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EFFECT OF POLYMER LOADING ON DRUG RELEASE FROM FILM-COATED IBUPROFEN PELLETS PREPARED BY EXTRUSION-SPHERONIZATION

[1,2]Dyer A.M., [2]Khan K.A. and [1]Aulton M.E.

[1]Department of Pharmaceutical Sciences, De Montfort University, Leicester LE1 9BH, U.K.
[2]Pharmaceutical Formulation Dept., Boots Pharmaceuticals, Nottingham NG2 3AA, U.K.

ABSTRACT

Many factors are capable of influencing the mechanism of drug release from pellets prepared by extrusion-spheronization. This study was designed to elucidate the effect of polymer type and loading and the effect of processing variables on the rate and mechanism of drug release from ibuprofen pellets coated using aqueous polymeric dispersions. Qualitative and quantitative assessment of the success of the film coating process and the quality of the resultant films is made using scanning electron microscopy and in-vitro dissolution testing. The importance of plasticizer in polymeric film formation is also discussed. Uncoated pellets containing 60, 70 and 80% ibuprofen were coated with aqueous polymeric dispersions of polymethacrylates, ethylcellulose and silicone elastomer films. The high drug loading of these pellets adds special interest to this study. Drug release from uncoated pellets appears to follow first-order kinetics. The application of a polymeric membrane to uncoated cores has the effect of retarding drug release. There appears to be a critical coating level below which core coverage by the polymer is incomplete, drug release is diffusion controlled and first-order release kinetics are observed. Above a defined polymer level, drug release appears to be membrane controlled and zero-order kinetics are observed. The presence of plasticizer in the polymeric film imparts a hydrophilic component to an otherwise hydrophobic membrane. This enhances the penetration of aqueous solvent into the pellet core during in-vitro dissolution testing, increasing the rate of drug release. Scanning electron micrographs reveal the nature of these hydrophilic pores, beneath which a fine tortuous skeletal network of drug-depleted core is exposed.

INTRODUCTION

Film formation in an organic solvent coating system is dependent upon the polymer molecules becoming entangled and in close proximity to each other as the solvent is evaporated. Film formation of water-insoluble polymers in a latex system however, in which the polymer is present as discrete particles in an

aqueous vehicle, relies upon the evaporation of water causing the latex spheres to soften, come within close proximity of like particles and then coalesce and deform by capillary force and the surface tension of the polymer to form a continuous film.

The dynamics of the film coating process is a carefully balanced equilibrium and is summarised in Figure 1.

The type of polymer system applied to a pellet surface is a major factor affecting drug release characteristics. The nature of the film coat is determined largely by the polymer, but also by the presence of other excipients within the coating dispersion. The importance of plasticizer within ethylcellulose aqueous dispersions is discussed by Goodhart et al. (1984). Since the latex forming process involves the fusion of individual polymer particles to form a continuous membrane, sufficient plasticizer must be present to cause a lowering of the minimum film-forming temperature (MFT), thus enabling polymer particle coalescence and deformation under the normal operating conditions of the coating chamber. The basis for film formation is therefore attributable to the capillary pressure exerted by the closely packed polymer particles as a result of water evaporation. Plasticizers enhance polymer pliability; in latex systems however they must also enable particle coalescence by reducing the glass transition temperature or the MFT. Assuming that polymer coalescence and film formation is complete, the drug release rate from a polymer coated product is a function of the plasticizer concentration in addition to the thickness of the polymeric membrane surrounding individual particles. Porter et al. (1989) state that coalescence may only occur completely as a result of viscous flow thus eliminating boundaries between adjacent polymer particles. Diffusion of polymer chains must occur across the boundaries; this process may be accounted for to some extent by the free volume theory which presumes that sufficient free volume (intermolecular space) exists in the bulk polymer thus accommodating the diffusion process.

Ozturk et al. (1990) reported that the presence of plasticizer is important in facilitating continuous film formation from such systems and that diffusion of drug through the plasticizer channels is unlikely to make a significant contribution to the overall drug release rate. These authors also indicate that for pellets coated with a plasticized ethylcellulose pseudolatex, lowering the plasticizer concentration significantly increases the drug release rate. This faster drug release observed at low plasticizer levels was shown by SEM to be attributable to major flaws in the film, thus indicating that there is a minimum level of plasticizer required for these ethylcellulose based systems necessary for continuous and complete film formation. To be effective a plasticizer molecule must interpose itself between the polymer chains and interact with the forces holding the chains together, thereby extending and softening the polymer matrix (Rowe, 1982). The mobility of a polymer chain influences the magnitude of the stresses due to shrinkage. Plasticizers increase polymer chain mobility and therefore have a significant effect on those stresses and hence the incidence of film cracking; non-plasticized films are therefore more brittle than plasticized films.

