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Research paper

Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system

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Abstract

The aim of the study was to provide a controlled release system, which could be used for the oral administration of highly water-insoluble drugs. Pellets have been prepared by extrusion/spheronization containing two model drugs (methyl and propyl parabens) of low water solubility. One type of pellets contained the drugs mixed with lactose and microcrystalline cellulose (MCC) and the other types of pellets contained the model drugs dissolved in a self-emulsifying system (4.8%) consisting of equal parts of mono-diglycerides and polysorbate 80 and MCC. Pellets of all types in the same size fraction (1.4–2.0 mm) were coated to different levels of weight gain, with ethylcellulose, talc and glycerol. A sample of pellets containing methyl parabens in the self-emulsifying system was pre-coated with a film of hydroxypropylmethyl cellulose from an aqueous solution and then coated as above. Dissolution experiments established that the presence of the self-emulsifying system enhanced the drug release of both model drugs and that the film coating considerably reduced the drug release from pellets made with just water, lactose and MCC. The coating reduced the drug release from the pellets containing the self-emulsifying system to a lesser extent but in relation to the quantity of coat applied to the pellets. The application of a sub-coating of hydroxypropylmethyl cellulose was able to reduce the release rate of methyl parabens self-emulsifying system ethyl cellulose coated pellets. Thus, the formulation approach offers the possibility of formulating and controlling the *in vitro* release of water-insoluble drugs from solid oral dosage forms.

Keywords: Controlled drug release; Film coating; Pellets; Self-emulsifying systems; Water-insoluble drugs

1. Introduction

In a previous paper, it has been shown that it is possible to prepare pellets into which a significant quantity of a self-emulsifying system had been incorporated to provide a solid dosage form [1]. It was later established that, if a sparingly water-soluble drug (progesterone) was dissolved in the self-emulsifying system and formed into pellets, the preparation was equally bioequivalent in dogs, to the same drug self-emulsifying system administered as a liquid in gelatin capsules. Both these formulations were far more bioavailable than an aqueous suspension of the micronised drug [2]. Thus, it should be possible to develop solid dosage forms for self-emulsifying systems of drugs, which have low water solubility, provided that they can be dissolved in a self-emulsifying system (SES). The improved absorption may be problematic if it results in frequent dosing where a once a day dosage is being sought. The composition of the core of pellets has been shown to have an important influence on the drug release from coated pellets [3] and therefore it could be anticipated that, the pellets with and without SES could behave differently in terms of dissolution performance. The question arises therefore, do conventional coating techniques provide a suitable method of providing a controlled release of the drug when the water-insoluble

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drug is in a solution within a SES within the pellets. Also, does the presence of the SES influence the ability of the polymer film to control drug diffusion through the film? In other words, is the film still the rate-controlling part of the system? Such formulations would offer considerable advantages as pellets are readily coated, having the minimum surface to volume ratio and no sharp edges. They can be readily filled into hard gelatin capsules, provided their shape does not depart appreciably from the spherical form [4]. Multiple particulate systems are also claimed to offer advantages of improved reproducibility of absorption compared to single unit tablet dosage forms [5–7]and they certainly avoid the possibility of causing obstruction of the gastro-intestinal tract by single unit systems.

2. Materials and methods

2.1. Materials

The model drugs were methyl (M) and propyl parabens (P) of PhEur. grade. They had number average particle diameter of 26.57 ± 19.72 and 24.81 ± 14.26 μm, respectively, and they were obtained from Nipa Laboratories, Pontypridd, UK. The microcrystalline cellulose (MCC) and α lactose monohydrate were of PhEur. grade supplied as Avicel PH101 (FMC Corp. Little Island, Cork, Ireland) and Sorbolac 400 (Meggle GmbH, Wasserburg, Germany) and had number average particle size of 54.80 ± 0.54 and 16.80 ± 0.32 μm, respectively. The self-emulsifying system (SES) was prepared by melting a mixture of mono- and diglycerides of capric and caprylic acids (Mono- and Diglycerides, US NF) supplied as Imwitor 742 (Condea, Chemie GmbH., Witten, Germany) at 50 °C and adding to an equal weight of Polyoxyethylene Sorbitan monooleate PhEur. supplied as Tween 80 (Surfachem, Ltd., Leeds, UK). The ethylcellulose was of PhEur. grade supplied as N100 by R W Unwin & Co. Ltd., Welwyn, UK. The talc, ethanol and glycerol were also of PhEur. grade and were supplied by Merck Ltd., Poole, Dorset, UK. The hydroxypropylmethyl cellulose was of PhEur. grade and was supplied as Methocel E6 by Colorcon Ltd., Dartford, UK. The water used in the preparation of the pellets and as the dissolution media was freshly purified water prepared by reverse osmosis (USF-Elga, Elga Ltd., High Wycombe, UK).

