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THE STRENGTH AND COMPACTION OF MILLISPHERES

The design of a controlled-release drug delivery system for ibuprofen in the form of a tablet comprising compacted polymer-coated millispheres.

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ABSTRACT

This paper reviews a case study of the design of a controlled-release drug delivery system for ibuprofen in the form of a tablet comprising compacted polymer-coated millispheres (multiparticulate pellets). The particular challenge was to prepare coated millispheres of ibuprofen (a high-dose drug) with the addition of minimal excipients so that the drug-release retarding polymeric membrane surrounding the millispheres remains intact during and after tablet compression, disintegration and release of the millispheres. The study included (a) the design of the uncoated core and its manufacture by wet massing, extrusion, spheronization and drying; (b) the coating of these millispheres with a range of possibly suitable polymers; (c) an assessment of the drug release profiles from these pellets; (d) the quantification by indentation rheology of the mechanical properties of the polymer films used to coat the spheres; (e) the measurement of the mechanical properties of individual uncoated and coated millispheres and

f. the design, manufacture and evaluation of compressed tablets containing coated millispheres.

The matching of millisphere and polymer mechanical properties was found to be essential in order to ensure minimal damage to the millispheres and the release of virtually intact coated spheres without destruction of their retarded drug-release characteristics. Aqueous polymeric dispersions which formed a film with similar elastic and tensile properties to the uncoated millisphere formulation resulted in the most satisfactory film coating for application to spherical particles which must withstand compaction. Those polymeric films exhibiting significantly greater resilience than the uncoated cores were inappropriate for the film coating of millispheres for compaction into tablets.

AIM OF THIS STUDY

It is recognised that a multi-unit controlled release dosage form presents a preferable alternative to a single-unit system for oral administration. However, it is not easy in practice to present a low-potency (and thus high-dose) drug in the form of multiparticulate delivery systems. This is due mainly to patient compliance problems associated with the large size of hard gelatin capsule shell required for such dosages. The aim of this present work was to design a tablet which, on peroral administration, disintegrates rapidly releasing intact polymer-coated spherical pellets which have maintained the integrity of both the cores and their release-retarding membrane such that their drug release kinetics are unaltered.

The case study which follows is reported in detail by Dyer (1). Ibuprofen was chosen as a model drug because it is advantageous to administer this drug perorally in controlled-release units of 800mg. This paper describes the design and testing of such a dosage form and involved the following stages.

1. Design and manufacture of the multiparticulates.

2. Measurement of the physical characteristics and drug release properties of these uncoated spheres.

3. Choice of a suitable polymer coating in order to achieve:
   a) the desired kinetics of drug release from coated spheres and
   b) suitable mechanical properties of the polymer films and resulting coated spheres in order that they can withstand the compaction process with minimal damage to the integrity of the spherical cores and its coating.

4. Compression of the coated spheres into tablets, involving the choice of suitable excipients and compression parameters.

5. Evaluation of the tablets with respect to:
   a) their strength and disintegration characteristics,
   b) the integrity of the millispheres observed by visual examination of *in-situ* and released spheres and
   c) a comparison between the drug release rates from uncompacted and compacted spheres in order to assess the extent of any damage.

For the purposes of this review, the work reported will be concerned mainly with the mechanical robustness of the system. Other aspects of the study will be discussed only briefly in this paper.

There is much confusing and unclear terminology in the pharmaceutical sciences relating to the nomenclature of the type of spherical multiparticulates studied in this work (pellets, beads, beadlets, even microspheres, etc). The term *millisphere* is suggested and recommended. Millispheres are defined as '*solid particles or agglomerates of particles with a high degree of sphericity having a diameter of around 1 millimetre.* The practical limits could be between, say, 0.5 to 2 mm.

A. PELLETIZATION STAGE

The physiological and pharmacological advantages associated with sustained-release multi-unit delivery systems for oral administration are now well established (see, for example, Bechgaard and Nielsen (2); Davis et al. (3), Ganderton (4)).

In the context of this present study, the requirement is to produce millispheres which have the following properties:

(i) contain the required high dose of drug (this high dose limits the volume of excipients that can be incorporated),
(ii) be of uniform size (thus be of suitable geometry for mixing with excipients and for filling into a tablet die),
(iii) have a smooth surface (which is necessary for the application of an intact and coherent polymer coating of uniform thickness),
(iv) have, when coated, the correct and desirable drug release profile and
(v) be robust enough to withstand tablet compression and disintegration processes with little or no damage.

It is widely accepted that many pelletization processing variables are capable of influencing the fundamental properties of the uncoated millispheres. These have been examined by many workers and the process of pelletization by extrusion and spheronization has been discussed in detail elsewhere (see, for example, Harrison et al. (5)(6)(7) and Nesbitt (8)).

In this present work, ibuprofen (The Boots Company) was used as an example of a medium-to-high-dose drug with relatively poor water solubility. In some formulations lactose (Fast Flo) was substituted as a water-soluble comparitor. It was possible to formulate and manufacture satisfactory spherical pellets, approximately 1 mm in diameter, containing either 80 %w/w ibuprofen or 80 %w/w lactose with 20 %w/w microcrystalline cellulose (Avicel PH101). These were manufactured by extrusion and spheronization and the resulting spheres dried by either fluidized-bed or tray drying.

Manufacture of millispheres

The solid ingredients were sieved into and then blended within a Diosna P25 Granulator. The required volume of purified water was added slowly to the blend which was then mixed until a cohesive, plastic mass was obtained. This material was passed through a GA65 Alexanderwerk Extruder fitted with a perforated (1 mm diameter) cylinder and a pressure cylinder rotating at 98 and 134 rpm respectively. A uniform, smooth-surfaced extrudate was produced. Spheronization was undertaken in a Caleva Model 15 Spheronizer with a rotating plate of regular cross-hatch geometry.

Each batch of spheronized material was divided into two parts and dried either (i) in an Aeromatic Fluidized Bed Dryer (10 litre capacity) using a drying temperature of 60 °C for 60 minutes or (ii) by tray drying in a hot air oven with an air temperature of 45-50 °C for 24 hours.

Dyer, Khan and Aulton (9)(10) explain that the main differentiating factor between the two drying methods is the rate of water removal from the spheres. Those millispheres dried by the fluidized-bed technique achieve the desired moisture content much more quickly than those dried by tray drying due to the rapid evaporation of water as a result of the turbulent motion of the air and the fluidized particles. The free movement of individual fluidized particles leads to rapid water removal and minimises the migration of solute particles within the spheres. In tray drying, water removal from dried material is slow due to the static nature of the technique; tray dried entities are more likely to exhibit greater solute migration during the lengthy drying process. The solubility of the excipients from which the millispheres are composed affects the degree of solute migration occurring during drying. For millispheres in which the main excipient is lactose (which is freely soluble in the granulating fluid), solute migration is inevitable and is exacerbated by the slow drying associated with static-bed dryers. These authors concluded that for a given millisphere formulation, the drying method employed has a significant effect on the mechanical strength of the product prepared by extrusion-spheronization methodology. Millispheres dried by tray drying are generally stronger, have a greater modulus of elasticity and are more brittle than their fluidized-bed dried counterparts.

Smooth-surfaced, spherical millispheres were produced by either technique but, for reasons outlined above, the fluidized-bed dried millispheres were used in subsequent studies; these were then coated.

B. COATING STAGE

Sustained release of ibuprofen was achieved by the application to the millispheres of a release-retarding polymeric membrane from an aqueous polymeric dispersion of either a polymethacrylate mixture, ethylcellulose or silicone elastomer (1). Plasticization was critical to the performance of the film (see later). For a full review of the materials and formulations

available for the modified release coating of multiparticulates, see Hogan (11) and for details of air suspension coating techniques available for the application of these coatings to multiparticulates, the reader is referred to the review by Jones (12).

A comprehensive study was made of the effect of the nature of the polymer and formulation variables on the quality of the resultant film and its suitability for use as a release retarding membrane. In the interest of clarity and brevity, this present review will only report data for polymethacrylate films made from Eudragit RS30D/RL30D combinations.

