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An observational study on the influence of solvent composition on the architecture of drug-layered pellets

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ABSTRACT

Pelletization for the manufacture of modified release multiparticulate drug delivery systems is often considered to be well defined and robust. However, small differences in formulation conditions can lead to surprising changes to the expected outcomes. We observed that extended release tramadol hydrochloride pellets, prepared by solution layering an ethanolic solution of drug on a non-pareil, resulted in highly unusual pellet architecture with deep indentations which prevented the application of a homogeneous outer coating of ethylcellulose and talc, and negatively influenced the desired modified release characteristics. Modification of outer coating thickness and process temperature showed no improvement in release characteristics. A solution to the problem was found in the incorporation of 10% v/v water into the ethanolic drug layering solution, resulting in the production of drug-loaded pellets with a smooth morphology which allowed the application of a coherent outer coating able to retard drug release. The surprising difference in pellet morphology between the two solvent drug layering systems may be attributed to differences in solvent evaporation rates. This demonstrates that established techniques are sometimes less straightforward than thought as small changes in formulation have significant effects on the resulting product in a way which is not always well understood.

1. Introduction

Pelletization is a process by which a drug and excipient mixture can be transformed into small, free flowing spherical units (Ghebre-Sellassie, 1989) for multiparticulate oral drug delivery. The uniform, spherical pellets demonstrate many advantages over the use of powders or granules, or over the use of single unit dosage forms, and hence have become widely used in the pharmaceutical industry. Sized between 100 and 2000 μm (Werner, 2006), pellets have a reduced surface area to volume ratio relative to powders; this means better flow and mixing properties and ultimately more reliable dosing. Increasingly relevant, with a need for better targeted dosage forms, is their ability to be modified and optimised in order to effectively control release of a drug from the dosage system (McConnell et al., 2008). With improved plasma profiles and decreased risk of dose dumping, pellets offer significant advantages over a modified release single unit system (Bechgaard and Nielson, 1978).

The manufacture of pellets is based on either one of two concepts; the production of a matrix pellet, in which the drug and excipients undergo direct pelletization, for example by extrusion spheronisation (Conine and Hadley, 1970; Reynolds, 1970; Basit et al., 1999), or alternatively the use of a non-pareil seed (a neutral starting core) as a base to which successive layers of drug are added (Nastruzzi et al., 2000; Sinchaipanid et al., 2004). Modified release coatings can then be applied to these drug loaded cores. It is the latter method which is the subject of this paper, specifically pelletization by a process of solution layering. Sugar spheres (non-pareil seeds) are often used as a core material (Jones, 1991) since their smooth surface provides the ideal base to build up successive layers of drug/excipient. Solution layering involves the spraying of an atomised drug solution onto the starting core, using simple spray coating technology. The droplets, once sprayed, come into contact with the core material, and spread out on the surface, and the solvent begins to evaporate forming a solid layer. Further layers are added until an optimum drug load is reached. The product can be further coated with various film coating materials.

As part of a larger study, attempts were made to prepare extended release tramadol hydrochloride pellets by solution layering. This seemingly straightforward formulation process yielded unexpected results, and we report these in this paper. Unusual pellet architecture was observed which prevented the application of a modified release coating. We were able to obviate this problem by the addition of a small amount of water to the spray coating solution, a simple step which had a significant influence on the pellet structure.

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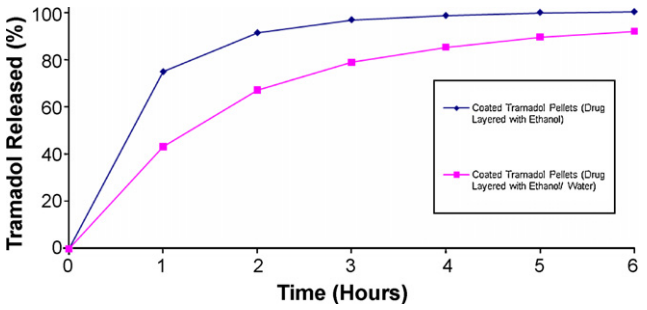

Fig. 1. Dissolution profiles of tramadol hydrochloride pellets, formed by solution drug layering with ethanol or ethanol/water (90:10), and coated with a talc/ethylcellulose modified release coating (coefficient of variation <5%).

2. Materials and methods

2.1. Materials

Ethylcellulose N7 was obtained from Hercules International Limited, Talc BP was supplied by Merck, and sugar spheres (500 μm) were from Hans G Werner GmbH and Co. Tramadol hydrochloride was from Cambrex Corporation (East Rutherford, NJ). All other reagents were analytical grade.

