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Design and characterization of a surfactant-enriched tablet formulation for oral delivery of a poorly water-soluble immunosuppressive agent

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Abstract

The feasibility of incorporating significant quantities of the anionic surfactant, sodium lauryl sulfate (SDS), into an immediate release tablet formulation of a poorly water-soluble immunosuppressive agent was investigated. Despite the extremely poor compressibility of SDS and poor chemical stability of the drug, a commercializable, direct-compression tablet formulation with satisfactory mechanical properties and acceptable chemical stability was achieved. Optimal in vitro release of the drug from the tablet formulation was achieved by establishing the minimum molar uptake ratio necessary to achieve complete micellar solubilization of the drug, after which formulation studies were conducted to determine the influence of formulation and process variables on the rate and extent of drug release. A model-independent analysis of dissolution results in a reduced volume (250 ml) of modified simulated gastric fluid demonstrated that the rate and extent of drug release was highly dependent on the mean particle size of the bulk drug, but independent of compression force above that required to achieve a compact of acceptable mechanical strength. Employing the Korsmeyer–Peppas model of Fickian and non-Fickian drug release, it was further shown that release of the drug from the dosage form was governed largely by surface erosion of the surfactant-enriched tablet matrix.

Keywords: Sodium lauryl sulfate; Surfactant; Micellar solubilization; Immunosuppressive agent; Poorly water-soluble drug; Tablet formulation

1. Introduction

L-733,725, C32-*O*-[4′-(3′,5′-dimethoxyphenyl)-imidazol-2′-ylmethyl] FK-520 (2R,3R)-hydrogen

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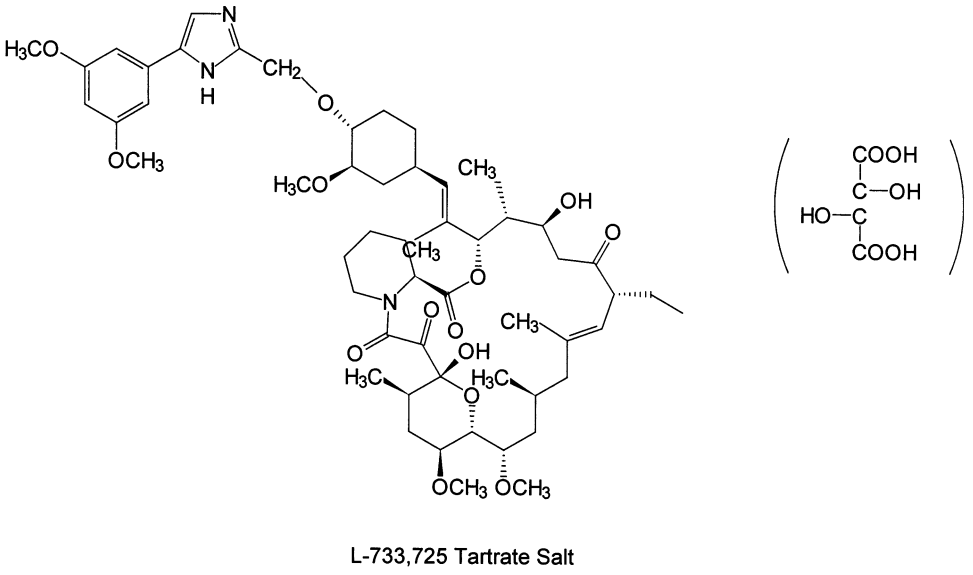

Fig. 1. Chemical structure of the immunosuppressive agent, L-733,725.

tartaric acid salt (Fig. 1), is a potent immunosuppressive agent intended for prevention of acute and chronic rejection following organ transplantation and treatment of autoimmune diseases such as psoriasis and rheumatoid arthritis (Goulet et al., 1998). Comparable in pharmacologic action to the marketed immunosuppressants, cyclosporine (Sandimmune, Neoral) and tacrolimus (Prograf), the compound elicits an immunosuppressive response primarily by inhibiting the activation of T-cells (particularly helper T-cells) secondary to initial interaction with cytosolic binding proteins. L-733,725 also shares many undesirable physicochemical properties with cyclosporine and tacrolimus, including very low aqueous solubility, thereby presenting considerable challenges in the development of a stable and bioavailable formulation for oral administration.