The aqueous dispersions were produced with low shear agitation, since excessive agitation caused frothing and increased the risk of dispersion coagulation. 500 g of uncoated millisphere cores were coated in a 1 kg Aeromatic fluidized-bed apparatus.

The film coating of multiparticulates using aqueous polymeric dispersions requires uniform application of polymer in a closely controlled drying environment. An equilibrium must be established between the rate of application of liquid to the fluidized bed and the subsequent rates of liquid evaporation, polymer coalescence and film formation. It was necessary to manipulate carefully the process conditions for each polymer formulation. These conditions are detailed in Dyer (1).

The success of a film coating operation may be assessed qualitatively by photomicrography and scanning electron microscopy (SEM), and quantitatively by *in-vitro* dissolution testing. It is important with the application of any aqueous dispersion to ensure that polymer coalescence and complete film formation is achieved during or very soon after the coating process. A post-coating curing stage is necessary with many aqueous dispersion coating formulations.

C. DRUG RELEASE FROM MILLISPHERES

A general discussion of drug release from millispheres can be found in a review paper by Schwartz et al. (13). In this present work, drug release

kinetics from uncoated and coated millispheres were evaluated using *in-vitro* dissolution testing. This enabled a study to be made of the influence of the nature of the polymer, polymer loading, formulation variables and overall film quality (as assessed by SEM examination) on the drug release mechanism(s) from uncoated and coated millispheres.

Dissolution testing was performed using a USP type II apparatus (with a paddle rotation speed of 100 rpm) containing 900 mL of pH 6.8 phosphate buffer maintained at 37 °C. Samples from a six-station flow-through dissolution apparatus were analysed for ibuprofen using a Hewlett Packard 8450A Diode Array Spectrophotometer (wavelength range 245-300 nm).

Drug release from uncoated millispheres

Drug dissolution from uncoated millispheres resulted in visibly intact spheres from which the drug had been leached. After dissolution of the ibuprofen from these cores only about 20 % of their skeletal volume remained yet the millispheres remained intact. The insoluble micro-crystalline cellulose was able to maintain the skeletal shape of the millispheres after complete drug removal. Drug release from uncoated millispheres containing ibuprofen appeared to exhibit first-order kinetics and this is sustained even when the initial drug loading is as high as 80 %w/w (as is shown in Figure 1, see 0 % coating curve).

Drug release from polymer-coated millispheres

The application of a retarding membrane in the form of an aqueous dispersion to the spherical multiparticulates has the effect of slowing the rate of drug release. There appears to be a critical coating level, below which core coverage by the polymer is incomplete and drug release is apparently diffusion controlled and first-order kinetics are observed; the drug release rate becomes more linear after a minimum polymer level has been achieved (see Figure 1). Dyer (1) also reported the visual appearance of pre- and post-dissolution millispheres by SEM. These observations assist greatly in understanding the structure of the resulting films.

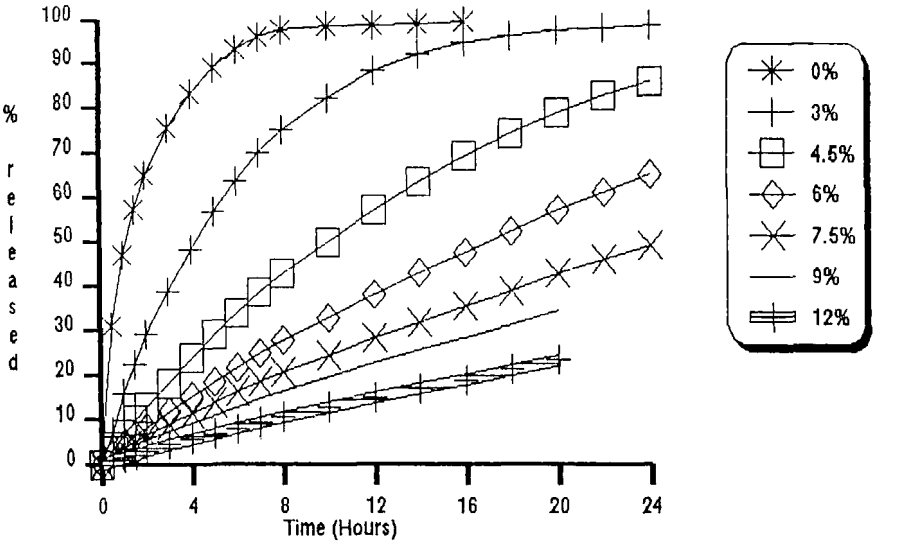

FIGURE 1

In-vitro drug release from 800 mg ibuprofen millispheres containing 80 %w/w ibuprofen coated with an aqueous dispersion of Eudragit RS30D/RL30D to give a millisphere weight increases between 0 %w/w (i.e. uncoated) and 12 %w/w.

Effect of curing

The formation of efficient polymer films from aqueous dispersions requires complete coalescence of the film. This was achieved by curing at 40°C for 24 hours after coating. However, this additional process produced negligible difference to the drug release curve. This can be observed in Figure 2. It can be concluded that the process conditions developed and reported by Dyer (1) resulted in good quality, fully-coalesced films.

Other polymers and plasticizers

Corresponding data has been generated by Dyer (1) for Surelease and silicone elastomer aqueous dispersion coatings of various composition. Drug release profiles were influenced by the presence of plasticizer.

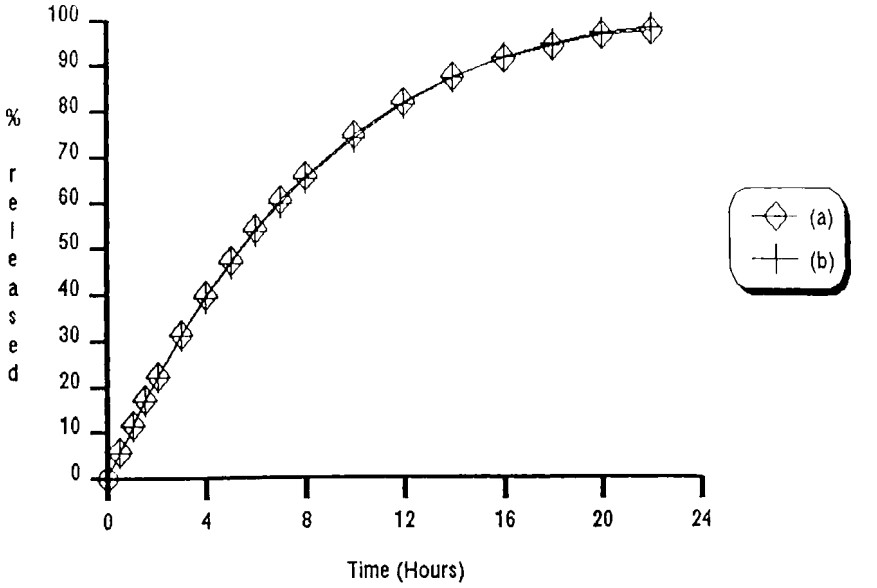

FIGURE 2

In-vitro drug release from 800 mg ibuprofen millispheres containing 80 %w/w ibuprofen coated with an aqueous dispersion of Eudragit RS30D/RL30D to give a weight increase of 4.5 %w/w; (a) millispheres not subjected to a post-coating 'curing' stage and (b) millispheres subjected to a post-coating 'curing' stage.

Dissolution of the water-soluble plasticizers from the film facilitates penetration of water molecules and creates pores in the membrane.

D. MECHANICAL PROPERTIES OF FREE FILMS

The assessment of the mechanical properties by indentation testing of the polymer films used for the coating of multiparticulate spheres provides information which will help to understand the ability of these films to contribute to the deformation resistance of the millispheres and thus their ability to withstand the stresses associated with their compaction into a tablet matrix. The theory, techniques, significance and consequences of the data obtained from the indentation testing of polymeric films is discussed briefly here and the reader is referred to Aulton (14) for further detailed information.

