a Beckman 930 air comparison pycnometer, while densities of molten binders were determined after storage of 20-30 g of binder in a 50 ml measuring glass at 80 °C, 90 °C,and 100 °C for at least 48 hours before reading the volume occupied by the liquified binder (Table 2).

Viscosity:

Viscosities of molten binders were determined with a Haake Rv12 viscosimeter (Haake, BRD) with the MV IIk spindle (128 rpm) and the MVI cup at 60 °C, 70 °C, 80 °C, 90 °C, and 100 °C.

Dissolution:

The release of paracetamol from the 710 - 1000 μm pellet fractions in simulated gastric fluid (USP, no enzymes) was measured. Basket rotational speed was 150 rpm, and paracetamol was determined spectrophotometrically at λ = 240 -244 nm. For products similar to the present ones Thomsen et al [5,6] found high reproducibility of the inter batch as well as the intra batch measurements of release profiles.

TABLE 1

Melting intervals of the substances investigated

The melting intervals were determined with a Perkin-Elmer DSC 7 Differential Scanning Calorimeter (Perkin Elmer Corp CT, USA) with a heating rate of 10°C/min and 50 μl aluminium pans.

Substances:	**melting interval °C**
Glycerol monostearate 40-50 Ph.Eur. (Grinsted A/S)	53-61
Glyceryl palmito-stearate (Precirol ATO5, Gattefossé)	48-56
Glyceryl stearate (Precirol WL2155, Gattefossé)	54-63
Glyceryl behenate NF XVII (Compritol 888, Gattefossé)	67-72
Hydrogenated castor oil NF XVII (Cutina HR, Henkel)	62-86
Cetyl palmitate (Precifac, Gattefossé)	47-50
Beeswax Ph.Eur.	56-60
Carnauba wax Ph.Eur.	75-83
Stearic acid Ph.Eur	55-59
Stearyl alcohol Ph.Eur.	56-60
Microcrystalline wax NF XVII (Petrolite 195, Petrolite Inc.)	60-90
Gelucire 50/02 (Gattefossé)	41-51

TABLE 2

Densities (g/cm^3) of the solid binders at room temperature, and of the molten binders at 80 °C, 90 °C,and 100 °C.

	room temperature	80 °C	90 °C	100 °C
Glyceryl monostearate	1.03	0.89	0.88	0.88
Precirol ATO5	0.99	0.87	0.87	0.86
Precirol WL2155	0.99	0.87	0.86	0.86
Compritol 888	0.99	0.86	0.85	0.85
Cutina HR	1.04	0.92	0.92	0.92
Precifac	0.95	0.82	0.81	0.80
Beeswax	0.96	0.82	0.82	0.81
Carnauba wax	1.00	-	0.84	0.83
Stearic acid	0.99	0.84	0.84	0.84
Stearyl alcohol	0.92	0.80	0.80	0.80
Petrolite 195	0.93	-	-	0.79
Gelucire 50/02	1.00	0.89	0.88	0.87

Equipment:

The pelletization equipment, a Pellmix PI 1/8, has been described in earlier reports [5,7,8]. Thomsen et al [5,6] found a high reproducibility of the pelletization process.

Formulations

In the study of the pelletization capability the following composition was used:

Paracetamol	90 g
Calcium hydrogen phosphate	510 g
Binder	21.5% v/m

For formulations with a binder ***mixture*** one half of the binder volume was glyceryl monostearate, and the other half the volume of the binder investigated. The binder content of 21.5% v/m was chosen because this level allowed estimation of the pelletization capability of the major part of the substances.

In the study of the effects of binder content and binder phase composition, glycerol monostearate and Petrolite 195 were used and it appeared that for these binders in particular, it was expedient to apply higher binder contents. The composition of these formulations are presented in Table 3:

TABLE 3

Formulations used for the investigation of binder composition and binder content. GMS : glyceryl monostearate, P 195: Petrolite 195. Binder content 23.0% v/m

	Binder composition (volume ratio)					
	GMS	GMS/ P 195 7:1	GMS/ P 195 3:1	GMS/ P 195 1:1	GMS/ P 195 1:3	GMS/ P 195 1:7
Paracetamol	120 g	120 g	120 g	120 g	120 g	120 g
Calcium hydrogen phosphate	680 g	680 g	680 g	680 g	680 g	680 g
GMS	162 g	141.7 g	138.0 g	81.0 g	40.5 g	20.2 g
P 195	0 g	18.2 g	36.4 g	72.7 g	109.2 g	127.2

The GMS/P 195 1:1 formulation was run with binder contents of 22.5% v/m and 23.5% v/m also. (All calculations of amounts of binder were based on densities at 100 °C (cf. Table 2)).