Li and Peck (1989) have studied controlled-release tablets coated with a silicone elastomer membrane. The suitability of this system for controlled release coating is primarily dependent upon the permeability of the coating to various drug molecules. Polydimethylsiloxane is hydrophobic and therefore a silicone elastomer membrane is relatively impermeable to hydrophilic and ionic compounds. Incorporation of water-soluble components within the hydrophobic silicone elastomer formulation in the form of the polyethylene glycols has been

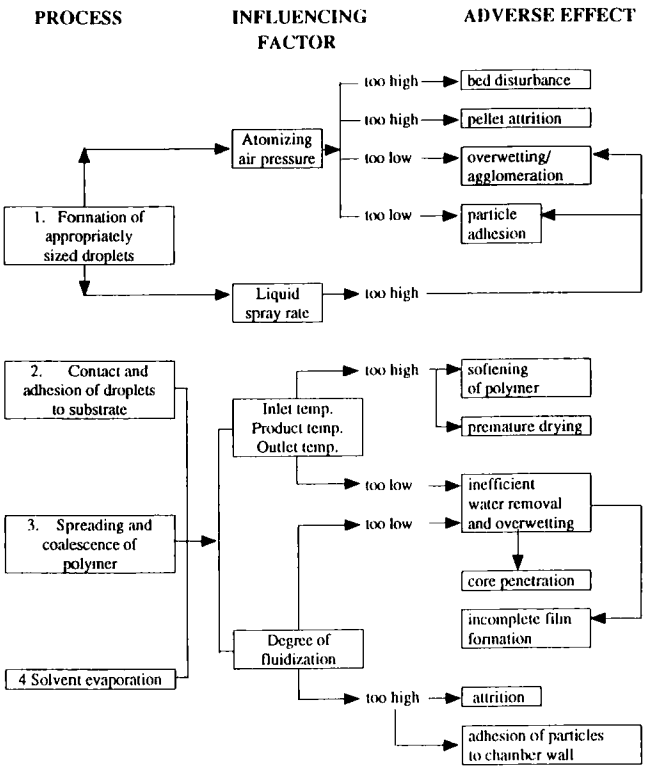

FIGURE 1 Factors affecting the film coating process.

shown to enhance the drug release from dosage forms coated with this system (Li and Peck, 1989).

In determining the dissolution rate of drugs from solid dosage forms it is necessary to consider several physicochemical processes in addition to processes involved in the dissolution of pure chemical substances. Factors which may influence the dissolution characteristics of a drug include the physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium and any swelling, disintegration or deaggregation of the dosage form. For drug-containing pellets surrounded by a release-retarding polymer membrane the process of dissolution is illustrated by Figure 2.

MATERIALS AND METHODS

Uncoated spherical pellet cores (Dyer et al., 1994) containing 60, 70 and 80 %w/w ibuprofen (Boots Pharmaceuticals) with microcrystalline cellulose (Avicel PH101, FMC Corporation) approximately 1 mm diameter, were coated with three different polymeric aqueous dispersion coating systems. The use of the different systems was designed to enable evaluation of three polymers with respect to their

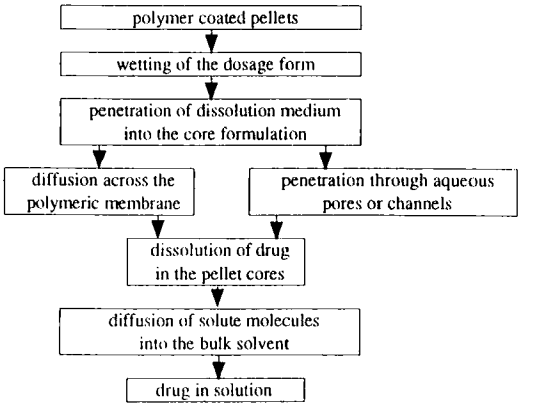

FIGURE 2
Schematic illustration of the process of in-vitro dissolution of drug from non-eroding pellets of spherical geometry surrounded by an aqueous-insoluble polymeric membrane.

effect on drug release, their relative mechanical strengths and elasticities and ultimately the ability of the coated pellets to retain their integrity following compression into tablets with an inert diluent formulation (Aulton et al., 1994).

Polymethacrylate (Eudragit)

Eudragit RS30D and Eudragit RL30D (Röhm Pharma GmbH, Germany) were used in combination (4:1) causing the resulting polymeric membrane to be the factor controlling the drug release rate rather than the quantity of plasticizer incorporated within the film coat. The RS30D exhibits low permeability but, when used in combination with the highly permeable RL30D, satisfactory drug release is obtained. The Eudragit aqueous dispersion applied contained 13.35 %w/w polymer solids. The dried film contained triethylcitrate (Citroflex 2, Pfizer Ltd., U.K.) 20 %w/w as a plasticizer and Syloid Silica 244FP (Grace GmbH, Worms, Germany) 30 %w/w as an anti-adherent.