Indentation rheology of polymer films

Indentation testing involves measuring the penetration of an indenter tip under a known fixed load into a film coat, either *in situ* on the dosage form (tablet or millisphere) or into a free film mounted on a horizontal platen. The indenter tip will penetrate the material to a distance which is dependent upon the applied load and the rheological properties of the film itself. For any given load, the indenter will travel further into a softer material than into a harder one.

Indentation hardness can be defined as '*the quasistatic resistance to localised non-homogeneous deformation caused by a point object*' and can be quantified in terms of the load applied to the indenter divided by the area beneath the indenter tip that will support that load. Hardness therefore has the dimensions of pressure (units: Nm^{-2} or Pa). The use of a spherical indenter tip gives Brinell or Meyer's hardness values and a square-pyramidal diamond gives Vickers hardness values. Each of these has been used for the testing of a variety of pharmaceuticals, see Aulton (14)(15).

However, due to the time-dependent nature of polymer films of the type used for coating multiparticulates, the indentation depth does not remain constant under any given set of conditions but changes gradually with time as the indenter penetrates slowly into the polymer. Thus, single hardness values for polymer films are meaningless. Possible solutions to this problem are available, see Aulton (14)(16). A mathematical solution involves the derivation of time-dependent viscoelastic parameters by the generation of creep compliance curves. This technique is described in detail in Aulton (14) and is referred to briefly here.

If the changing depth of penetration of a spherical indenter under a fixed load is followed with time and recorded as the indenter moves into a polymeric film sample, the time-dependency of this process can be followed. It is possible to convert the depth of indentation at any time into creep compliance (strain/stress, Pa^{-1}) and then to perform a classical creep analysis in order to generate quantitative 'spring and dashpot' mechanical models (see Aulton (14)). Analysis of these data

gives us an extremely useful insight into the viscoelastic nature of the material.

Indentation testing provides a valuable means of assessing the mechanical properties of the polymer and the effect of the presence of other excipients within the film. This is fundamental to the further understanding of the manner in which polymer films will perform during tablet compression. Those parameters which are particularly useful in this respect include instantaneous elastic deformation and elastic modulus, time-dependent viscoelastic deformation, Newtonian viscosity, and elastic and time-dependent viscoelastic recovery on load removal.

The instantaneous elastic compliance of a material is the reciprocal of the elastic modulus. Those materials exhibiting a relatively low elastic modulus will therefore undergo a relatively high instantaneous elastic strain at low loads during and following compression. This will confer a high resilience to the millisphere but reduce its brittleness during compression.

The apparent Newtonian viscosity of the film gives an insight into how the material will flow under applied stress and is inversely proportional to the slope of the linear non-recoverable portion of the compliance *versus* time curve. Hence materials exhibiting a low apparent Newtonian viscosity will have a correspondingly large non-recoverable viscous deformation on the application of stress.

In general, the effect of increasing the plasticizer content in a given polymeric film formulation will be to increase the instantaneous and time-dependent deformation and decrease the apparent Newtonian viscosity. That is, the permanent non-recoverable plastic deformation associated with applied stress increases with increasing plasticizer concentration.

In addition to the polymer and the plasticizer, the presence of other excipients within a polymer film (e.g. opacifiers, pigments) may also exert a considerable influence on the mechanical properties of a given polymer film formulation (see Aulton (14)).

Sample preparation for mechanical testing

The film preparation technique must facilitate uniform spreading of the polymer solution or dispersion with minimal adherence of the dried film to the test substrate. The resulting film must be of a uniform, realistic thickness, have a smooth surface and be free from air bubbles and unwanted particulate contamination.

The physical characteristics of the dispersions used in this work (low viscosity and containing suspended solids) meant that casting onto a glass plate using a simple applicator (as is commonly used for, say, aqueous HPMC films) was not possible. Aqueous dispersions require a different approach. The technique of Devereux (17) was adapted to facilitate the formation of films of the required quality as defined above. This technique involves casting the film into a rotating polytetrafluoroethylene (PTFE) cylinder (see Figures 3 and 4).

The cylinder was rotated at 20 rpm and the temperature of the environment maintained at 42 °C ± 2 °C. After a prewarming period of two hours, 60 g of the dispersion was poured into the rotating cylinder and left to dry for 24 hours (the majority of the water was removed in the first two hours). The continual rotation of the cylinder ensured that sedimentation of the dispersed particles did not occur and the use of PTFE ensured that the resulting film was easily removed without damage.

Indentation testing

The indenter used was an adapted ICI micro-indenter originally developed for the indentation testing of paint films. The indenter was modified (Aulton et al. (18)) by replacing the original pneumatic amplifier with a LVDT, the output of which is proportional to the movement of the indenter tip and is logged by computer. This enabled easy mathematical manipulation of indentation depth *versus* time data to yield creep compliance and to allow subsequent creep analysis. It is important during such testing to manipulate the load on the indenter to ensure that the depth of indentation is not too great. If the depth of penetration is greater than about 1/6th of the thickness of the film, the readings are

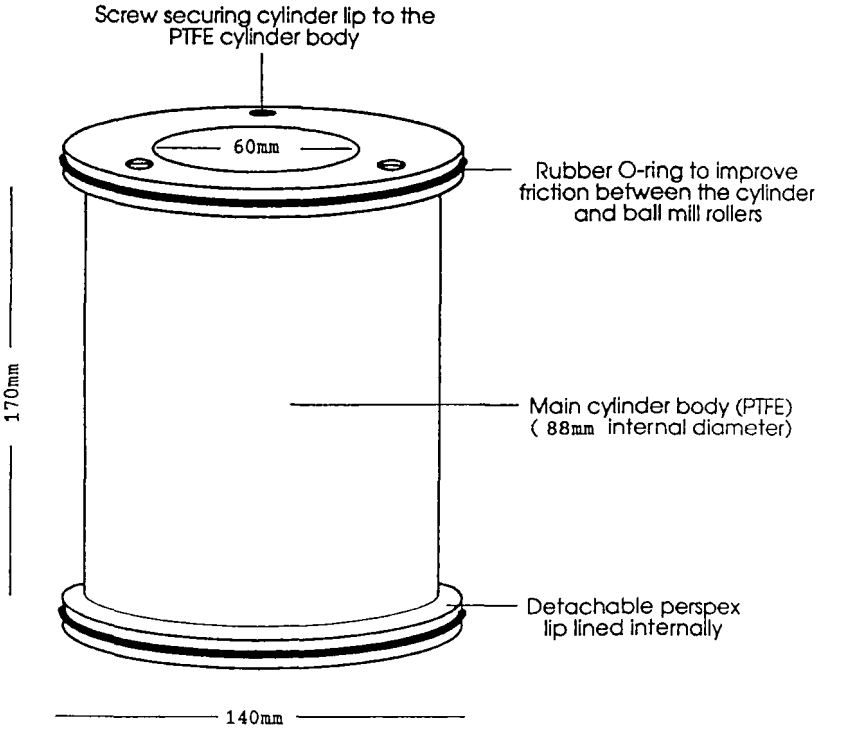

FIGURE 3

Dimensions and construction of the hollow PTFE rotating cylinder used in the film casting of aqueous polymeric dispersions.

inaccurate since they are influenced by the substrate on which the film is sitting.