L-733,725 is a relatively non-hygroscopic, crystalline tartrate salt that possesses satisfactory solid-state stability when protected from light. However, the compound is highly susceptible to acid- and base-catalyzed hydrolysis, as well as oxidation, when formulated in the solution state. Moreover, solid compositions comprising amorphous drug are prone to chemical instability, arising from hydrolysis due to residual moisture or from oxidative degradation catalyzed by trace levels of divalent metals. In addition to the significant stability issues cited above, the compound is virtually insoluble in water (<10 ng/ml), but moderately soluble in aqueous ionic and non-ionic micellar solutions, alcohols and glycols (Table 1).

Table 1
Equilibrium solubilities of L-733,725 in selected vehicles at 25°C

Vehicle	Solubility (mg/ml)
Water	<0.0001
Ethanol	17
Polyethylene glycol 400	25
75% Ethanol in water	70
10% Polysorbate 80 in 10 mM citrate buffer	9.9
5% Polyethylene glycol 400 and 5% polysorbate 80 in 10 mM citrate buffer	4.7
3% Polysorbate 80 and 10% ethanol in polyethylene glycol 400	25
0.25% Polysorbate 80 in normal saline solution	0.16
1.0% Sodium lauryl sulfate in water	4.1
3.0% Sodium lauryl sulfate in water	14
5.0% Sodium lauryl sulfate in water	25

Due to the apparent limitations associated with drug stability and solubility, bioavailability studies in preclinical animal models were conducted to determine whether satisfactory oral absorption of crystalline L-733,725 could be achieved by co-administering the drug with surfactants. In the absence of surfactants, or in the presence of insufficient quantities, oral absorption of the drug was shown to be erratic and poor. However, the drug was found to be well absorbed from a 1:3 w/w blend of L-733,725 and sodium lauryl sulfate (SLS). This binary mixture was also shown to afford satisfactory chemical stability of the drug under conditions of elevated temperature and relative humidity. Accordingly, the challenge of transforming this simple composition into a scaleable, commercializable solid dosage form was undertaken with the primary aim of designing and developing film-coated tablet formulations of the drug ranging in potency from 1 to 30 mg.

1.1. Theoretical considerations

Solubilization in aqueous surfactant solutions at surfactant concentrations exceeding the critical micelle concentration (CMC) has long been recognized as a means to formulate a variety of slightly soluble to practically insoluble compounds in the solution state (McBain and Hutchinson, 1955; Florence, 1982). Recent examples include the solubilization of clofazimine analogues by SLS and Triton X-100 (Fahelelbom et al., 1993) and the solubilization of carbamazepine (Ammar and Omar, 1994) and bromhexine hydrochloride (Ammar and El-Nahhas, 1994) by Cetomacrogol 1000 and Triton X-100. Though the concentration of surfactant needed to establish micelles is dependent upon the physicochemical properties of the surfactant and the medium into which it is incorporated, several important conclusions can be drawn. Typically, the CMC of pharmaceutically acceptable anionic and cationic surfactants is reached at concentrations in the order of 1–10 mM. Non-ionic surfactants, on the other hand, approach their respective CMC values at considerably lower concentrations (0.01–0.1 mM), but tend to form larger micelles with greater aggregation numbers (Rieger, 1996). Furthermore, the CMC of ionic surfactants typically increases with temperature, while that of non-ionic surfactants generally decreases. Irrespective of the nature of the surfactant, however, solubilization of poorly water-soluble compounds in surfactant solutions is dependent upon the presence of micelles, the number of which directly influences the rate and extent of the solubilization process (Rosen, 1989).

In certain cases, however, the quantity of surfactant needed to achieve complete solubilization of a drug precludes its use in pharmaceutical formulations for this purpose. In particular, micellar solubilization of large, asymmetric, rigid molecules (e.g. steroids and fat-soluble vitamins) frequently necessitates surfactant-to-drug ratios of 25:1–100:1 or more on a molar basis (Attwood and Florence, 1983). These molar ratios are dictated by the aggregation number of the surfactant and the size of the hydrophobic domain within the interior of the surfactant micelle relative to that of the drug molecule. For example, Sjoblom (1958) reported molar uptake ratios (drug-to-surfactant) of 7.0×10^{-4} and 4.4×10^{-3} for the solubilization of 17α-ethynyl testosterone in aqueous solutions of polysorbate 20 and tetradecyltrimethylammonium bromide, respectively, at 20°C. The molar uptake ratio for the same compound in SLS solution at 40°C was determined to be 7.4×10^{-3}.