Ethylcellulose (Surelease)

Commercially available Surelease contains 25 %w/w solids; however, the product was diluted to 15 %w/w solids for application as an aqueous polymeric dispersion. It is necessary with this product to apply an overcoat formulation (1 % weight increase) in order to minimise sticking during subsequent processing. The film coating dispersion and overcoat formulations are as follows:

Surelease Dispersion (15 %w/w solids)	%w/w
Surelease Dispersion (25 %w/w solids)	60.0
Purified water USP	40.0

Overcoat Formulation	%w/w
Opadry Clear (YS-1-7006)	10.0
Purified water USP	90.0

Silicone Elastomer

The X7-2837 Silicone Emulsion (Dow Corning) is a polymerized latex and is a cross-linked product of hydroxyendblocked polydimethylsiloxane (PDMS). When this material is combined with colloidal silica particles and a water dispersible organic material, an aqueous latex dispersion results which may be used as a controlled release system for oral dosage forms.

Formulations containing silicone to silica ratios of 2:1, 4:1 and 6:1 were prepared and applied to ibuprofen pellets as aqueous polymeric film-coating emulsions. Further work included a study of the effect of plasticizer {PEG (polyethylene glycol) 6000 USP 10 %w/w} on the quality of the film coating.

This present work shows that an increase in the silicone to silica ratio and the incorporation of PEG within the emulsion increases the tendency for sticking and reduces the ease with which fluidization is achieved and maintained throughout the coating process. Favourable release profiles appear to negate the need for the incorporation of plasticizer within the polymeric film. *In-vitro* drug release profiles shown subsequently illustrate the effect of the silicone to silica ratio and the presence of plasticizer on drug release from pellets containing ibuprofen.

Preparation of film coating dispersions

The components of each of the film coating dispersions were mixed with low shear immediately prior to processing. In addition low shear mixing was maintained throughout the coating process; excessive agitation causes frothing and increases the risk of dispersion coagulation.

Uncoated pellets (500 g) were placed in the stainless steel chamber of a 1kg Aeromatic Fluidized Bed (Strea 1) with top spray attachment. A spray gun (of nozzle diameter 1.10 mm) and 2 mm bore diameter silicone tubing were used to apply the film coating dispersion. Pellets were fluidized to nozzle height and pre-warmed to an inlet air temperature of 50°C and an outlet air temperature of 28-32°C. The product temperature did not exceed 40°C during the coating process. A liquid spray rate of approximately 10 g min^{-1} per kg of product and an atomising air pressure of 2 bar was maintained throughout.

Each batch of uncoated ibuprofen pellets was coated with progressively increasing polymer loadings (expressed as percentage increase in weight of product). Plasticizer content is expressed as percentage weight of dry polymer.

For all batches of coated pellets, the following procedures were adhered to:

i) pre-warming of the pellet bed to approximately 30°C
ii) atomising air pressure of 2 bar
iii) uncoated batch size of 500 g
iv) post-coating drying for 30 minutes under existing drying conditions

A post-coating tray drying process (the so-called "curing" stage) was performed on certain coated pellets; 24 hours tray drying at 40°C. A control sample was taken and the *in-vitro* drug release profiles were obtained. The effect of this "curing" stage on film quality and on *in-vitro* drug release is discussed subsequently.

In summary, ibuprofen pellet formulations were coated with different levels of three different polymers. This study highlighted that it is possible with such coating systems to apply an accurate polymer loading to multiparticulates such that a specific *in-vitro* release profile may be obtained.

In-vitro dissolution

In-vitro dissolution testing was performed in standard USP XXII, type II (paddle) apparatus containing 900 ml of pH 6.8 phosphate buffer USP maintained at 37°C using a paddle rotation speed of 100 rpm.

RESULTS AND DISCUSSION

Uncoated pellet cores containing 60, 70 and 80 %w/w ibuprofen were coated with aqueous polymeric dispersions of the polymethacrylates, ethylcellulose and silicone elastomer. The success of the film coating procedure and the quality of the resulting films were assessed qualitatively by scanning electron microscopy and quantitatively by *in-vitro* dissolution testing.

Scanning electron micrographs of the surface of pellets coated with polymethacrylate, ethylcellulose and Silicone Elastomer polymers are presented subsequently. All qualitative evidence presented illustrates the smooth surface characteristics exhibited by these coated multiparticulates.

Comparison of the *in-vitro* release profiles of coated pellets subjected to the post-coating "curing" stage with the control samples, confirms that polymer coalescence and complete film formation is achieved whilst the pellets are in the coating chamber. This is apparent as a consequence of the negligible difference in the release profiles of the control samples and pellets subjected to a post-coating drying stage, consisting of 24 hours storage at 40°C in a hot air oven (Figures 4, 5 and 6).

DRUG RELEASE FROM UNCOATED AND COATED PELLETS

Figure 3 shows *in-vitro* drug release profiles for uncoated pellets and pellets coated with increasing levels of polymethacrylate.

The incorporation of ibuprofen in a pellet formulation containing microcrystalline cellulose (Avicel PH101), results in the formation of multiparticulates which are essentially spherical solid matrices. Drug removal from these uncoated entities by *in-vitro* dissolution of pellets containing ibuprofen and microcrystalline cellulose, yields visibly intact spheres from which the drug has been leached; microcrystalline cellulose as a consequence of being virtually water insoluble, present in quantities as low as 20 %w/w, is able to maintain the spherical shape of the original particle. Dissolution kinetics from uncoated pellets comprising drug mixed with an insoluble excipient, in this case microcrystalline cellulose, may be considered as drug release from homogeneous matrices.