2.2. Methods

2.2.1. Preparation of drug self-emulsifying system (SES) solutions

Preliminary experiments established that a self-emulsifying system, which contained 4.8% of either model drug, could be diluted with water to give a final water content of 31.5% without resulting in the precipitation of either of the model drugs. The ability to be able to dilute with water was necessary because it has been shown that without water, pellets cannot be formed and that as the amount of water increases, the mechanical strength of the pellets increases [1]. Hence while a higher quantity of drug could be incorporated into the self-emulsifying system, it was precipitated by dilution with water. Too high a concentration of the self-emulsifying system would provide pellets, which were too soft to be able to be subjected to fluidization without deforming significantly during the coating process. Thus, 4.8% solutions of methyl (SESM) and propyl (SESP) parabens were prepared by adding the weighed quantity of the drugs to the pre-prepared self-emulsifying system, and stirring with a magnetic stirrer until all the solid had dissolved.

2.2.2. Preparation of pellets

The composition of the pellet is set out in Table 1.

To 55.5% by weight of MCC, 14% of water by weight was added and mixed intimately for 10 min with a planetary mixer (Kenwood Chef, Kenwood, Croydon, UK). To this damp mass, 30.5% of the drug containing self-emulsifying system was added and mixing continued for a further 10 min. Approximately 100 g of this wet mass was packed into the barrel of a ram extruder, which was fitted with a multi-hole (33 in number) die, each hole being 1 mm in diameter and 8 mm in length. A piston was inserted into the barrel and the system attached to a mechanical press (MX50, Lloyds Instruments, Warwash, Southampton, UK), which was activated to extrude at a ram speed of 200 mm/min. The extrudate was spheronised in 100 g quantities for 5 min at 1800 rpm on a 12.0 cm diameter crosshatched plate of a spheronizer (Caleva model 120, Caleva Process Solutions, Sturminster Newton, Dorset, UK). The resultant pellets were dried for 12 h at 30 °C in a fan-assisted hot air oven (Pickerston Instruments Ltd., Romford, UK).

A set of control pellets were prepared containing the same final % of the model drug, but this time, the other ingredients of the pellets were 50% of MCC and the remaining material being α-lactose monohydrate. This time the wet mass was extruded through a single-hole die of 1.5 mm diameter and 8 mm in length, at 200 mm/min. The extrudate was spheronised and dried by the same conditions as those containing the self-emulsifying system.

Each set of pellets was sieved with a set of $\sqrt{2}$ British Standard Sieves attached to a sieve shaker (Endecott, London, UK) to provide sieve fractions. The pellets containing the drug in the self-emulsifying system produced approximately 80% of the pellets in the size fraction

Table 1
Composition of the pellets

Lactose pellets		Drug/SES		SES pellets	
Ingredients	%	SES	%	Ingredients	%
Parabens	1.7	Parabens	4.8	Drug/SES	30.5
MCC	31.6	SES	95.2	MCC	55.5
Lactose	30.0			Water	14.0
Water	36.7				

1.40–2.00 mm, while those containing the model drug, lactose and MCC produced approximately 85% of the pellets in this same size fraction. The value of the shape factor e_R [8], for all the pellet formulations, was 0.6 ± 0.05.