Creep compliance data

The resulting data for plasticized polymethacrylate films are shown in the following graphs (Figures 5 to 8). Figure 5 shows that as more plasticizer is added to the polymethacrylate formulation, the instantaneous elastic compliance increases. This is an indication of the increased flexibility and deformability of the film. This in turn is reflected by a corresponding decrease in the elastic modulus (and therefore the rigidity) of the film (Figure 6). The time-dependent elastic compliance of the films follows a similar pattern to its instantaneous counterpart, i.e. increased

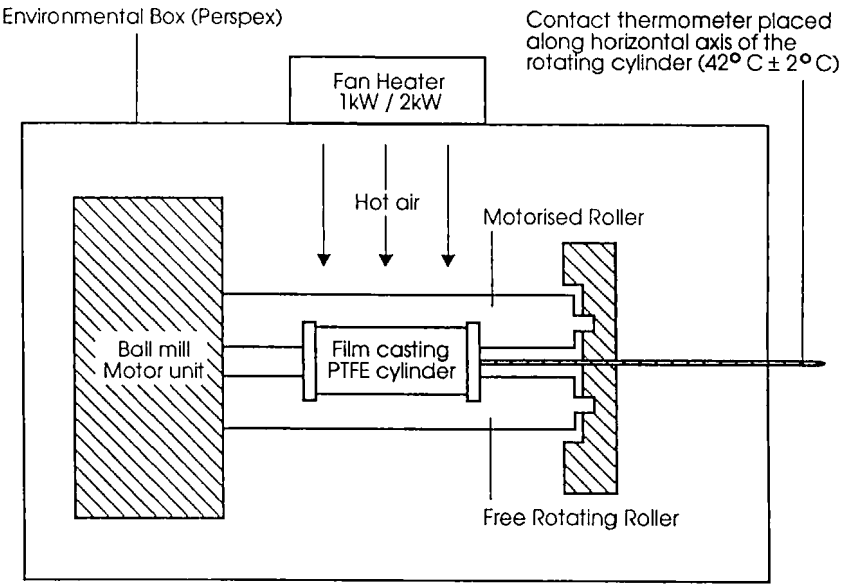

FIGURE 4

The free-film casting assembly within its environmentally controlled cabinet.

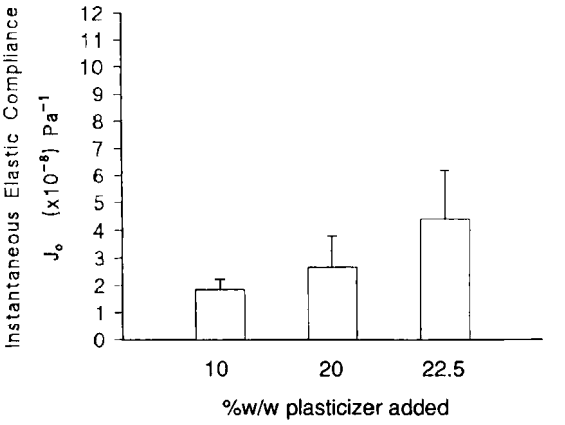

FIGURE 5

Influence of plasticizer concentration on the instantaneous elastic compliance of polymethacrylate free films.

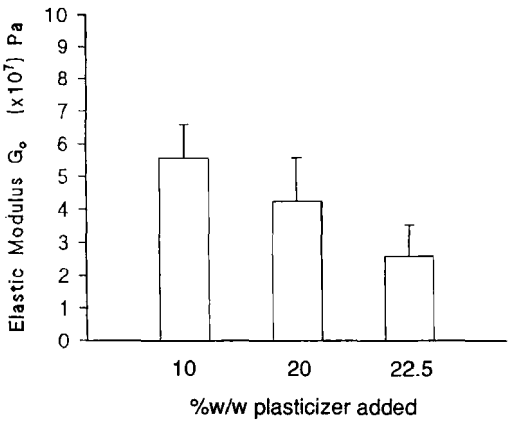

FIGURE 6

Influence of plasticizer concentration on the elastic modulus of polymethacrylate free films.

deformability with increased plasticizer addition (Figure 7). Figure 8 shows the influence that increasing levels of plasticizer have on the non-recoverable deformability of the film. The Newtonian viscosity of the film shows a marked reduction as increased plasticizer levels are included in the film. All these observations follow the trends expected as a consequence of the addition of an efficient plasticizer and similar trends have been observed and reported for many polymer/plasticizer combinations (see Aulton (14)). What is significant about these result is that they indicate how major changes in the mechanical properties of the films can be manipulated by relatively simple formulation changes. This is extremely important in the context of this study in which one is attempting to design a coated multiparticulate dosage form which will withstand the strains involved with both compression and stress release during tabletting.

Conclusions

When combining the data generated in the indentation study of the mechanical properties of polymeric films with that of the study (discussed later) regarding the effect of compression on the integrity of the millisphere core and the film coat, it is evident that polymeric films

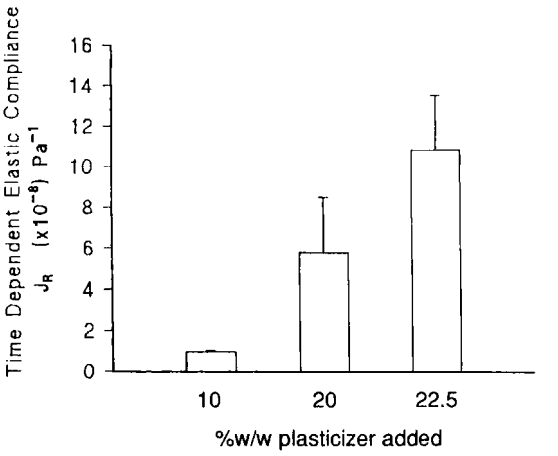

FIGURE 7

Influence of plasticizer concentration on the time-dependent elastic compliance of polymethacrylate free films.

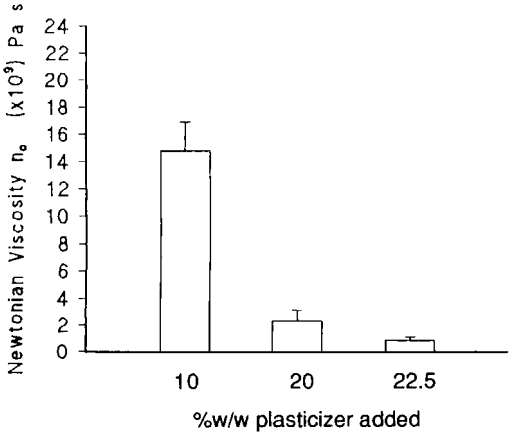

FIGURE 8

Influence of plasticizer concentration on the Newtonian viscosity of polymethacrylate free films.

exhibiting a relatively high instantaneous and time-dependent elastic compliance (i.e. low elastic and viscoelastic moduli) are unlikely to satisfy the requirements for favourable tablet preparation due to the associated elastic recovery which will occur immediately on removal of the applied stress.

It may also be concluded that those films exhibiting a relatively high elastic modulus and a relatively high apparent Newtonian viscosity provide greatest protection to the millisphere core and coat on compression.

Within the scope of this work, of those aqueous polymeric film coating systems evaluated, a polymethacrylate dispersion (Eudragit RS30D/ RL30D mixture) appeared to form an effective film coat with the required mechanical properties, as outlined above, for the coating of ibuprofen millispheres which are required to withstand compression into tablets. The effect of the compression process on the ability of coated millispheres to withstand applied stress and the effect on the integrity of the film coat and the millisphere core is discussed again later.

Since the process of millisphere compaction involves the application of stress to polymer-coated spherical cores, in order to fully understand the interrelationships between the mechanical properties of the film, the millispheres and the resulting compacts, it is necessary not only to evaluate and quantify the mechanical properties of polymers as free-films but also to study the properties of the polymeric membrane *in situ* on the millisphere core. The following section is therefore a study of the mechanical properties of uncoated and coated single millispheres.

E. MECHANICAL PROPERTIES OF MILLISPHERES

Particles may fracture on the application of stress. Initially, when stress (force per unit area) is applied to a solid, the solid undergoes strain (ratio of change in a given dimension to its original value). An elastic material deforms under stress but returns to its original size and shape when the stress is removed. Initially stress is directly proportional to the resulting strain and the quotient stress/stress is the modulus of elasticity. If a particle is stressed further, the solid will either flow plastically and/or

fracture at a stress known as its tensile strength (or its crushing strength if the fracture is not purely in tension). The aim of this formulation exercise was to prevent fracture of the millisphere from occurring. This means that the desirable mechanical properties of the millispheres should be that they are strong, not brittle and have low elastic resilience. They should deform under load application and load recovery without fracture. It is important in this dosage form that the millisphere *and its coating* remain undamaged and intact.

It is postulated that by gaining an insight into the mechanical properties of these coated millisphere formulations it should be possible to design a compacted millisphere tablet formulation in which the compression process has minimal effect on the integrity of the cores, the polymeric membrane and, consequently, the drug release mechanism from the multiparticulates.