The mechanisms of release from these systems can be treated in two ways, firstly by extraction of the drug by a simple diffusional process through the homogeneous matrix and secondly leaching of drug by the solvent phase, which is able to enter the drug-matrix phase through pores, cracks and intragranular spaces. In the former case, drug presumably partitions from the crystal surfaces into the uniform matrix and out into the bathing solvent, which acts as a perfect sink. In the latter case however, drug dissolves slowly in the permeating fluid phase and diffuses from the system along the cracks and capillary channels filled with the extracting dissolution medium. Swarbrick (1992) comments that in most cases it is accepted that intragranular diffusion is minimal.

Drug release from pellets coated with water-insoluble polymers may occur by several mechanisms including solute diffusion through the continuous polymeric membrane, through plasticizer channels and/or through aqueous pores; the solute molecules being driven by the difference in osmotic pressure between solute within the core of a pellet and that in the dissolution medium. Ozturk et al. (1990) considered the effect of the presence of cracks within the film coat on drug

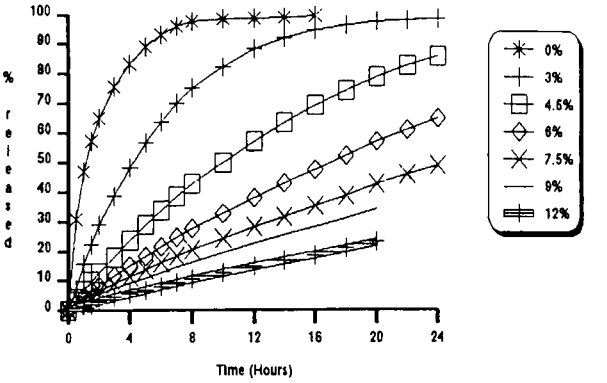

FIGURE 3
In-vitro drug release from pellets containing 80 %w/w ibuprofen coated with different weight increases (see key) of Eudragit RS/RL30D.

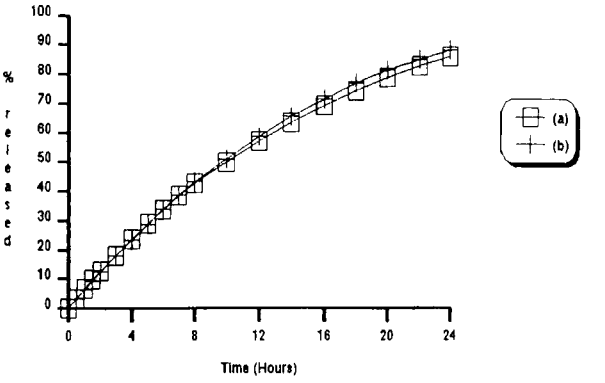

FIGURE 4
In-vitro drug release from pellets containing 80 %w/w ibuprofen coated with a 4.5% weight increase of Eudragit RS/RL30D; (a) "cured"; (b) not "cured".

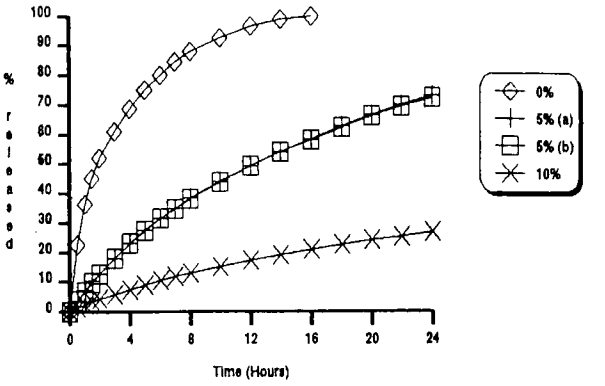

FIGURE 5
In-vitro drug release from pellets containing 60 %w/w ibuprofen coated with 5% and 10% weight increases of Surelease; (a) "cured"; (b) not "cured".

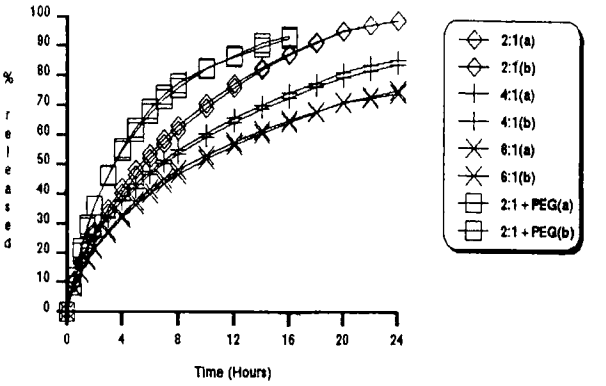

FIGURE 6
In-vitro drug release from pellets containing 80 %w/w ibuprofen coated with a 10% weight increase of Silicone Elastomer; (a) "cured"; (b) not "cured". The ratio of Silicone Emulsion:Colloidal Silica in the coating formulation is given in the key; one of the coating formulations contains PEG 6000 (polyethylene glycol) 10 %w/w.

release. These authors confirm the presence of plasticizer being of paramount importance in forming a continuous film, however that diffusion of drug through plasticizer channels is unlikely to make a great contribution to the overall drug release rate. These authors concluded that drug release from pellets coated with an ethylcellulose pseudolatex is attributable to both diffusion of solute molecules and also as a function of the relative osmotic pressure of the medium.