Pelletization procedure, pelletization capability study

Two jacket temperatures were chosen because the jacket temperature should not differ substantially from the melting interval of the binder as deposition of the mass on the walls of the mixer is unwanted [5]. The manufacture of products with Cutina HR, Petrolite 195 and carnauba wax was made with a jacket temperature of approx. 90 °C. After the product temperature reached 90 °C the impeller speed was lowered from 1200 rpm to 500 rpm, and the products were processed for 5 minutes whereafter the impeller speed was lowered to 400 rpm, and the products were processed for additionally 6 minutes. The products were discharged, spread in thin layers on metal trays and allowed to cool for at least 20 minutes. The manufacture of formulations with the other binders was made with a jacket temperature of approx. 75 °C, and the impeller speed was lowered from 1200 rpm when the product temperatures reached 80 °C. The remaining part of the process was identical to the last part of the process described above.

Pelletization procedure, binder composition and binder content study

The jacket temperature was approx. 85 °C, and the experiments were started at an impeller speed of 1200 rpm. After the product temperature reached 90 °C, the impeller speed was lowered to 500 rpm. After 5 minutes of massing at 500 rpm the machine was stopped, and the lid was dismounted. After one minute, massing was continued for 4 minutes, and the machine was stopped again. The products were discharged onto a 26 x 28 cm plastic tray and allowed

to cool for 4 minutes before they were transferred to the mixer and run for one additional minute. Finally, the mixer was emptied and the products were spread in thin layers onto metal trays allowing the products to cool for at least 20 minutes. Thus, the total massing time was 10 minutes. This special procedure was chosen on basis of experience obtained with the effects of product temperature during pelletization (cf. ref. 5 and 6).

RESULTS AND DISCUSSION

The pelletization capability

Few of the substances investigated possessed adequate pelletization capability directly (Table 4). For the rest of the substances tested it could be observed that the mass became electrostatically charged, that the major part of the mass adhered to the wall of the bowl, and that pelletization did not occur. The partly hydrophilic glyceryl monostearate (HLB: 3-4) was in fact the only substance which showed pronounced potential as a meltable binder. Melt pelletization in a high shear mixer with meltable substances like the present hydrophobic substances has not been described in the literature. Only melt granulation [3,4], and an unsuccessful attempt to pelletize have been reported [9]. This may indicate that the performance of such substances is highly dependent on process - and product variables. In particular, it is noteworthy that the mixers previously used were not lined with polytetrafluoroethylene on the walls and bottom of the mixing bowl as is the Pellmix PI 1/8 used here.

The products made with Gelucire 50/02 and a combination of glyceryl monostearate and stearic acid demanded less binder to pelletize. No explanation of these findings was found.

TABLE 4

Pelletization capability of meltable substances (binder content 21.5% v/m).

Binder	Able to pelletize alone.	Able to pelletize in a (1:1) combination with glyceryl monostearate.
Glyceryl monostearate	+	
Precirol ATO 5	+	+
Precirol WL 2155	-	+
Compritol 888	-	+
Cutina HR	+[1]	+
Precifac	-	+[1]
Beeswax	-	+[1]
Carnauba wax	-	+
Stearic acid	-	+[2]
Stearyl alcohol	-	+[1]
Petrolite 195	-	+
Gelucire 50/02	+[3]	+[1]

[1]: Necessary to scrape down deposits when impeller speed was lowered to 500 rpm.

[2]: Binder content was 19.5 % v/m

[3]: Binder content was 20.5 % v/m

TABLE 5

Dynamic viscosity in mPa·s of a selection of molten binders.

	60 °C	70 °C	80 °C	90 °C	100 °C
Glyceryl monostearate	49	36	26	21	-
Precirol ATO 5	33	26	20	17	-
Precifac	10	8	8	8	-
Beeswax	-	22	18	15	-
Carnauba wax	-	-	-	43	-
Stearic acid	-	11	11	10	-
Stearyl alcohol	-	10	8	8	-
Petrolite 195	-	-	-	-	17
PEG 3000	374	282	213	166	-
PEG 6000	-	-	895	682	-

Due to the screening nature of the experiments a definite optimization of each formulation was not conducted in the pelletization capability study.

Viscosity of the molten binders

Differences in the performance of PEG 3000 and PEG 6000 as molten binders have been ascribed to different viscosities in the molten state [10]. Viscosities of a selection of the binders used in the present experiments are presented below in Table 5. Substances representing different functional groups were selected and measured.