The mechanical properties of both uncoated and coated ibuprofen-containing millispheres and placebo millispheres were measured using a Single Particle Crushing Assembly (Wong et al. (19)). This apparatus (shown in Figure 9) records the force required to cause single millisphere fracture and particle displacement under applied load. The generation of this information facilitated estimation of the tensile stress, elastic modulus, percentage strain and work done in causing fracture for each of the various millisphere formulations. These properties were related to the fundamental bonding forces arising from the pelletization process which determine the strength of the millisphere, and to the contribution made to the overall mechanical properties of the millispheres by the presence of the film coating (and thus, in turn, its mechanical properties).

Results

The resulting mechanical properties of the millispheres, as assessed using the Single Particle Crushing Assembly, are shown in the following representative series of bar charts (Figures 10 to 13). Figures 10 and 11 show the influence of drug:excipient ratio on the crushing strength and elastic modulus of uncoated spheres. These figures show an increase in strength and an increase in elastic modulus resulting from a decrease in

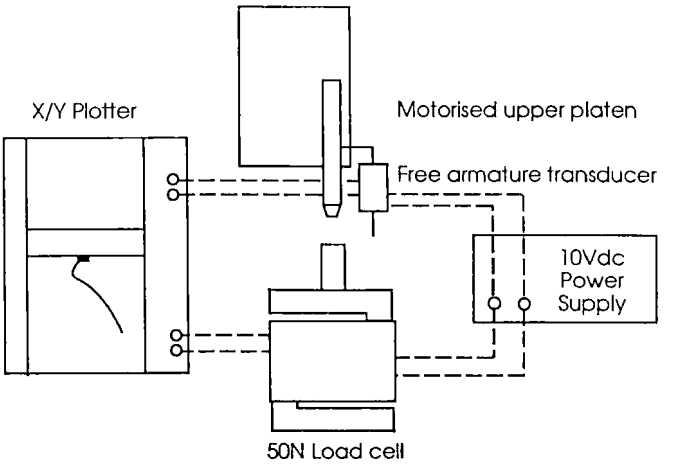

FIGURE 9

Single Particle Crushing Assembly (schematic diagram).

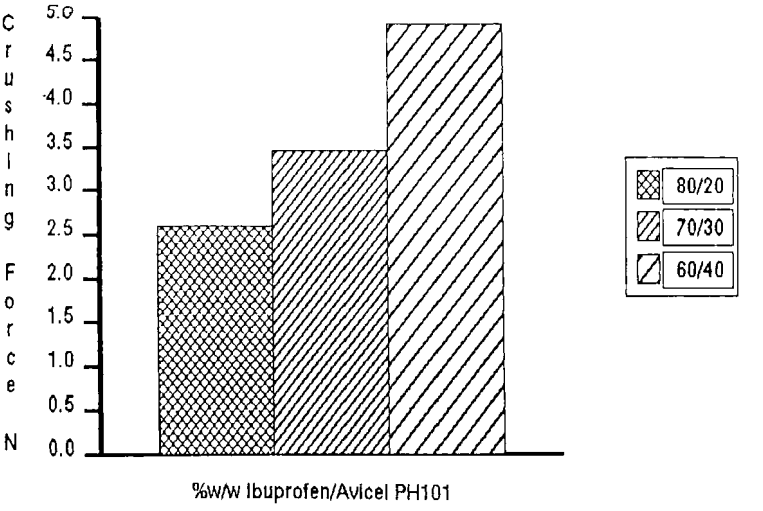

FIGURE 10

Effect of drug loading on the crushing force required to fracture ibuprofen pellets dried in a fluidized bed.

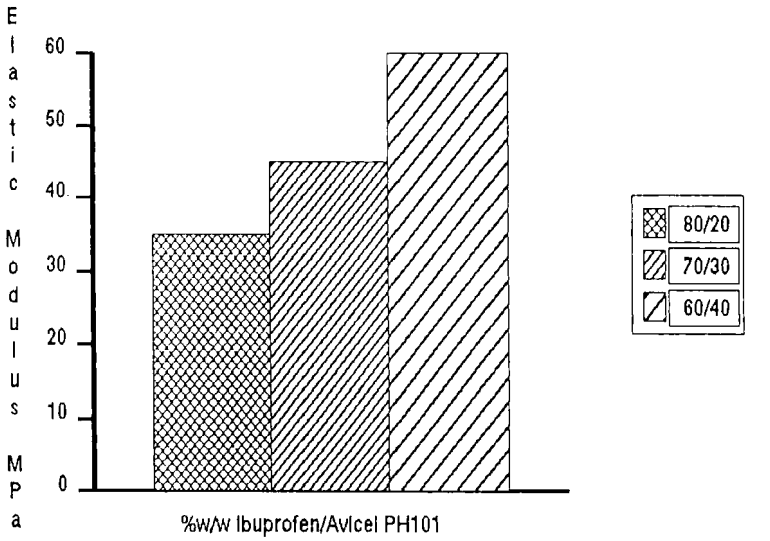

FIGURE 11

Effect of drug loading on the elastic modulus of ibuprofen pellets dried in a fluidized bed.

drug content of the millispheres, i.e. as the drug is replaced by microcrystalline cellulose. It is well established that microcrystalline cellulose is an excellent excipient for extrusion/spheronization and that the resulting spheres are of excellent quality. These data confirm this.

What is relevant to consider in the context of this design exercise, however, is that we do not have the freedom to add excessive amounts of excipient to this formulation. The aim here is to produce satisfactory multiparticulates containing a high drug dose (800 mg). Excipients must be kept to their absolute minimum.

The influence of increasing levels of polymer coating on the mechanical properties of millispheres is shown in Figures 12 and 13. These figures compare the crushing force and elastic modulus of uncoated spheres with those which have been coated with 4.5 and 12 % weight increase of a polymethacrylate polymer formulation.

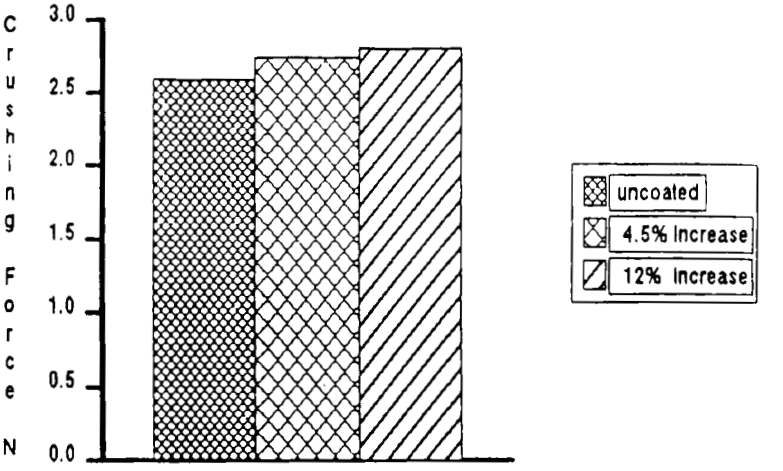

FIGURE 12

Effect of the presence of a film coat of Eudragit RS30D/RL30D on the crushing force required to fracture millispheres containing 80 %w/w ibuprofen dried in a fluidized bed.

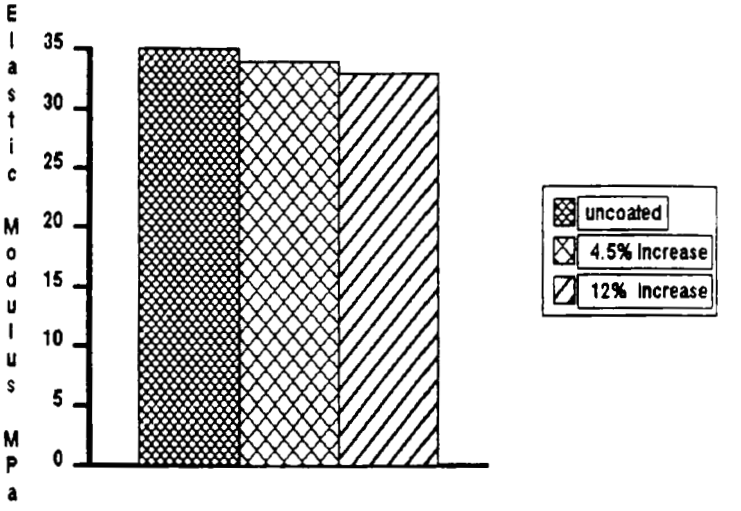

FIGURE 13

Effect of the presence of a film coat of Eudragit RS30D/RL30D on the elastic modulus of millispheres containing 80 %w/w ibuprofen dried in a fluidized bed.