Additional limitations to the use of surface-active excipients as solubilizing agents in solid dosage forms are predicated by their physicochemical nature, as the majority of water-soluble surfactants exist as oily liquids or wax-like solids at ambient temperatures. For obvious reasons, such materials are generally not conducive to the formulation and manufacture of traditional pharmaceutical tablets and capsules. Lerk and Sucker (1993) proposed a novel surface-active excipient, sucrose laurate, for use in formulating solid oral dosage forms of poorly water-soluble drugs. These investigators prepared a prototype formulation (containing 50 mg of cyclosporine and 312.5 mg of sucrose laurate in a 600-mg tablet) that was found to release 90% of the dose in approximately 2 h in vitro. Considerable problems in the processing of sucrose laurate were reported, however, and no further efforts were taken to optimize the formulation to enhance the rate of drug release.

From a tolerability standpoint, many surface active agents can be safely ingested in reasonable quantities for prolonged periods without untoward effects. In the case of SLS, a chronic feeding study in rats at daily consumption levels of up to 10 000 ppm for a period of 2 years produced no compound-related effects. A similar study in beagle pups at daily consumption levels of 20 000 ppm over 1 year failed to reveal any gross or microscopic abnormalities associated with chronic ingestion of SLS (Safety Assessment Expert Panel, 1983).

This paper describes how incorporation of a significant amount of SLS into a direct compression tablet formulation was successfully achieved to afford rapid and near-complete in-vitro release of a poorly water-soluble drug from a tablet matrix possessing acceptable mechanical strength. Drug solubilization was achieved by establishing a locally high concentration of SLS micelles in direct contact with crystalline drug particles upon continuous erosion of the surfactant-enriched tablet core. The in-vivo performance of this dosage form, both in preclinical species and in man, is the subject of a separate publication.

2. Materials and methods

2.1. Excipients and reagents

The following excipients were used in the preparation of L-733,725 compressed tablets: granular mannitol, USP (Pearlitol™ 400DC and Pearlitol™ SD200, Roquette Corp.), microcrystalline cellulose (MCC), USP (Avicel™ PH-102, FMC Corp.) and sodium lauryl sulfate (SLS), USP (Accurate Chemical & Scientific Corp.). Analytical reagents were purchased from EM Science and used as received.

2.2. Determination of equilibrium solubility of L-733,725 in dilute SLS solutions

Solubility measurements of L-733,725 in dilute solutions of SLS in simulated gastric fluid (SGF) at 37 C were performed in triplicate by adding approximately 250 mg of crystalline L-733,725 to 10-ml volumes of SGF ranging in surfactant concentration from 0.25 to 20 mM. Individual mixtures were prepared in sealed glass vials and incubated in a thermostatically controlled water bath (Model BT-23, Yamato Corp.) under maximum agitation for 96 h. Samples were assayed spectrophotometrically at 261.5 nm (Lambda 4B UV/VIS Spectrophotometer, Perkin-Elmer Corp.) following centrifugation (Microfuge E, Beckman Instruments) for 2 min. Equilibrium was confirmed by repetitive sampling.

2.3. Determination of particle size distributions of granular mannitol products

The particle size distributions of two grades of granular mannitol were determined by sieve analysis. Quantities of 100 g of each grade were added to a series of pre-weighed stainless steel sieves (Gilson Co) of decreasing mesh size, after which the sieves were mechanically agitated for 15 min (Octagon 200 Test Sieve Shaker, Endecott Corp.). Resulting mass distributions of the various particle size fractions were determined gravimetrically by reweighing each sieve and calculating the mass of material retained.

2.4. Powder compaction studies

A series of studies were performed on prototype tablet formulations to compare the compaction properties of various precompression powder blends, and to determine the influence of powder composition on the mechanical properties of resulting compacts. Dry powder mixtures containing a fixed quantity of SLS and varying quantities of MCC and mannitol were prepared by passing individual components through a 25 mesh (710 μm) stainless steel screen and mixing in a twin-shell blender (Patterson-Kelley) for 20 min. Resulting blends were subsequently compressed at nominal forces of 10, 15, 20 and 25 kN using a single-station tablet press (Model F3, F. J. Stokes Machine) equipped with 12/32″ round, plain, flat-faced, beveled-edge tooling. A target fill weight of 350 mg was maintained for each tablet formulation studied. Compaction data were simultaneously obtained using instrumentation and

Table 2
Composition of L-733,725 10-mg potency film-coated tablets

Component	Amount (mg)
L-733,725	11.49[a]
Sodium lauryl sulfate, NF	30.00
Microcrystalline cellulose, NF	140.0
Granular mannitol, USP	168.5
Total	350.0

[a] Equivalent to 10 mg of free base (salt to free base conversion factor = 1.149).

software (Metropolitan Computing) capable of measuring individual values of upper compression force, dwell time and ejection force. Mean values of upper compression force, punch displacement, work of compaction (i.e. area under the upper compression force-versus-displacement profile) and dwell time were calculated based upon ten consecutive compression sequences for each formulation at each nominal force employed. To compensate for differences in the bulk densities of the various test formulations, mean work of compaction values were normalized for tablet weight.