Figures 3 and 5 show that drug release is retarded simultaneously with increasing polymer loading, indicating that the film is controlling the release process. This is confirmed by Ozturk et al. (1990) and Zhang et al. (1991), all of whom indicate that the mechanism controlling drug release is influenced by the thickness of the applied coating.

Figures 3 and 5 also show that at zero or low polymer loading, the drug release rate cannot be described as being time-independent. However at higher coating levels corresponding to an increasing membrane thickness (above a critical coating level or CCL) the drug release profile illustrates zero-order kinetics (the rate of drug release is independent of time); the release profile of cumulative percent ibuprofen released against time is linear. At low coating levels the membrane is relatively more porous and the drug takes the route of least resistance for release from the core of the individual multiparticulates. Zhang et al. (1991) found that the drug release rate and the drug release mechanisms were dependent upon the coating level. At low coating levels the pore control mechanism predominates, while at higher coating levels drug release is mainly membrane or barrier controlled.

As the coating thickness increases, fewer pores are available for drug transport thus retarding drug release. It is more likely that drug release is now occurring by diffusion across the polymeric membrane rather than by diffusion through pores or channels or imperfections within the film coat. All coated and uncoated pellets studied remained intact during drug removal by *in-vitro* dissolution testing. Wouessidjewe et al. (1991) consider the effect of multiple film coverage in sustained release pellets. As the film is applied to individual pellets, a continuous membrane is formed by the building up of overlapping segments. Above the CCL, it may be concluded that all of the "holes" are covered and that a continuous and complete membrane is enveloping each individual pellet. As a consequence of building a continuous film by spraying atomised dispersion, one might expect that imperfections within the film coat are present. Wouessidjewe concludes that polymeric membrane formation by spraying leads to the formation of discrete films overlapping each other. Once the CCL is exceeded, it may be assumed that complete membrane formation has occurred.

It is essential that polymer coalescence and complete film formation is achieved during the film coating process with these aqueous polymeric dispersions. Coated pellets were therefore subjected to an additional "curing" stage of 24 hours in a hot air oven at 40°C. Those *in-vitro* release profiles for which the additional "curing" stage was not part of the manufacturing process are given in profile (b) of Figures 4, 5 and 6. The *in-vitro* release profiles of coated pellets not subjected to the "curing" process indicates that complete film formation and polymer coalescence is occurring during the coating process under the drying conditions of the coating chamber. This may be concluded as a consequence of the negligible difference in the *in-vitro* drug release from tray-dried and control samples within this study. Again by exposing these pellets to an additional "curing" stage, it is apparent that complete polymer coalescence occurs during the coating process. Comparison of the *in-vitro* release of ibuprofen from those pellets coated with a Silicone Elastomer dispersion containing a ratio of silicone emulsion:colloidal silica of 2:1, with and without plasticizer {polyethylene glycol

(PEG 6000) 10 %w/w}, results in an enhanced rate of drug release (Figure 6). It is therefore apparent that a consequence of incorporating plasticizer within a polymer film surrounding multiparticulates (essentially homogeneous matrices in their uncoated form), is an enhanced rate of drug release. This enables postulation that diffusion of solute drug molecules through plasticizer channels created as a consequence of the pore-forming properties of an incorporated plasticizer within the otherwise impermeable membrane, is at the very least, contributing to the mechanism of drug release from such a system.

The effect of increasing the ratio of silicone to silica leads to a corresponding reduction in the rate of drug release. Increasing the silicone content of the dispersion with a corresponding decrease in the content of the colloidal silica, enhances release retarding capacity of the membrane. It was not possible to successfully coat pellets with a dispersion containing a ratio of silicone:silica greater than 6:1, nor with a dispersion containing PEG 6000 in any formulation with a higher ratio of silicone:silica than 2:1, due to sticking and pellet agglomeration during the coating process under the equilibrium conditions within the coating chamber.

In summary, the presence of plasticizer or a reduction in the ratio of silicone to silica, will have the effect of increasing the rate of drug release by increasing the permeability of the membrane.

QUALITATIVE EVALUATION OF PELLET AND FILM COAT APPEARANCE

Uncoated and coated pellet surface and cross-sectional characteristics have been examined qualitatively by scanning electron microscopy, both pre and post *in-vitro* dissolution testing.

Pellet surface characteristics prior to and post drug removal

Figures 7 and 8 show scanning electron micrographs (SEMs) of the surface appearance of uncoated pellets containing 60 %w/w ibuprofen before and after drug removal by *in-vitro* dissolution testing.