Discussion

Much quantitative and qualitative information is generated by studying the effect of formulation factors and processing variables on the properties of both placebo and ibuprofen millispheres.

Of great importance is the influence of the drying technique on the resultant mechanical properties of millispheres containing excipients which are either poorly or freely water soluble (9)(10). In summary, millispheres prepared using extrusion and spheronization technology and dried using fluidized-bed methodology, exhibit lower moduli of elasticity and lower crushing strengths than their tray-dried counterparts.

The aqueous solubility of the excipients from which millispheres are composed also has a significant effect on the crushing strength. For millispheres containing a freely water-soluble excipient, it is not unreasonable to anticipate the presence of solute molecules of this component which have dissolved in the aqueous granulating fluid during the wet massing stage. Water removal from these multiparticulates during drying following spheronization of the material would thus lead to the formation of solid bridges within the spheres by fusion at the points of contact of the primary powder particles. This will result in a greater degree of bonding and hence the formation of millispheres of greater strength. This is supported by the data for the relative crushing strengths and elastic moduli of millispheres containing 20 %w/w microcrystalline cellulose with 80 %w/w of either ibuprofen or lactose (see Figures 14 and 15 later). Fluidized-bed-dried ibuprofen millispheres exhibit a strength which is only approximately 20 per cent of that of lactose-containing millispheres prepared using the same process.

The quantity of the spheronization enhancer microcrystalline cellulose (Avicel PH101) in millisphere formulations has a significant effect on the crushing strength and other mechanical properties of millispheres containing ibuprofen. An increase in the microcrystalline cellulose content of millispheres, and thus a corresponding decrease in the ibuprofen content, increases the strength of the millispheres (Figure 10) with a corresponding increase in their elastic modulus (Figure 11). The

presence of microcrystalline cellulose in millisphere formulations serves not only to facilitate the production of high quality millispheres, but in its capacity as a binder it enhances the adhesion between the components of the blend resulting in more robust millispheres of greater mechanical strength. For example, millispheres containing only 20 %w/w microcrystalline cellulose with 80 %w/w ibuprofen required a mean force for fracture of 2.59 N, compared with millispheres containing 40 %w/w microcrystalline cellulose which required a mean force of 4.91 N. In addition, millispheres containing only 20 %w/w microcrystalline cellulose exhibited a mean elastic modulus of 35 MPa, whilst millispheres containing the higher percentage of binder (40 %w/w microcrystalline cellulose) exhibited a mean elastic modulus of approximately 60 MPa.

The presence of a film coat applied by means of an aqueous polymeric dispersion of polymethacrylates also influences the crushing strength and the elastic properties of ibuprofen millispheres. Increasing the polymer loading has the effect of increasing the crushing strength of millispheres (Figure 12) whilst simultaneously enhancing millisphere resilience (characterised by a reduction in the elastic modulus, Figure 13). This is not true for all polymers, however (1).

One of the consequences of increasing the crushing strength of millispheres is that there is usually a corresponding increase in their elastic modulus. It is evident, therefore, that the effect of a polymer coating surrounding a millisphere core serves not only to influence its mechanical strength but also its resilience.

Conclusions

An understanding of the mechanical properties of uncoated millispheres, coated millispheres and free polymeric films was considered fundamental to the design of a satisfactory tablet formulation comprising compacted polymer-coated millispheres in which the integrity of the millisphere cores and the film coating is to be preserved. The next section considers tablet design and incorporates a quantitative study of millisphere distribution within the tablet matrix and of drug release from the millispheres following compaction into tablets.

F. DESIGN AND EVALUATION OF COMPRESSED TABLETS CONTAINING POLYMER-COATED MILLISPHERES.

Tablet compression

The objective of this part of the study was to design a tablet containing 1 mm diameter coated ibuprofen-containing millispheres which would release these millispheres on tablet disintegration with minimal damage. The spheres must be robust, and the core and its coating must deform without fracture. The compression of multiparticulates has been discussed previously (e.g. Maganti and Çelik (20)(21), Çelik and Maganti (22) and Schwartz et al. (13)) and the reader is referred to these publications for further information.

In this present study it was essential to design a suitable inert compression diluent. In this context the diluent should, in addition to all normal tabletting considerations, have minimal segregation propensity, cushion the millispheres during compression so as to minimise damage, disintegrate rapidly to release intact millispheres and have minimal effect on drug release kinetics. Tablet formulations containing 800 mg ibuprofen were studied. The particle size of the excipients and their relative proportions were carefully optimised. The large drug dosage necessitated the minimum quantity of diluent to fill the void volume within the tablet during compression.

Good blending and minimal segregation are essential in order to achieve satisfactory uniformity of weight and content of the tablet dosage form. The potential problem of segregation in any particulate system must be addressed. Segregation is influenced by factors such as markedly differing particle size, density or shape. In order that the occurrence of segregation between the drug-containing millispheres and the excipient particles is minimised, it was deemed necessary to choose large particle size excipients. This can achieved either by the preparation of placebo millispheres or by use of large particle size powders.

No single ingredient is ideal as a direct compression vehicle and therefore it was considered appropriate to blend excipients of differing properties. The excipients chosen were microcrystalline cellulose and alpha-lactose

monohydrate; a mixture of microcrystalline cellulose and lactose offers such a combination of properties. Microcrystalline cellulose is highly compressible and consolidates by plastic deformation, whereas alpha-lactose monohydrate fragments on compression. Microcrystalline cellulose, being highly compressible, produces hard tablets of low friability which are water insoluble; lactose possesses reasonably good compactibility and is readily soluble in water.

Use of placebo millispheres as the diluent

It was postulated that anticipated problems associated with blending and segregation of drug-containing millispheres and excipients might be prevented or at least minimised by admixing active and placebo spheres of the same size and approximately the same density. To ensure that the coated ibuprofen millispheres remained intact on compaction, the placebo spheres must be mechanically weaker than the coated drug-containing ones. Additionally, the placebo spheres should preferably exhibit fragmentation rather than plastic deformation during their compaction with the ibuprofen millispheres in order not only to fill the voids between the millispheres but also to surround them so that the tablet is held together by excipient-excipient contact. Ideally the placebo millispheres should fracture into progeny primary powder particles thus facilitating maximum tablet bonding. To this end 1 mm diameter placebo millispheres containing microcrystalline cellulose and lactose were produced by extrusion and spheronization.

Numerous formulae containing various lactose/microcrystalline cellulose combinations were made in an attempt to produce relatively weak millispheres but, in brief, many were either of poor quality with respect to uniformity of size and sphericity or possessed a mechanical strength in excess of that of the ibuprofen-containing entities.

Placebo millispheres containing high microcrystalline cellulose levels were, by virtue of the inherent bonding capacity of this material, exceedingly hard. In addition, it became evident that placebo millispheres containing high lactose levels were also very hard. This results from the partial dissolution of the lactose during wet massing and extrusion and the formation of solid bridges during drying. It was

thought that the replacement of all or part of the granulating water with isopropyl alcohol (in which lactose is insoluble) might enable the preparation of softer placebo millispheres which would readily fragment at low pressure during tabletting. However, the resulting millispheres were still too strong.

The best potential placebo millispheres contained 80 %w/w lactose and 20 %w/w microcrystalline cellulose (Avicel PH101). Figures 14 and 15 compare the relative mechanical strengths and elastic moduli of fluidized-bed millispheres containing these ingredients with those containing 80 %w/w ibuprofen and 20 %w/w microcrystalline cellulose.