2.5. Production of film-coated tablets

Film-coated tablets containing 10 mg of L-733,725 (free base equivalent) were prepared according to the formulation described in Table 2. All components were initially weighed and passed through a 25-mesh screen. A precompression blend was then prepared by mixing the drug with granular mannitol in a twin-shell blender for 30 min to establish a premix, after which MCC and SLS were added and mixed for an additional 20 min. The resulting powder blend was compressed on a 6-station rotary tablet press (Korsch PH-106) equipped with 12/32″ round, plain, standard concave tooling. In-process samples were obtained at 5-min intervals for the purpose of monitoring tablet weight (target = 350 mg) and hardness (target 12 kP). Compressed tablets were subsequently film coated (Freund HCT30, Vector Corp.) with an aqueous dispersion comprising hydroxypropyl cellulose, hydroxypropyl methylcellulose and titanium dioxide. A pan speed of 15 rpm and outlet temperatures of 42–44°C were maintained during application of the coating material. A target weight gain for the film-coating operation was approximately 2.5%.

2.6. Physical characterization of compressed tablets

Sets of ten compressed tablets were characterized with respect to tablet weight, thickness (Mitutoyo digital thickness gauge), crushing strength (Holland C50 tablet hardness tester), disintegration time (USP disintegration apparatus, without discs, VanKel Industries, Inc.) and friability (400 rev., VanKel Industries).

2.7. In-vitro dissolution studies

The dissolution behavior of coated and uncoated L-733,725 10-mg potency tablets in 250 ml of modified SGF containing 0.06% SLS was determined in triplicate at 37°C using a VanKel dissolution apparatus equipped with rotating paddles at 50 rpm. Samples of 1-ml volume were removed at 5, 10, 20, 30, 45 and 60 min, centrifuged for 2 min and assayed spectrophotometrically at 261.5 nm. The fraction of the total dose dissolved at each time point was subsequently determined by comparing the absorbance value of each test sample to those of standard solutions.

2.8. Comparative analysis of in-vitro dissolution data

Mathematical comparison of dissolution data to quantify observed differences in the rate and extent of drug release as influenced by formulation and process variables was performed according to the model-indepedent approach of Moore and Flanner (1996). A similarity factor (f_1) and difference factor (f_2) were calculated from mean dissolution data according to the following equations:

$$f_1 = \left\{ \left[\sum_{t=1}^{n} |R_t - T_t| \right] \div \left[\sum_{t=1}^{n} R_t \right] \right\} \cdot 100 \quad (1)$$

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\} \quad (2)$$

where n is the number of time points, R_t is the mean dissolution value of the reference profile at time t and T_t is the mean dissolution value of the test (comparator) profile at the same time point.

2.9. Determination of the mechanism of in-vitro drug release

The mechanism of in-vitro drug release from L-733,725 10-mg potency tablets was determined by fitting a semiempirical model of Fickian and non-Fickian drug release from polymeric matrices (Korsmeyer et al., 1983; Peppas, 1985; Ritger and Peppas (1987a,b) to mean dissolution data as follows:

$$\frac{M_t}{M_\infty} = k \cdot t^n \quad (3)$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, k is a constant which takes into account structural and geometric features of the matrix and n is a release exponent indicative of the mechanism by which drug is released. Values of n and k for each data set were determined from the slope and y-intercept of a logarithmic plot of percent released versus time.