In-vitro dissolution testing of uncoated pellets (even those containing only 20 %w/w microcrystalline cellulose) yields visibly intact entities; pellets were removed from the dissolution vessels following removal of the drug, allowed to dry under ambient conditions examined by scanning electron microscopy. Figure 9 illustrates the structural skeletal matrix network of the microcrystalline cellulose. Voids created in the pellet surface by drug removal from those pellets initially containing 80 %w/w drug are more profuse; a consequence of the product initially containing a greater drug loading. The resultant uncoated pellet surfaces are sponge-like in appearance. The voids created on drug removal in the pellet surface appear to be evenly distributed and of regular size for a given drug loading.

Pellet cross-sectional characteristics prior to and post drug removal

Figures 9 and 10 show SEMs of the cross-sections of uncoated pellets prior to and after drug removal.

The initial drug content of the pellets in these figures is 80 percent. Comparison of the cross-sectional appearance of drug-depleted skeletal entities following dissolution indicates that the drug appears to have been evenly distributed throughout the pellet matrix. Dissolution testing facilitated the creation of a pore network as a consequence of solvent penetration and the diffusion of solute molecules from the matrix. It is postulated that whichever drug release mechanism predominates for coated pellets, drug release from uncoated pellets is diffusion controlled and exhibits first-order kinetics (c.f. uncoated pellet release profile in Figure 3).

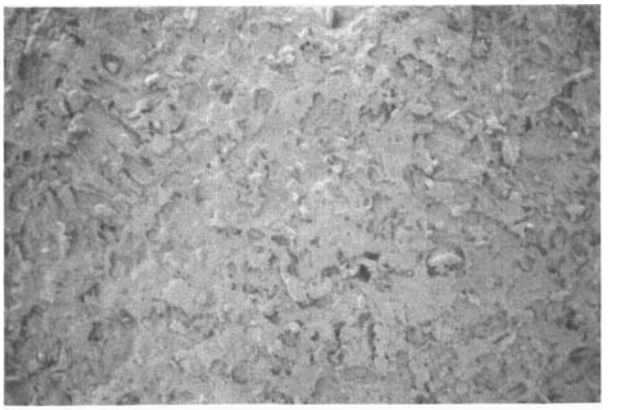

FIGURE 7
SEM of uncoated pellet surface containing 60 %w/w ibuprofen (pre-dissolution); x400.

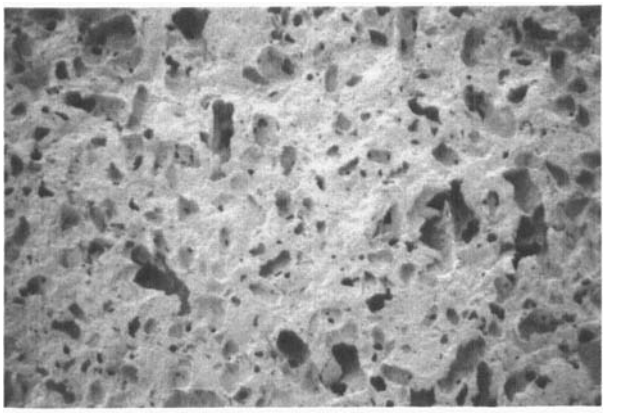

FIGURE 8
SEM of uncoated pellet surface initially containing 60 %w/w ibuprofen (post-dissolution); x400.

FIGURE 9
SEM of uncoated pellet cross-section containing 80% w/w ibuprofen (pre-dissolution); x400.

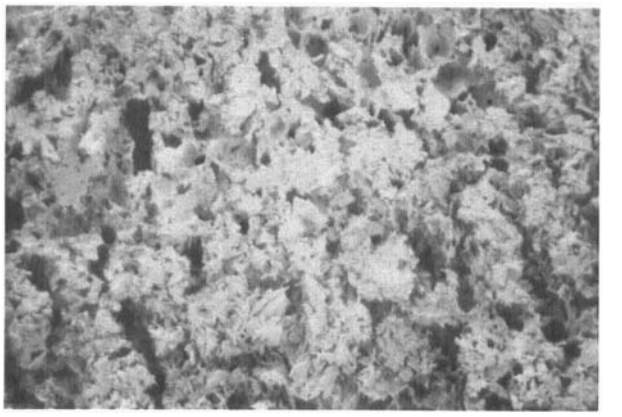

FIGURE 10
SEM of uncoated pellet cross-section initially containing 80 %w/w ibuprofen (post-dissolution); x400.

Effect of polymer type on pellet surface characteristics

Figures 11 to 13 show the quality and surface characteristics of pellets coated with the three polymer systems. Pellets coated with aqueous dispersion formulations of Eudragit, Surelease and Silicone Elastomer exhibit uniform smooth surface characteristics.