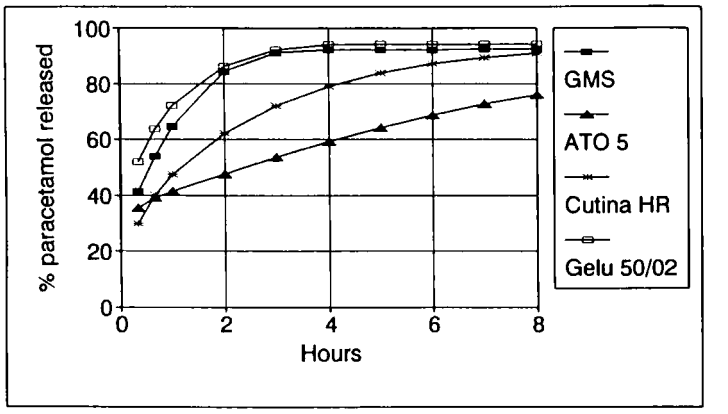

Figure 1 Release of paracetamol from pellets made with binders able to pelletize directly. Key: **GMS**: glyceryl monostearate, **ATO 5**: Precirol ATO 5, **Gelu 50/02**: Gelucire 50/02

Only small differences in viscosity could be observed among the hydrophobic binders. The viscosity of PEG 3000 and PEG 6000 was considerably higher. Both PEG's are known to be able to pelletize despite the large difference in viscosity. It is concluded that the different pelletization capabilities of the hydrophobic binders (cf. Table 4) could not be attributed to differencies in viscosity.

Assessment of drug release from products with one meltable binder

Although glyceryl monostearate was applicable as binder under the present circumstances the drug was leached out very fast. Also the other three products prepared with binders able to pelletize directly (cf. Table 4) showed relatively fast release of the drug as shown in Figure 1.

Effect on the release of combining meltable binders

Being aware of the partly hydrophilic nature of glyceryl monostearate it was obvious to test whether it was possible to combine the

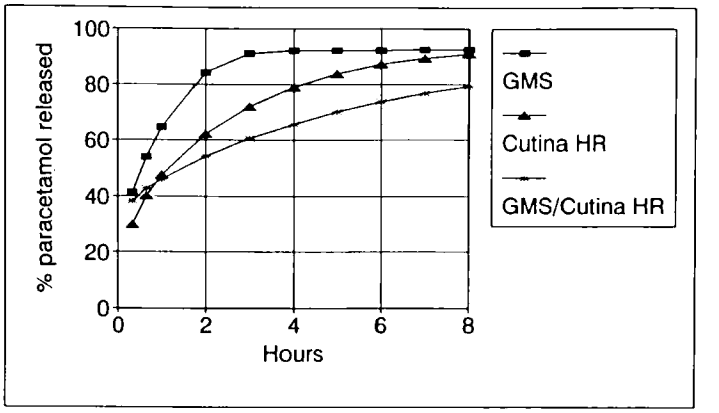

Figure 2 Release of paracetamol from pellets made with single binders and combination of binders. Key: **GMS**: glyceryl monostearate, **GMS/-Cutina HR**: glyceryl monostearate + Cutina HR.

favorable technical features of glyceryl monostearate with the hydrophobic nature of other substances. Initially, combinations of glyceryl monostearate with Cutina HR were investigated (Figure 2). It was generally assumed that volumes of the molten binders were additive. It was observed that combinations of glyceryl monostearate and Cutina HR could in fact prolong the release to a higher extent than could the two substances when used alone. It was seen that the presence of glyceryl monostearate facilitated a harmonic ropelike and regular movement of the mass during pelletization and that deposits and electrostatic charging were absent. It is believed that the regular movement of the mass lead to a more homogeneous embedding of the drug crystals in the lipophilic Cutina HR. Next, combinations of glyceryl monostearate with more hydrophobic compounds were investigated.

Effect of fatty acid chain length on release

In Figure 3 the effect of fatty acid chain length on release is shown. The fatty acid chain length increases from Precirol ATO 5,