2.2.3. Coating of pellets

Two coating systems were employed. The first consisted of 3% ethyl cellulose, 2% talc, and 0.6% glycerol dissolved in 96% ethanol/water. The second used the same final coat, but the pellets were pre-coated with a 6% aqueous solution of hydroxypropylmethyl cellulose plus 2% talc. The coating process was undertaken with 40.0 g of pellets placed into a fluid bed coater (Aeromatic Strea-1, ACM Machinery, Tadley, UK) fitted with a bottom pneumatic spray nozzle. For the ethyl cellulose coat, the inlet air temperature was 54 °C, the outlet air temperature was 46 °C, the nozzle outlet was 0.5 mm in diameter, the atomizing air pressure ranged between 0.8 and 0.9 bar and the solution was sprayed at an initial pumping rate of 0.9 g/min gradually increasing to 1.5 g/min as the coating process proceeded. The coating process was continued for sufficient time to give coating levels in terms of weight gain of 7.5%, 12.0%, 15.0% and 20%.

For a set of pellets containing methyl parabens in the self-emulsifying system a sub-coating was applied. This was achieved with an inlet air temperature of 60 °C, outlet air temperature of 46 °C, while the other conditions were the same as those for the outer coat. The coating process provided a 5% increase in weight, to which was applied a further top coating of ethyl cellulose of 7.5% and 20.0% weight gain.

2.2.4. In vitro dissolution

The dissolution test was undertaken with the USP Method II, paddle method (Caleva ST8, Caleva Process Solutions Stourminster Newton, UK), in 1000 ml of deaerated purified water, at 37 °C with a paddle speed of 100 rpm. Samples for analysis were collected at appropriate time intervals through filters and the quantity of drug established by UV spectrophotometer (Cary E3, Varian Inc., Walton on Thames, UK). The weight of pellets introduced into the dissolution test was adjusted to maintain a constant quantity of the model drug, allowing for the quantity of coating added. Irrespective of the quantity of coat, the quantity of drug contained in the pellets was such that sink conditions existed in the dissolution bath. Three vessels were used to test each pellet formulation.

3. Results and discussion

To be able to produce pellets of approximately the same diameter from all the systems, which retain the liquid self-emulsifying system within the pellets and those, which did not retain the liquid, i.e. simple water systems, it was found necessary to use a different die diameter. From the formulations containing the self-emulsifying systems a 1.0mm diameter die produced pellets predominately in the size fraction 1.40–2.00 mm.To reduce the extrusion pressures involved with such systems, a multi-hole die system was used. For the aqueous extrusion formulations, a 1.5 mm die was found to provide pellets predominately in the same size fraction at similar extrusion forces as the non-aqueous formulations. Preliminary experiments established that it was necessary to incorporate talc into the coating fluid to avoid the pellets becoming sticky and adhering to themselves or the side of the coater.

The ability of the formulation to enhance the dissolution of the model drugs is illustrated in Fig. 1 where the dissolution results for the uncoated pellets containing methyl or propyl parabens with and without the addition of the self-emulsifying system are compared. The enhancement is greater for the propyl parabens, which is about 10 times less water-soluble than the methyl (230 mg/L as opposed to 2500 mg/L [9].

The application of the ethyl cellulose coating to pellets containing methyl parabens, without the self-emulsifying system, clearly reduced the rate of dissolution, see Fig. 2. It can be observed that 7.5% weight gain had a significant effect and the 20% weight gain virtually inhibited drug release over the 6 h of the test period. The same response was observed with the pellets prepared containing propyl parabens, see Fig. 3. Here again the application of a 20% weight gain to the pellets formulated with lactose completely blocked the dissolution. The same coat thickness applied to pellet containing the self- emulsifying system still allowed some drug release. The retardation of the dissolution by the ethyl cellulose coating of the pellets containing the model drugs in the self-emulsifying system was not reduced to the same extent, see Figs. 4 and 5. To be able to provide a reduction in the drug release, the 20% weight gain coating is required. For an equivalent level of coating, there is a slightly lower release from the pellets containing the less water-soluble propyl parabens, but nowhere near as great as the tenfold difference in water solubility. When the methyl parabens model is considered, it is possible to achieve a similar release profile from the pellets either by