These diagrams illustrate clearly that the placebo millispheres require more than three times greater applied force before they crush, and exhibit a much higher elastic modulus, than their drug-containing counterparts. Other formulations tested required a crushing force beyond the capability of the Single Particle Crushing Assembly and in each case they clearly possessed a strength far in excess of the drug-containing millispheres.

Thus it was decided that the admixture of ibuprofen-containing millispheres and placebo millispheres was not a viable proposition for this product.

Use of dry powder mix as the diluent

As an alternative to mixing ibuprofen-containing and placebo millispheres, an attempt was made to mix the drug-containing spheres with large particle size powdered excipients. Avicel PH200 (a microcrystalline cellulose grade comprising relatively large, spherical particles) was chosen for investigation. It has a size specification of 10 % by weight not less than 250 μm and 50 % not less than 150 μm. Its size and shape impart good flow properties to the material. The largest particle size of lactose which is readily available commercially at present is Meggle lactose EP, grade D10. It is a coarse-crystalline product exhibiting favourable flow properties. Its particle size specification is 100 % less than 800 μm, 12 to 35 % less than 400 μm and a maximum of 75 % less than 200 μm, giving a mean size of around 500 μm.

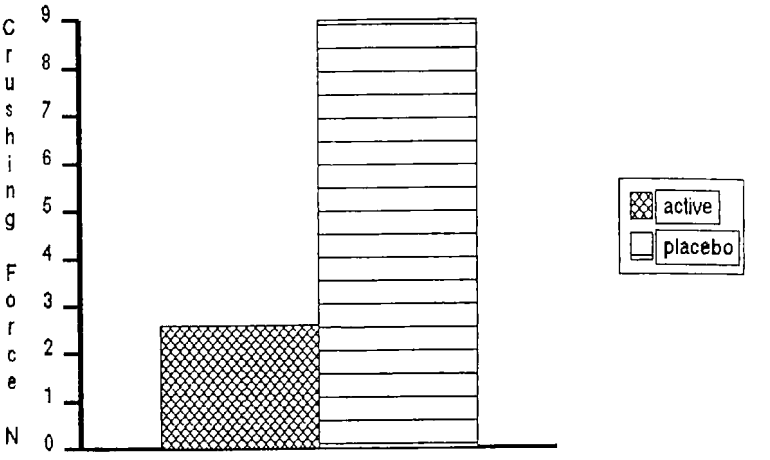

FIGURE 14

Crushing force required to fracture fluidized-bed dried millispheres containing 80 %w/w ibuprofen or 80 %w/w lactose with 20 %w/w microcrystalline cellulose.

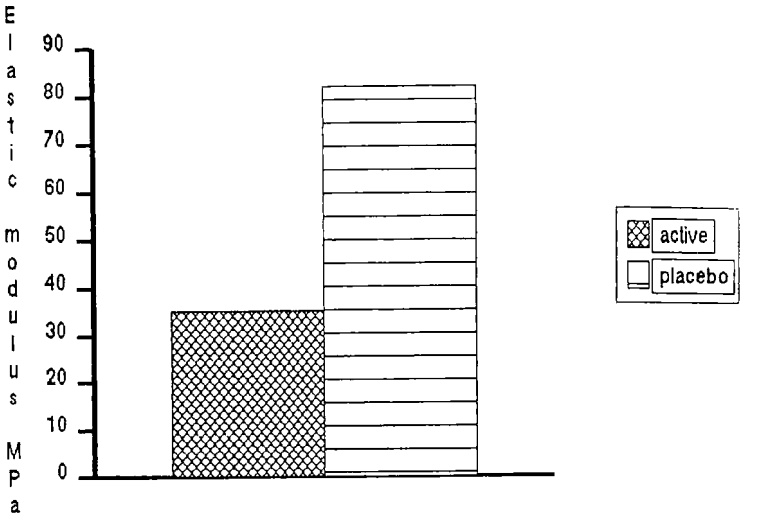

FIGURE 15

Elastic moduli of fluidized-bed dried millispheres containing 80 %w/w ibuprofen or 80 %w/w lactose with 20 %w/w microcrystalline cellulose.

Coated ibuprofen millispheres were blended in a Turbula mixer with Meggle D10 lactose and Avicel PH200 for 15 minutes. The optimum formulation for compression was found in each case (see later) to be 60 % of millispheres (each containing 80 % drug) and 40 % inert diluent blend. Magnesium stearate 0.5 % was included and blended for a further 10 minutes.

Tablet compression

Tablets were compressed on a single-punch tablet machine (Manesty F3) fitted with pillow-shaped concave punches of dimensions 25 mm x 9 mm. Tablets were compressed at a range of compaction pressures in order to determine the minimum and maximum compression force which would yield tablets of low friability, rapid disintegration and cause the minimum damage to the integrity of the millispheres.

Tablet properties

The tablets were subjected to analysis of their diametral crushing strength, friability, disintegration, uniformity of tablet weight, uniformity of ibuprofen content and *in-vitro* dissolution characteristics.

Tablet mechanical properties

The mean diametral crushing strengths of the resulting tablets were measured with a Schleuniger 4D Tablet Tester with the compressive force being applied longitudinally to the tablets. Tablet friability was determined using an Erweka Friabilator (five tablets for 6 minutes). Tablet disintegration was performed in a vertically oscillating basket-rack assembly containing purified water at 37 °C.

The compression of millispheres in a powder matrix consisting solely of lactose did not produce a proportional increase in the diametral crushing strength of the resulting tablet with increasing compression force. It was not possible to form very strong tablets where lactose was the single or main component of the diluent. These tablets were very friable to handle and indeed did not maintain their integrity during friability testing. Addition of microcrystalline cellulose to the powder mix resulted in

stronger tablets on compression. Additional benefits of its addition are a reduction in tablet disintegration time and a reduction in tablet friability at a given compression force. The optimised diluent blend was found to be lactose 19.5 %w/w (Meggle D10), microcrystalline cellulose 20 %w/w (Avicel PH200) and magnesium stearate 0.5 %w/w.

The minimum amount of excipient required to fill efficiently the void space between the millispheres (in order to leave an excess to facilitate bonding and cushioning of the millispheres) was found to be 40 %. Tablets containing between 30 and 40 % of diluent were excessively friable and if less than 30 % was added there was incomplete tablet formation. The detection of this minimum amount is important in the case of high-dose drugs in order to minimize the bulk size of the final peroral dosage form.

Millispheres coated with polymethacrylate polymers compacted satisfactorily into tablets (as assessed qualitatively with respect to their appearance), but millispheres coated with polymers exhibiting a high degree of instantaneous elastic recovery resulted in tablets which disintegrated into their original components on ejection from the die.

The optimised compressed formulation consisted of 60 % of millispheres (each containing 80 %w/w ibuprofen and 20 %w/w microcrystalline cellulose) coated with Eudragit RS/RL30D (4.5 % weight increase) in a powder matrix of the formula above. This mixture was compressed at 4.75 kN to produce shiny tablets with a crushing strength of about 200 N and a friability of 1.74 %. These tablets disintegrated *in vitro* releasing apparently intact coated millispheres within 90 seconds.

Uniformity of tablet weight and uniformity of ibuprofen content

Uniformity of tablet weight was satisfactory. The relative standard deviation (rsd) was less than 1 %.

The uniformity of ibuprofen content in the tablet were assessed by assay of a filtered solution from disintegrated tablets and crushed millispheres which had been shaken in contact with water for 24 hours. The uniformity of content of ibuprofen in the compacted tablets was 4.22 %

rsd, i.e. within the target value of 5 % rsd. The inference of this is that, under the pilot-scale conditions used in this work, segregation of the diluent blend from the active millispheres does not appear to be a problem. It is accepted, however, that this may not be the case on scaling up the process.