2.2. Solubility testing of tramadol hydrochloride

Tramadol hydrochloride was added in excess to ethanol (96%), or an ethanol/water mixture (90:10) ($n = 3$). These were shaken at 25 °C for 24 h. The suspension was centrifuged, and the supernatant removed, and diluted. The diluted supernatant was then assayed for tramadol hydrochloride, using UV-spectroscopy at a wavelength of 272 nm.

2.3. Surface tension measurements

Tramadol hydrochloride (16.7% w/v) was dissolved in ethanol or ethanol/water (90:10) at 25 °C. Surface tension measurements were calculated using the CAHN Dynamic Contact Angle Analyzer (DCA-312). Cover glasses were used applying the Wilhelmy plate method ($n = 3$).

2.4. Application of drug layer to sugar spheres

Tramadol hydrochloride (16.7% w/v) was dissolved in (a) ethanol (96%), (b) ethanol/water (90:10) or (c) water and sprayed onto sugar spheres using a Strea-1 bottom spray fluidized bed coater (Aeromatic AG, Bubendorf, Switzerland; inlet temperature of 60 °C, an outlet temperature of 38–42 °C, an atomizing air pressure of 1.8 bar and the fluid feed rate was 10 g/min). A batch size of 350 g was used. The water only system resulted in dissolution of the spheres, and was discontinued. This process was continued until drug loading of 80% w/w was achieved, at which point the pellets were dried in the spray coater for 5 min, and then sieved, with the 0.85–1.4 mm fraction retained. These were transferred onto trays, and dried in a fan oven at 45 °C for 1 h, and then overnight at ambient temperature. Each formulation was prepared 6 times.

2.5. Application of modified release coating to drug-layered sugar spheres

Ethylcellulose (0.8% w/v) was dissolved in ethanol, and mixed with talc (12% w/v), and mixed continuously throughout the spray coating process. The drug loaded sugar spheres (batch size 400 g) were spray coated with this suspension, to a weight gain of 22.5% w/w, using a Strea-1 bottom spray fluidized bed coater (inlet temperature of 60 °C, an outlet temperature of 40 °C, an atomizing air pressure of 1.5 bar and the fluid feed rate was 4 g/min).

2.6. Dissolution testing

Dissolution of the drug-layered pellets (immediate release) and the coated drug-layered pellets (modified release) was carried out using a USP type II automated dissolution apparatus (PTWS, Pharma Test, Hainburg, Germany). The dissolution medium was 0.1 M HCl (900 ml) at 37.0 ± 0.5 °C. The paddle rotational speed was 100 rpm. The tramadol hydrochloride release into the dissolution media was detected by UV-spectroscopy at a wavelength of 272 nm. Quantities of pellets were used so as to give 200 mg of tramadol hydrochloride per dissolution test, and each dissolution test was carried out 6 times.

2.7. Scanning electron microscopy

Samples of uncoated, and coated pellets, were adhered to SEM stubs using carbon discs, and were gold coated, using a EMITEC

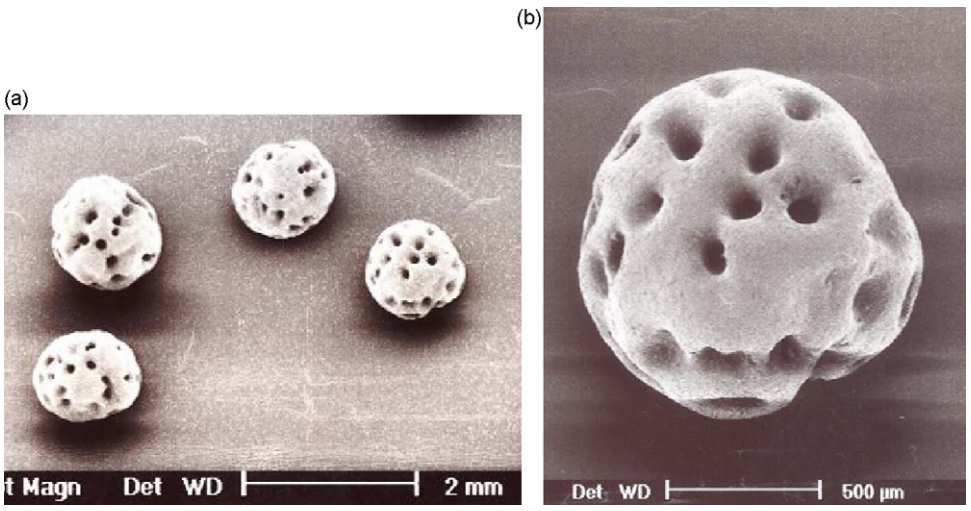

Fig. 2. Scanning electron micrographs of drug-layered pellets prepared by solution drug layering with ethanol (a: multiple pellets and b: close-up of one pellet).