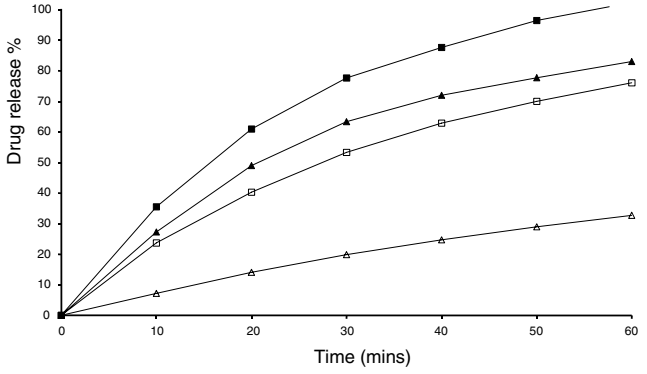

Fig. 1. Drug release from pellet formulations containing model drugs formulated with and without SES. Methyl parabens/lactose pellets □: methyl parabens SES pellets ■: propyl parabens/lactose pellets, ▲: proply parabens/SES pellets △.

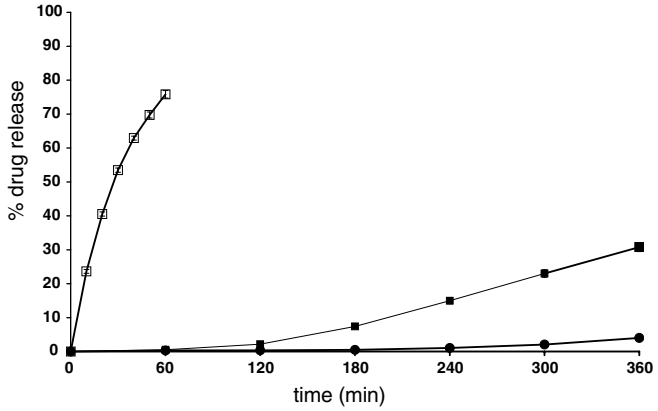

Fig. 2. Drug release from pellet formulations of methyl parabens containing lactose, uncoated □, and coated with 7.5 ■ and 20% ● weight gain of ethylcellulose.

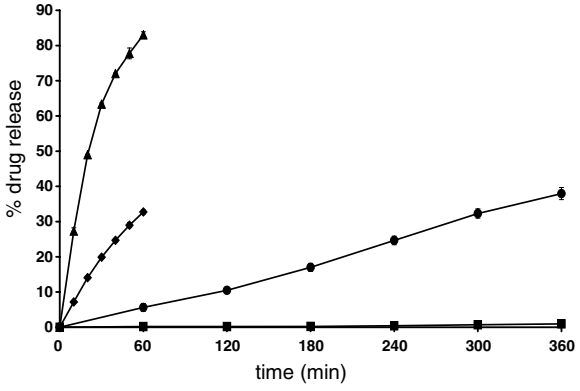

Fig. 3. Drug release from pellet formulations of propyl parabens and either lactose ◆, SES ▲ uncoated and ■ (lactose), 7 ● (SES), coated with 20% weight gain of ethylcellulose.

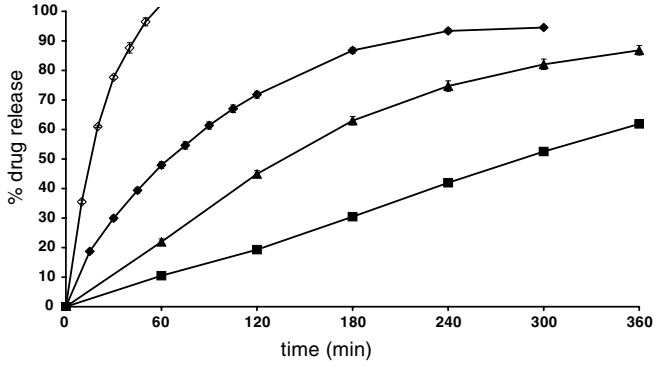

Fig. 4. Drug release from pellet formulations containing methyl parabens and SES uncoated ◇ and coated 7.5 ◆, 12 ▲ and 20% ■ weight gain of ethyl cellulose.