One effect of the presence of plasticizer in a film coating (in addition to enhancing the elasticity of that film) is to enhance the rate of drug release. This is attributable to the creation of hydrophilic pores or channels within the otherwise hydrophobic polymeric membrane as a consequence of the affinity of the plasticizer for the penetrating aqueous solvent during dissolution testing. The process involving dissolution of the plasticizer within the polymeric membrane leading to the creation of aqueous pores or channels, may or may not play a significant role in the drug release from polymer-coated pellets containing ibuprofen. *In-vitro* dissolution data have enabled confirmation of the drug release enhancing properties of incorporated plasticizer and illustrate that these pores or channels do have a role in facilitating diffusion of solute molecules from the pellet core into the bulk solution. Drug release from pellets coated with the silicone emulsion without plasticizer appears to be membrane controlled as a consequence of the hydrophobic nature of the film. It is possible however that at least part of the rate controlling mechanism may be attributable to the relative osmotic pressures caused by the presence of solute molecules within the pellet core and the solute concentration within the bulk solvent.

Drug release from coated pellets without plasticizer exhibits first-order kinetics. The creation of plasticizer pores within the membrane for those pellets coated with silicone emulsion 2:1 containing polyethylene glycol, appears initially to display first-order kinetics, although the rate controlling mechanism appears to become zero-order as the final 25% of drug is leached from the pellet core.

It may be concluded that the presence of hydrophilic pores within an otherwise hydrophobic membrane, does contribute to drug release from pellets. It would appear however that the major release controlling mechanism is not due to the presence of plasticizer pores, but largely by the diffusional transport of solute molecules across the polymeric membrane and possibly the relative osmotic pressure within the pellet core and the bulk dissolution medium.

Effect of polymer type on pellet surface characteristics post drug removal

Figure 14 is an SEM showing the surface characteristics of a pellet which has been coated with the polymethacrylate dispersion containing the plasticizer triethylcitrate. Thus a water-soluble component is incorporated into an otherwise aqueous insoluble polymeric membrane. It is not unreasonable to expect the plasticizer to dissolve in the aqueous phase resulting in the creation of pores within the film coat. The integrity of the film has been compromised by the removal of plasticizer from the membrane into the bulk solution. This has the consequence of at least contributing to drug release from the pellet core; this figure shows the exposed core of the pellet where the integrity of the polymeric film has been compromised as a consequence of plasticizer removal. The skeletal network of drug depleted cores containing only microcrystalline cellulose is exposed; the core formulation in this case initially contained 30% microcrystalline cellulose and 70 %w/w ibuprofen. The incorporation of plasticizer into aqueous dispersions containing the polymethacrylates was necessary for film formation. It was therefore not possible to prepare coated pellets using the same formulation without plasticizer. It is postulated that although solute transport through aqueous pores within the otherwise hydrophobic membrane contributes to drug release, it is not necessarily the main mechanism of drug removal from the pellet core.

FIGURE 11
SEM of pellet surface coated with Eudragit RS/RL30D (pre-dissolution); x400.

FIGURE 12
SEM of pellet surface coated with Surelease dispersion (pre-dissolution); x400.

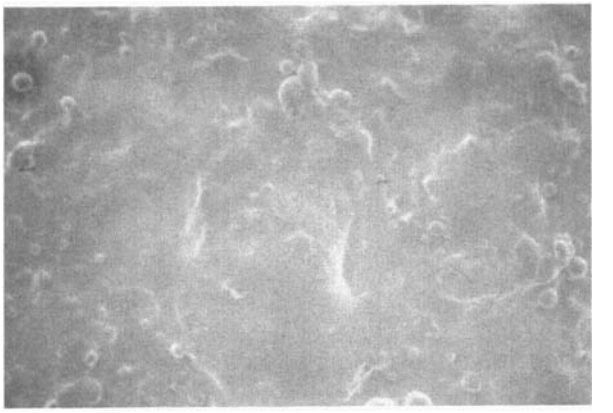

FIGURE 13
SEM of pellet surface coated with Silicone Elastomer 2:1 (pre-dissolution); x800.

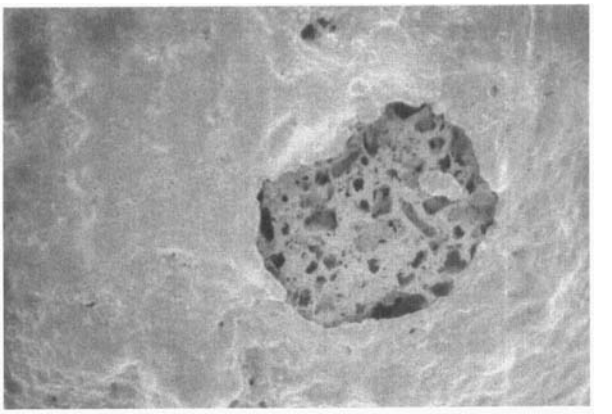

FIGURE 14
SEM of pellet surface coated with Eudragit RS/RL30D (post-dissolution); x400.