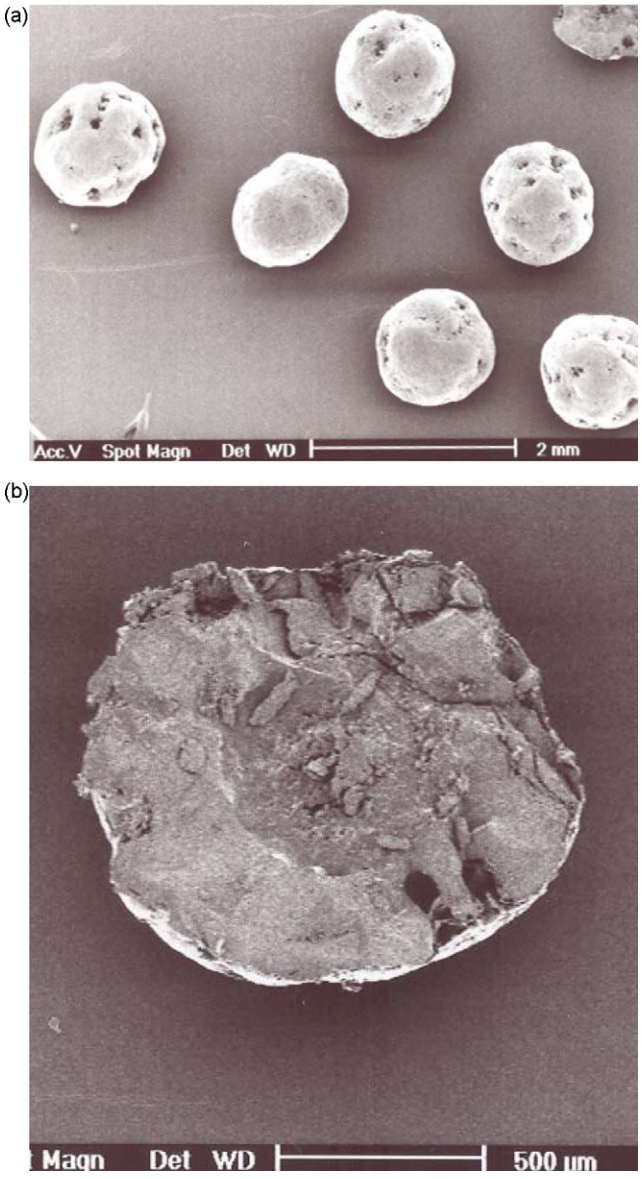

Fig. 3. Scanning electron micrograph of modified release coated drug-layered pellets prepared by solution layering with ethanol (a: multiple pellets and b: cross-section of one pellet).

K550 sputter coater for 3 min at 40 mA. After coating, the samples were transferred to a Philips XL20 Scanning Electron Microscope for imaging.

3. Results and discussion

The aim of this study is to report the observations from solution layering tramadol hydrochloride (tramadol) pellets using two different solvent systems. The solution layering process was used to add tramadol to a non-pareil pellet core, and ethylcellulose and talc were subsequently applied as a hydrophobic modified release coating to try to achieve a sustained drug release profile. The first pellet formulation involved the solution layering of tramadol onto sugar spheres using an ethanolic solution of the drug. These drug-layered pellets showed rapid tramadol release, with 100% of drug being released in less than 30 min (data not shown). The application of a hydrophobic coating (talc and ethylcellulose) to the pellets to convert them to a modified release pellet system was undertaken. However, the results indicated that the hydrophobic coating was unable to control drug release in aqueous conditions (Fig. 1). At 2 h, more than 90% of the drug had released into the dissolution medium. This problem was only explained when the pellets (before the addition of the outer layer of hydrophobic coating) were examined using scanning electron microscopy. The drug-layered pellets, solution layered using ethanol, have an unusual architecture (Fig. 2). Solution layering was expected to produce solid particles, rather than the striking, porous structures seen here. These pores are deep and smooth walled of similar size, and distributed throughout the drug layer and are responsible for an increase in surface area of the pellets. Fig. 3 reveals that the highly porous architecture prevented the application of a coherent outer coating; coated pellets had multiple areas where coating integrity was compromised and this accounts for the lack of extended release seen with these pellets. The presence of the pores, or any uneven morphology, also increases the surface area through which dissolution can occur (Porter and Ghebre-Sellassie, 1994). Similar trends were seen with porous microspheres (Wang and Wang, 2002) which have immediate release characteristics due to increased water ingress and increased effective surface area, in comparison to non-porous particles which show retarded drug release.