sub-coating the pellets with 5% of a water-soluble polymer, hydroxypropylmethyl cellulose and a 7.5% ethyl cellulose top coating, or by using a single layer coating with 20% of ethyl cellulose, see Fig. 6. There is the possibility that, with the drugs being in solution in the pellets containing the self-emulsifying system, it may be able to migrate into

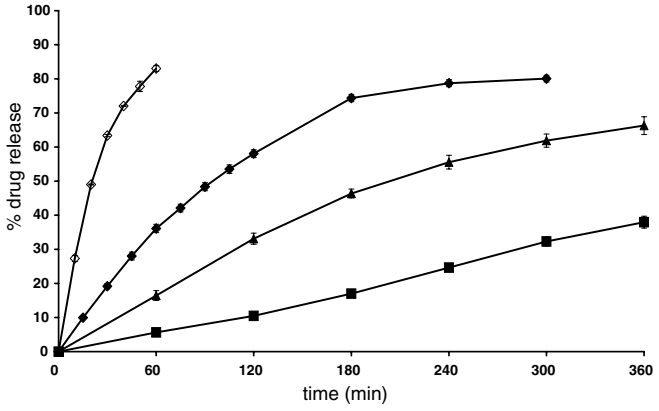

Fig. 5. Drug release from pellet formulations containing propyl parabens and SES uncoated ◇ and coated with 7.5 ◆, 12 ▲ and 20% ■ weight gain of ethyl cellulose.

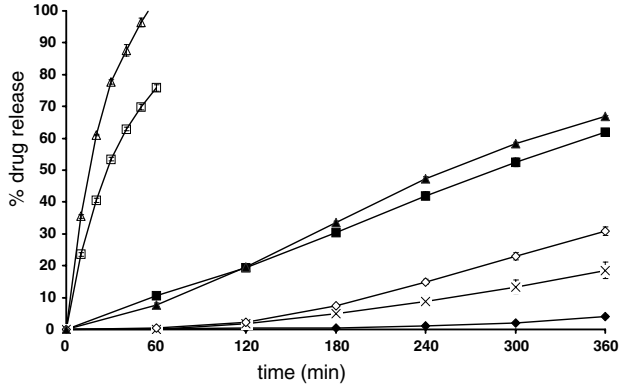

Fig. 6. Drug release from pellets containing methyl parabens/lactose, □; uncoated: coated with ◇ 7.5% and ◆ 20% weight gain ethyl cellulose: from pellets containing methyl parabens/SES, △ uncoated and coated with a sub-coat of hydroxypropylmethyl cellulose plus a coat of ▲ 7.5% and × 20% weight gain of ethyl cellulose: from pellets containing methyl parabens/SES coated with ■ 20% weight gain ethyl cellulose, without a subcoat.

the non-aqueous solvent of the ethyl cellulose coating system during the coating process. Attempts to identify this by testing the pellets with near infra-red analysis proved inconclusive. The presence of a water-soluble coat may be able to prevent this migration during the coating process. Alternatively, the subcoat may prevent the ingress of the polymer dispersion coat into the pellets.

4. Conclusion

The study has established that, it is possible to provide the control of the release of water-insoluble drugs from pellet formulations by incorporating them into self-emulsifying systems, which enhances their rate of release and then, by applying a water-insoluble polymer containing a water-soluble plasticiser and talc, reduce the rate of drug release. Changing the coat thickness and/or pre-coating the pellets

with a sub-coat of a water-soluble polymer can refine the control of the in vitro release of the drug from such pellets to provide a range of release rates. The quantity of coating required to reduce the drug release was greater than that for pellets, which did not contain SES systems.

This combined approach of a SES system to enhance the solubility, and then adding a polymer film to the pellet, allows an increased control of the drug release profile to match the biological requirements of such drugs.

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