3. Results and discussion

3.1. Effect of formulation and process on the physical properties of compressed tablets

A significant obstacle to the formulation of compressed tablets containing appreciable quantities of SLS originated from the extremely poor compactability of surfactant-enriched powder blends, which assumed wax-like physical properties. Therefore, the initial objective of the present study was two fold: (1) to minimize the quantity of SLS in each dosage form by determining the molar uptake ratio for drug solubilization in micellar SLS solutions, and (2) to identify powder compositions with sufficient dilution capacity to minimize the impact of SLS on the mechanical strength of resulting compacts. Fig. 2 shows the equilibrium solubility of L-733,725 as a function of SLS concentration in SGF at 37°C. Consistent with a micellar solubilization mechanism, the equilibrium solubility of the drug remained relatively constant below a threshold SLS concentration of approximately 2 mM, above which drug solubility increased markedly with increasing surfactant levels. Based upon solubility data to the right of the break point (i.e. the observed CMC), a micellar molar uptake ratio (surfactant-to-drug) of approximately 13:1 was determined, indicating that a surfactant-to-drug weight ratio of approximately 3:1 would be necessary to achieve complete solubilization of the drug.

Results of preliminary formulation studies demonstrated that compressed tablets of sufficient strength and acceptable friability could not be achieved at SLS levels exceeding 10%. Furthermore, for reasons of chemical compatibility, tablet compositions were necessarily restricted to those containing only microcrystalline cellulose and mannitol, in addition to SLS and drug. Lactose was found to be incompatible with L-733,725 in the solid state, while dibasic calcium phosphate was eliminated from further consideration due to known instability of the drug in the presence of divalent cations. A variety of additional excipi-

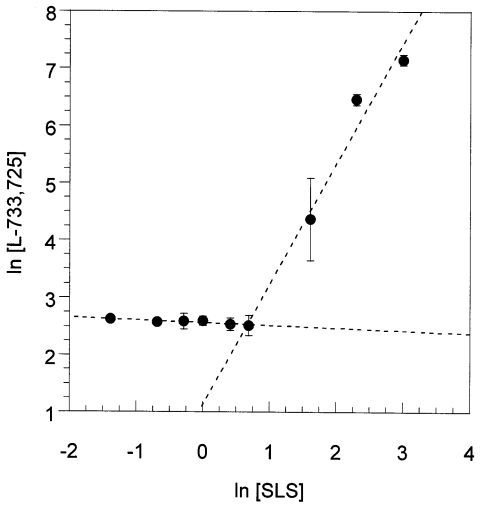

Fig. 2. Equilibrium solubility of L-733,725 (μmol/l) as a function of sodium lauryl sulfate concentration (mmol/l) in simulated gastric fluid at 37°C. Each data point represents the mean of three determinations. Error bars denote the standard deviation.

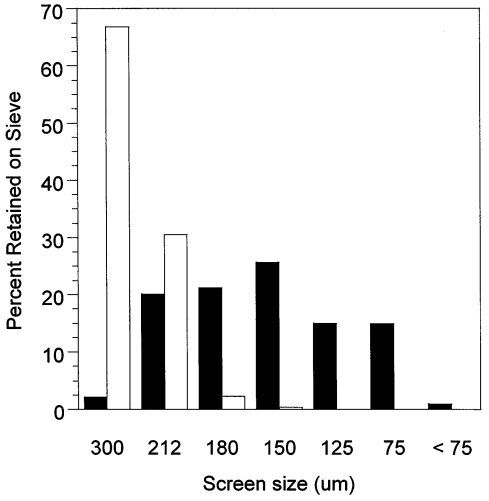

Fig. 3. Particle size distributions of selected granular mannitol products as determined by sieve analysis: Pearlitol™ SD200 (shaded bars) and Pearlitol™ 400DC (unshaded bars).

ents, such as pregelatinized starch and several superdisintegrants that typically possess much higher levels of equilibrium moisture, were avoided on account of the potential for moisture-induced degradation of the drug on storage.

Tablet formulations of L-733,725 were initially developed using Avicel PH-102, a direct-compression grade of microcrystalline cellulose, and Pearlitol 400DC, a granular mannitol product of large particle size and high bulk density. Resulting powder blends possessed excellent flow properties, but yielded compacts of marginal strength that were prone to visible chipping and edge wear upon subsequent film coating. Accordingly, formulation studies were repeated using a newly introduced, spray-dried grade of granular mannitol (Pearlitol SD200) with physical properties more amenable to direct compression processing. It was anticipated that the lower bulk density of SD200 (0.45 vs. 0.68 g/cm^3), arising from the increased porosity of spray-dried granules, together with its smaller overall particle size (Fig. 3) would contribute to improved inter-particle bonding within the tablet matrix.

As illustrated in Fig. 4A, B, compressed tablets containing SD200 were characterized by substantial increases in mechanical strength (as measured by diametral crushing force) without concomitant increases in disintegration time. Crushing forces in excess of 17 kP were achieved for tablets containing SD200 as compared to 9 kP for corresponding tablets containing 400DC.