Common problems in the solution layering process stem from the surface moisture or drying rate, causing irregularities in drug deposition, attrition or agglomeration, although structures like those described here have not been reported before. In order to overcome this problem in the pellet production process, changes to the modified release coating process, such as lowering the process temperature, or increasing the talc/ethylcellulose coating

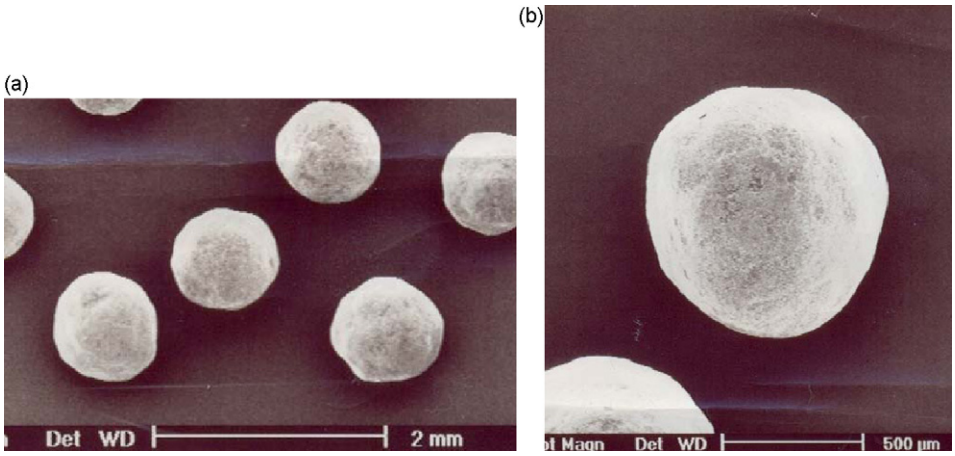

Fig. 4. Scanning electron micrographs of drug-layered pellets prepared by solution drug layering with ethanol/water (90:10) (a: multiple pellets and b: close-up of one pellet).

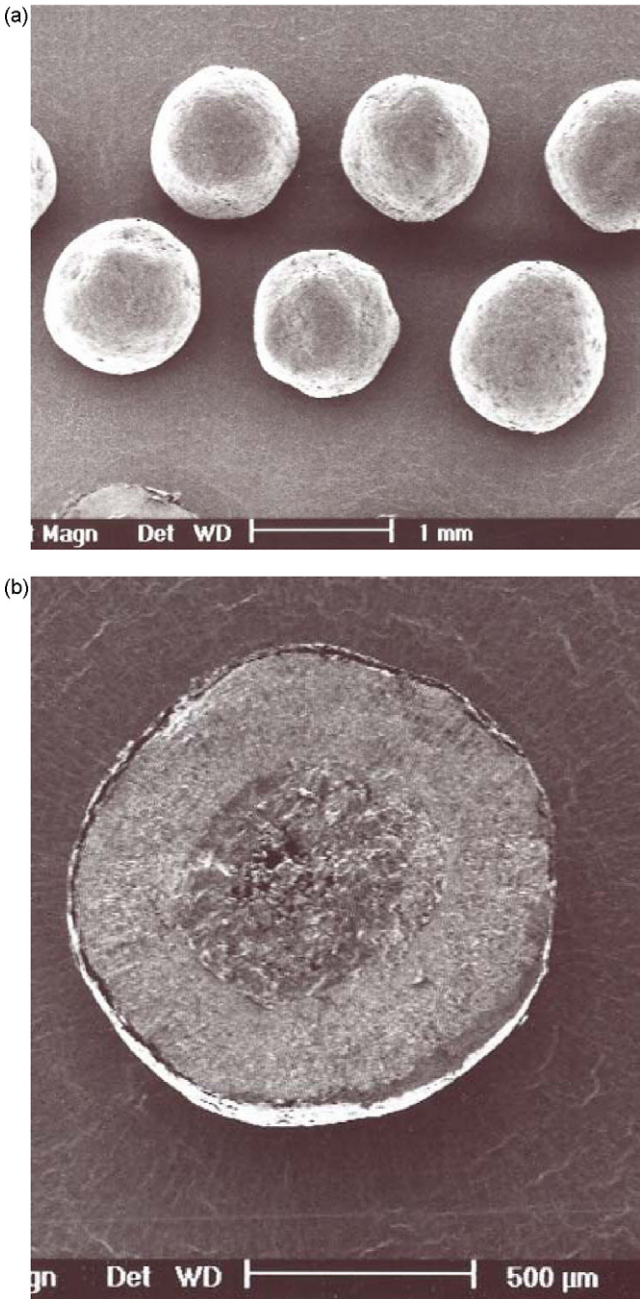

Fig. 5. Scanning electron micrographs of modified release coated drug-layered pellets prepared by solution layering with ethanol/water (90:10) (a: multiple pellets and b: cross-section of one pellet).