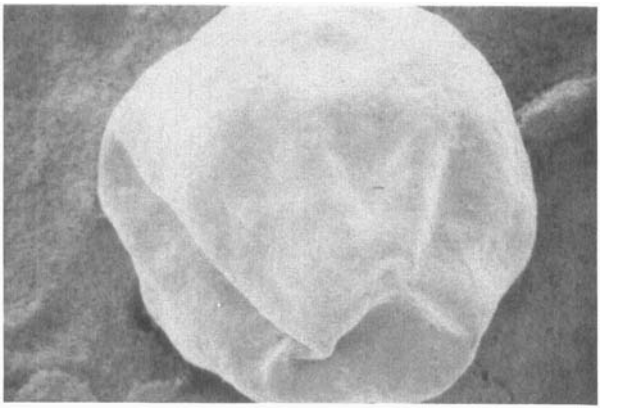

FIGURE 15
SEM of pellet surface coated with Surelease dispersion (post-dissolution); x80.

Figure 15 shows the surface of a drug-depleted pellet coated with a commercial ethylcellulose formulation (Surelease) containing plasticizer. This figure illustrates how the film coat envelopes the pellet which initially contained 80 %w/w ibuprofen; some pellet shrinkage is apparent. This may be attributable to core shrinkage as a consequence of drug removal and the drying out of the pellet after dissolution testing. Pellets were dried under ambient conditions in order to minimise core shrinkage due to drug removal and increased voidage within pellet cores.

Alternatively, it is possible that the relative osmotic pressures between the solute concentration in the coated pellet core and in the bulk solution during *in-vitro* testing, caused a degree of swelling of the pellet with a resultant "expanding" or "stretching" of the film coat which was unrecovered after drug removal and subsequent drying of the coated pellet. This effect was not seen with the other coating systems studied. The proposed mechanism of drug release from these entities is by diffusion of solute molecules across the polymeric membrane, with a possibility of the process of osmosis contributing the release mechanism. Exposed core is not visible through these polymer films following complete drug removal. This is as expected since these films are very hydrophobic and there is no plasticizer-created pores within the film.

Plasticized Silicone Elastomer films, following contact with an aqueous solvent, will cause the formation of aqueous pores as the hydrophilic plasticizer is leached from the otherwise hydrophobic film by the penetrating aqueous phase. The extent of this process is dependent upon the concentration of plasticizer within the emulsion. This factor may not be used as means of controlling drug release from this polymer however, since increasing the polyethylene glycol content leads to product sticking and agglomeration during the film coating process. It is anticipated that the presence of plasticizer does not have a major effect on the drug release mechanism from pellets coated with these silicone formulations.

CONCLUSIONS

The success of a film coating procedure may be assessed qualitatively by scanning electron microscopy and quantitatively by *in-vitro* dissolution testing. It is important, with the application of any aqueous polymeric dispersion, to ensure that polymer coalescence and complete film formation are achieved during the coating process. This may be confirmed by there being negligible difference between the *in-vitro* release profiles of coated pellets subjected to a post-coating drying operation or so-called "curing" stage and those which are not.

The combination of ibuprofen and microcrystalline cellulose as an uncoated pellet formulation results in the formation of multiparticulates which are essentially spherical porous matrices. Drug removal by *in-vitro* dissolution from pellet cores containing as much as 80 %w/w drug, and therefore only 20 %w/w microcrystalline cellulose, yields visibly intact spheres.

Using the technique of scanning electron microscopy under high magnification to examine pellet surface and cross-sectional characteristics, it is apparent that drug has been leached from the pellet cores resulting in a fine tortuous skeletal network of microcrystalline cellulose.

Drug release from uncoated pellets containing ibuprofen appears to follow first-order kinetics.

The application of a polymeric membrane in the form of an aqueous dispersion to spherical multiparticulates, has the effect of retarding drug release. There appears to be a critical coating level, below which core coverage by the polymer is incomplete and drug release is diffusion controlled and first-order kinetics are observed. Above this critical coating level, drug release appears to become membrane controlled and zero-order kinetics are observed; the drug release rate becomes time independent after a minimum polymer level has been achieved.

The presence of plasticizer within the coating formulation not only influences the glass transition temperature of the polymer and the elasticity of the film, but it imparts a hydrophilic component to an otherwise hydrophobic membrane. As a consequence of the presence of plasticizer in the film coat, during *in-vitro* dissolution testing of coated pellets penetration of aqueous solvent molecules into the pellet core is facilitated and the drug release rate from the pellet is thus enhanced. This is due to the creation of hydrophilic pores formed in the membrane by the leaching of plasticizer into the dissolution medium.

Polymeric membranes derived from aqueous dispersions and applied to pellets using the methodology described in this work, enables polymer coalescence and complete film formation to occur under the operating conditions of the coating chamber. This is characterised by the *in-vitro* release profiles for coated ibuprofen pellets, which were subjected to an additional "curing" stage involving 24 hours storage at 40°C following coating. There is negligible difference between the release of ibuprofen from those pellets exposed to this additional "curing" stage and those which were not. It may be concluded therefore that complete film formation and polymer coalescence was facilitated by the use of equilibrium conditions within the coating chamber for each of the three polymer systems studied.

The incorporation of plasticizer into the Silicone Elastomer aqueous emulsion leads to an enhanced rate of drug release and also appears to enhance the adhesion between the uncoated pellet surface and the polymeric membrane. Increasing the ratio of silicone to silica in the emulsion formulation, leads to a decrease in the rate of drug release.

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