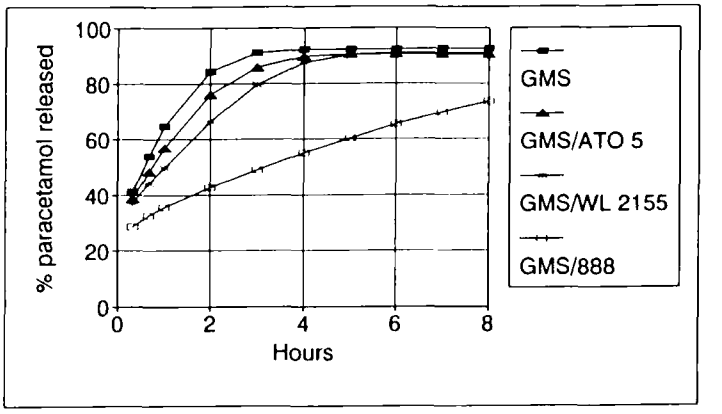

Figure 3 Effect of fatty acid chain length on the release of paracetamol. Key: **GMS**: glyceryl monosterate, **ATO 5**: Precirol ATO 5, **WL 2155**: Precirol WL 2155, **888**: Compritol 888.

which is glyceryl palmito-stearate, over Precirol WL 2155 which is glyceryl tristearate, to Compritol 888 which is glyceryl tribehenate. As expected, application of binder combinations with long chain triacyl glycerols demonstrated the most extensive prolonging of the drug release. The results were in good agreement with reports on application of triacyl glycerols in prolonged release formulations [11,12]. The effect of fatty acid chain length on release from compressed physical mixtures was studied by Shaikh et al [12] who found that increasing fatty acid chain length decreased the release rate.

Combinations with waxes.

Naturally occurring waxes have been used extensively as release prolonging excipients [2,13,14]. In Figure 4 the effect of application of waxes as molten binders is shown. Precifac is cetyl

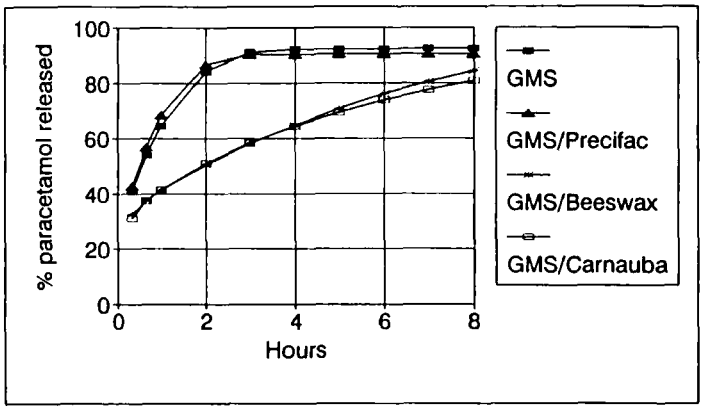

Figure 4 Effects on paracetamol release of combining of glyceryl monostearate (**GMS**) with waxes.

palmitate. Although beeswax and carnauba wax have different melting points superimposable release profiles characterized the products made with combinations of glyceryl monostearate with these natural waxes

Combinations with a fatty acid and the corresponding alcohol.

Application of a fatty acid (stearic acid) was compared with the use of the corresponding fatty alcohol (stearyl alcohol) as shown in Figure 5. It should be noted, however, that the optimal binder amount was significantly lower for the glyceryl monostearate/stearic acid product. As drug release from matrix systems is known to decrease with increasing amount of hydrophobic matrix forming material [15,16] it was not surprising that the product containing stearic acid demonstrated slightly faster release than the product made with stearyl alcohol. For the time being, it cannot be explained why the optimum binder volume differed as much as was the case. Probably wetting of the solid material by the molten binder is involved.

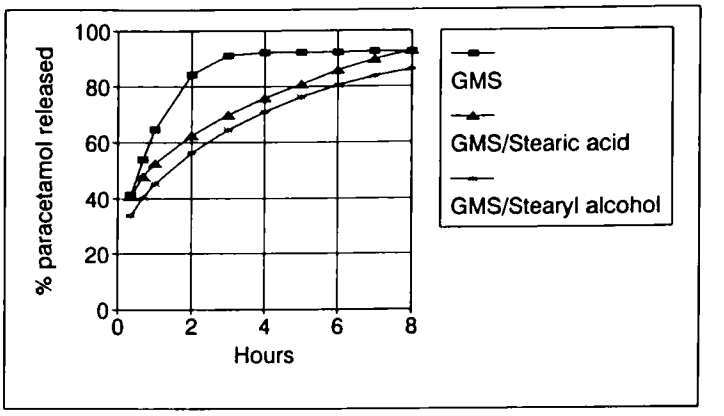

Figure 5 Effects on paracetamol release of combining a fatty acid and its corresponding alcohol. Key: **GMS/Stearic acid** : Combination with stearic acid, binder content 19.5% v/m. **GMS/Stearyl alcohol** : Combination with stearyl alcohol, binder content 21.5% v/m.

Combination with microcrystalline wax.