In-vitro drug release from polymer-coated compressed millispheres compared with uncompressed millispheres

In order to quantify the extent of millisphere damage it is necessary to consider the effect of compaction on the *in-vitro* release profiles from those millispheres which have been subjected to a compression process and those which have not. *In-vitro* drug release was determined over a 24 hours period by the methodology described earlier (Section C). As explained previously this paper will not consider drug release kinetics in detail but it is important to emphasise that examination of changes in release kinetics is a useful way of quantifying the degree of damage to the release-controlling polymer film. Figure 16 shows the effect that compaction has on ibuprofen release. These millispheres have been coated to 4.5 % weight increase with polymethacrylate polymer from an aqueous dispersion formulation.

It is evident that slight damage is caused to the millispheres as a consequence of compaction; this is highlighted by an increase in the rate of drug release from compacted millispheres compared their non compacted equivalents. However the controlled release characteristics of the dosage form are not destroyed and the release kinetics are still useful for controlled drug release therapy. These data also show that changing the compaction force from 2.80 kN to 4.75 kN has little significant effect on drug release, thus inferring that there is little extra damage caused by the higher compaction force. This is important evidence because the increased compaction force produces tablets with increased diametral crushing strength, reduced friability and enhanced product appearance with no apparent increase in damage to the millispheres. As later evidence shows, this damage is mainly associated with those millispheres present at the surfaces of the tablets during compression. These observations indicate that it is not compaction pressure *per se* which causes damage to the millispheres but the actual process of

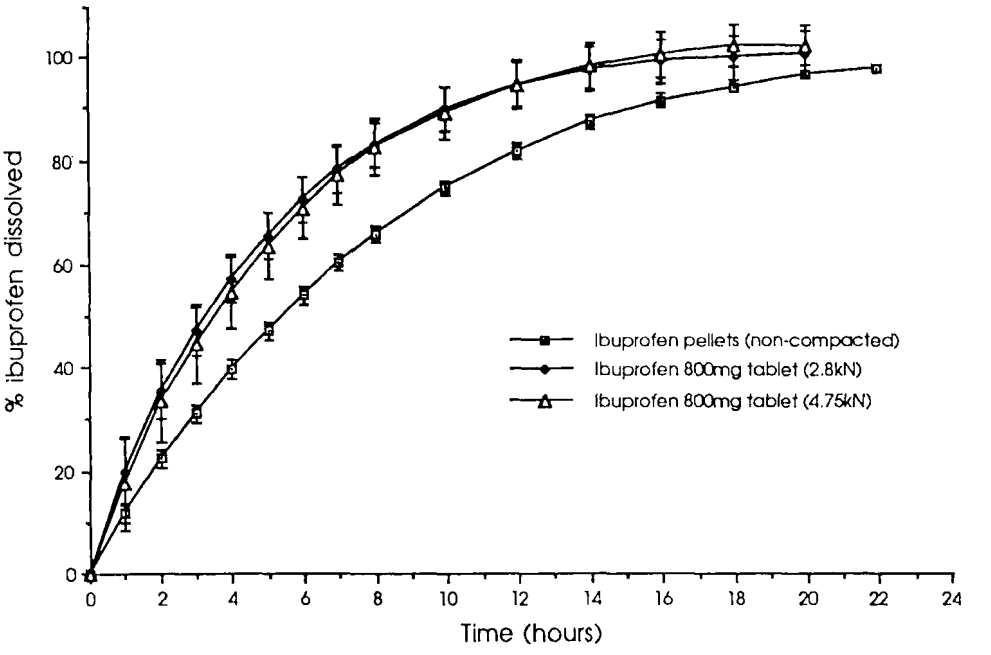

FIGURE 16

In-vitro drug release from compacted and uncompacted millisphere formulations containing 800 mg ibuprofen.

compaction. The damage is probably associated with factors relating to excessive distortion of the millispheres and their coating when in direct contact with the die wall and tablet punch.

Qualitative study (using photomicrography and scanning electron microscopy) of the effect of the compaction process on millisphere integrity

Millisphere integrity was assessed by photomicrography of the released millispheres, paying particular attention to the resulting particle shape of the pellets and any deformation or damage to the film coating resulting from compression. Disintegration of the tablet matrix yields discrete, visibly intact, single entities. The millispheres were recovered from the disintegration tubes by filtration and allowed to dry under ambient temperature and humidity. This procedure was carefully controlled in order to eliminate shrinkage of the millispheres during drying.

Comparison of photomicrographs of coated millispheres prior to compaction and of those released from tablets following compaction and disintegration shows that the compacted millispheres have remained basically intact but most have undergone a certain degree of permanent deformation as a consequence of the compaction process. Investigations to assess any damage to the film coat was carried out by scanning electron microscopy. This evidence illustrates that limited damage is being incurred by some millispheres, particularly those at the tablet surface which are unprotected by the excipient mixture from direct contact with the punches and die during compaction.

Closer examination of the film by SEM showed evidence of some slight cracking of the film coat on isolated millispheres but no significant flaking or holes were visible.

Quantitative evaluation of millisphere distribution within the tablet matrix by image analysis

Quantitative evaluation of the distribution of the millispheres within the tablet matrix was performed by image analysis using an Eltime III Image Analysis System. This facilitated a study of any potential segregation of the millispheres within the tablet. Samples of ibuprofen-containing millispheres were coated and then stained with a 0.1 % aqueous solution of Green S, a water-soluble dye used in the food industry. Samples of tablets were examined with respect to the shape of the millispheres and their distribution at the tablet surface, tablet edge and across the section of intentionally broken tablets. There was no evidence of segregation.

OVERALL CONCLUSIONS

Some thoughts on mechanical properties

The particular direction of this review paper was to consider the role that the mechanical properties of all components had contributed to the difficulties or success of the proposed dosage form. Aqueous polymeric dispersion which formed a film with similar elastic and tensile properties to the uncoated millisphere formulation result in the most satisfactory film coating for application to spherical particles which must withstand

compaction. Those polymeric films exhibiting significantly greater resilience than the uncoated cores were inappropriate for the film coating of millispheres for compaction into tablets. This was due to the tendency of these films to exhibit excessive elastic recovery on removal of the compaction load, such that even the application of maximum compression force was not capable of producing cohesive tablets containing these particular polymer-coated entities.

The hoop stress associated with the physical presence of the polymeric membrane surrounding a millisphere core is capable, with some polymer formulations, of enhancing the diametral crushing strength of a coated millisphere, provided that sufficient polymer of the correct mechanical properties is applied. Increasing the amount of such a film added to the millispheres has the effect of enhancing their crushing strength thus increasing in the stress that the particles can withstand without fracture.

Concluding comments

The resulting dosage form was satisfactory. The compact designed here is of acceptable size and robustness and the tablets were found to have suitable mechanical properties and to disintegrate rapidly *in vitro* releasing virtually intact sustained-release coated millispheres. Slight damage to the millispheres was visible and photomicrographs showed that most spheres had undergone a certain degree of deformation on compression. This was examined further by scanning electron microscopy which indicated that although the millispheres had became somewhat deformed, their film coating remained virtually intact.

Quantitative evaluation of the distribution of millispheres within the matrix of the compacted tablets was made by image analysis of sections of a matrix comprised of coloured millispheres in white excipient. This showed a uniform, non-segregated matrix. It also showed that the millispheres protected within this matrix were deformed but intact, but there was some significant damage to those spheres exposed to the tablet punches and die during compression.

In order to quantify in real terms the extent of this damage, the drug release profiles from uncompacted millispheres and millispheres released

from the tablet matrix was compared. This showed that although millisphere compaction slightly enhances the rate and extent of drug release, as a result of damage to the film coating of some of the millispheres during compaction, it has little significant influence on the mechanisms and kinetics of drug release. Their controlled release characteristics are not destroyed.

Thus this paper has shown both qualitatively and quantitatively that with careful optimisation of formulation variables, it is possible to design a rapidly disintegrating sustained-release tablet drug delivery system for peroral administration comprising compacted polymer coated millispheres containing a high-dose drug. In order to minimise the physical damage to the millispheres during compaction, it is prudent to ascertain certain physical and mechanical properties of the components of the dosage form and to utilise this information in order to generate a satisfactory product based on an application of the principles highlighted by this research.

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