thickness were carried out. However, these produced no improvement on modified release (data not shown), nor did changes to the drug layering process (drug concentration or temperature). The choice of excipient was also considered as the use of binders in the solution layering process can help minimise the presence of cracks/fissures or delaminations (Jones, 1989). In preliminary investigations, binders (polyvinyl pyrrolidine and hydroxypropylmethylcellulose) were incorporated into the tramadol solution but this showed no improvement in the release characteristics. The key factor was determined to be the incorporation of water into the ethanolic solvent system.

Pellets prepared by drug layering with an ethanol/water mixture (90:10), and further coated with the talc/ethylcellulose modified release coating showed improved extended release characteristics. At 2 h approximately 65% of the drug was released (relative to more than 90% with the pellets prepared from ethanol alone) and 90% of drug released at 6 h (Fig. 1). These pellets are smooth, spherical and solid when examined under the electron microscope (Fig. 4) and allow the application of a smooth, unbroken outer coating (Fig. 5).

The reasons for the atypical morphology seen in uncoated pellets prepared with ethanol were unclear. There were differences in the solubility of tramadol in the two solvent systems (650 mg/ml in 90:10 mixture of ethanol/water and 467 mg/ml in ethanol) and the surface tensions of the tramadol in the solvent systems (24.5 dynes/cm in the 90:10 mixture of ethanol/water and 22.5 dynes/cm in ethanol) which may have caused differences in tramadol application and solvent removal. The pores exhibit smooth surfaces, suggesting that they may have formed during the drug layering process, when some moisture was still present in the system. They do not exhibit sharp or rough edges, which would be indicative of cracking or delamination caused by abrasion or attrition of dry and friable particles. Nor do they suggest the "picking" that is sometimes seen with film coated tablets. The addition of water may have had effects on several aspects of the formulation, and these may be interlinked. It is thought that the two main forces that may be responsible for the differences in particle morphology are changes in evaporation potential, and changes in viscosity. The addition of water will change the evaporation potential of the solvent system, meaning that at a fixed temperature, solvent removal will occur more slowly. Rapid solvent removal has been shown to be responsible for the formation of "blowholes", a morphological flaw in microspheres produced by spray drying with volatile solvents (Gander et al., 1995; Bain et al., 1999; Wang and Wang, 2002). This occurs by the formation of a thin outer crust, formed by the rapid removal of solvent from the outer layers. This produces a build up of pressure inside the particle, which eventually causes the drug crust to rupture, producing holes in the matrix; the movement or mass flux, of a solvent through a crust is said to be dependent on the permeability of the crust, and the parameters of the ambient gas (Lin and Gentry, 1996). The deposition of further droplets may then spread over the pore edges and inner surface, accounting for the smooth appearance noted here. Reuge and Caussat (2007) describe bubble formation in the liquid beneath the crust of a spray dried particle, which occur if the boiling point is exceeded, and this causes inflation or rupture. It is thought that such a process could be occurring here, and the higher evaporation number and heat of evaporation and lower vapour pressure of water (evaporation potential of water = 60, ethanol = 8.3 [relative to diethyl ether = 1]; vapour pressure of water = 17.5 mbar, ethanol 60 mbar; heat of evaporation of water = 2265 J/g, ethanol 85 J/g [Lehman, 1994]) could contribute to improving morphology. Choice of solvent can therefore be a critical factor, and morphology is highly dependent on this.

4. Conclusions

Pellets were prepared by solution layering tramadol solutions onto non-pareils using an ethanolic drug solution, or a mixture of ethanol and water. A hydrophobic outer coating was applied to modify drug release. The attempts to prepare an extended release tramadol pellet using solution layering were precluded by the formation of unusual pellet architecture when ethanol was the solvent. Poor retardation of drug release was seen and this was attributed to the presence of surface flaws which presented as large pores. These were thought to be formed by rapid evaporation of ethanol forming a solid outer crust which prevented the diffusion of residual solvent and the resulting build up of solvent pressure causing the tramadol layer to rupture. Pellet morphology was improved by changing the solvent to an ethanol water mixture (90:10) which reduced the evaporation rate in the solution layering process. The

process of pellet formation by solution layering, often considered to be straightforward, can be dramatically affected by small changes to the formulation and surprising results can ensue.

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