Finally, the applicability of microcrystalline wax was investigated. As long chain hydrocarbons are inert with respect to enzymatic cleavage in the gastro-intestinal tract, and the formulation with combination of such a compound and glyceryl monostearate showed prolonged release in particular, it is concluded that combination of a long chain hydrocarbon and glyceryl monostearate is specially suitable as binder for the preparation of prolonged release pellets by means of a melt pelletization process (Figure 6).

The effects of binder content and binder composition.

The effects of binder content and binder composition were investigated by means of the formulations listed in Table 3 (Figure 7). These formulations were prepared under process conditions found to be favorable for these formulations in particular (cf. ref. 5). The binder content was varied ± 0.5% v/m from what was considered the

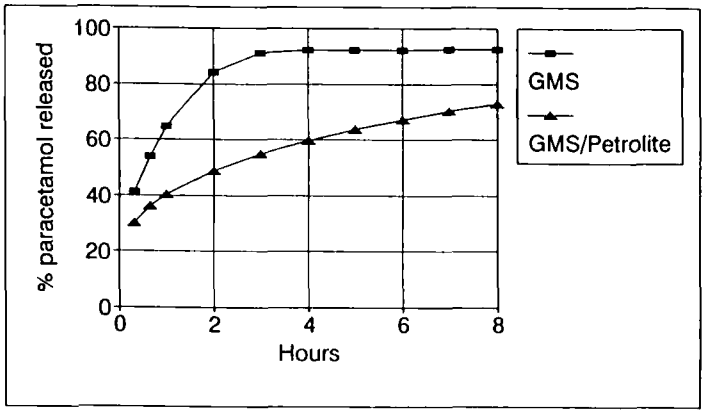

Figure 6 Key: **GMS/Petrolite**: Combination with Petrolite P 195

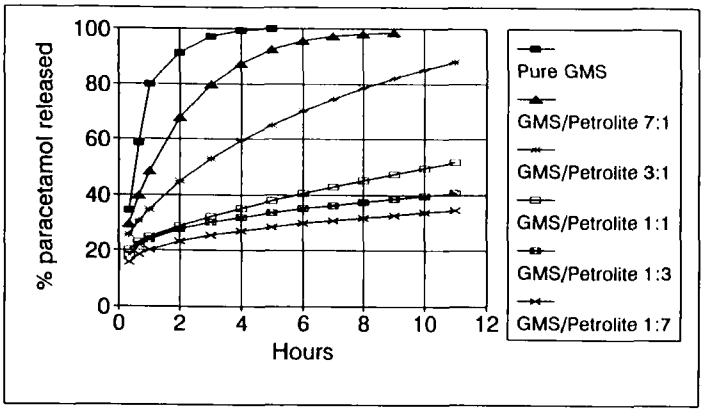

Figure 7 Effect of binder composition on drug release. Key: **GMS:** glyceryl monostearate, **Petrolite** : Petrolite P 195.

optimum value (23.0% v/m) and only minor differences could be observed between the three products. The release properties of the three products were almost identical. Formulations with larger variations of the binder content were not studied systematically, as the performance of such formulations in preliminary experiments appeared to be poor from a technical point of view.

As shown in Figure 7 it was observed that the release rate decreased as the relative amount of the hydrophobic Petrolite P 195 increased, and very slow release of paracetamol was observed when the amount of glyceryl monostearate was minimized. Thus it was concluded that the release of drug from the system investigated could be varied within wide limits by adjusting the binder phase composition. Due to electrostatic charging of the mass and adhesion to the walls of the mixer bowl, it was not possible to pelletize products with a Petrolite P 195 content of more than 7 times the glyceryl monostearate content. Note that Figure 7 are not to be compared directly to Figure 6 because process conditions and binder content are different for the two product groups.

CONCLUSIONS

In the present report a number of hydrophobic meltable substances have been studied with respect to their potentials as meltable binders and release prolonging agents. Few substances demonstrated applicability as binders, and glyceryl monostearate appeared to be the most suitable substance. It was observed that the presence of glyceryl monostearate in a binder combination enabled the pelletization process to proceed in a controlled, regular and harmonic way, while the presence of more hydrophobic substances in the binder mixture ensured constitutive prolonging of the release. Whenever a choice of binder has to be made it appears from the present investigations that the optimum binder is a *mixture* of substances such as glyceryl monostearate and microcrystalline wax. The release of drug from the system investigated could be varied within wide limits by varying the composition of the binder phase.

The exact physicochemical explanation of the fact that some meltable substances were able to pelletize while others were not are not known for the time beeing.

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