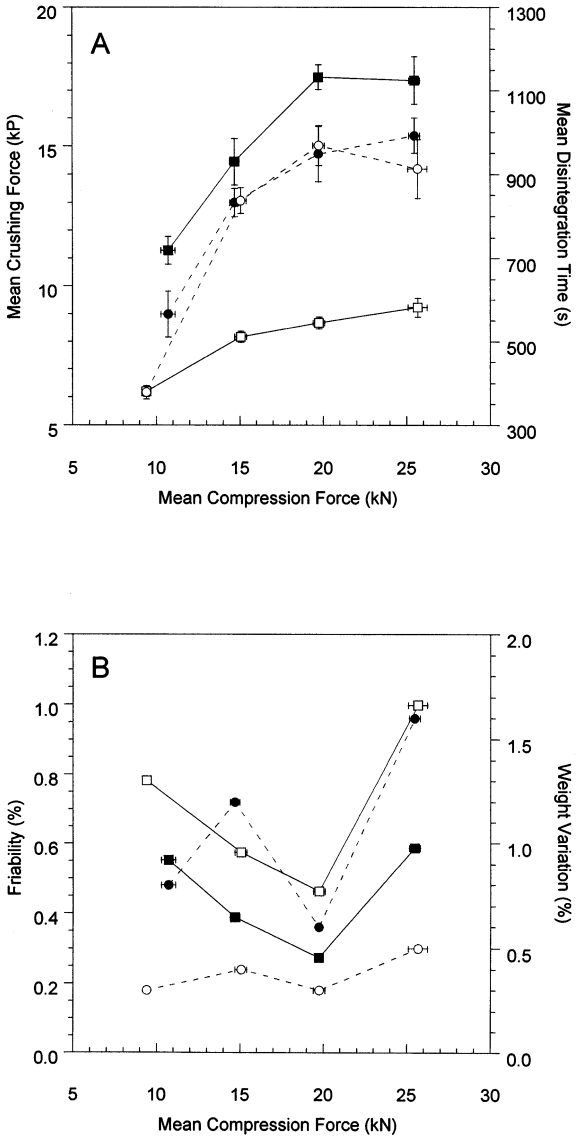

Fig. 4. Physical properties of surfactant-enriched, L-733,725 10-mg potency tablets formulated with Pearlitol™ SD200 (filled symbols) and Pearlitol 400DC (open symbols). Squares denote mean crushing force and friability. Circles denote mean disintegration time and weight variation. Each data point represents the mean of ten determinations. Error bars denote the standard deviation.

Disintegration times remained largely unchanged, however, yielding a mean value of approximately 16 min (range: 12.7–18.1 min). Of equal importance, tablets containing SD200 demonstrated improved resistance to edge wear and chipping, as indicated by the substantial decrease in friability at each compression force employed. Not surprisingly, variation in tablet weight increased with SD200, undoubtedly arising from the impact of lower bulk density and smaller particle size on powder flow. Despite this increase, however, flow properties of blends containing SD200 remained highly satisfactory and tablet weight variation at applied forces of 15–20 kN did not exceed 1%.

Based upon the known water sorption capacity of MCC and the need to minimize water uptake in the finished dosage form, a second series of studies was conducted to determine the lowest level of MCC necessary to achieve compressed tablets of acceptable mechanical strength. Such studies were conducted by replacing MCC with an equivalent weight of SD200. As shown in Fig. 5A, B, values of diametral crushing force and friability confirmed the benefits of higher MCC levels (45 and 50% w/w) for tablets prepared under applied forces of 10 and 15 kN. Yet, the same levels of MCC resulted in comparatively weaker tablets under compression forces of 20 and 25 kN. This unexpected behavior was attributed to physicochemical interaction between MCC and SLS, resulting in a greater than expected degree of elastic recovery in compacts containing high MCC levels under the largest applied forces.

Exploring this concept further, values of mean normalized work of compaction (work per gram of compressed material) were plotted as a function of mean compression force for each of the formulations studied. As illustrated in Fig. 6, each data set yielded non-linear profiles that were equally well described by both exponential (shown) and non-exponential power functions. Powder blends containing 45 and 50% MCC yielded larger exponential coefficients (0.082 and 0.081) than corresponding blends containing 35% and 40% MCC, which yielded coefficients of 0.065 and 0.062, respectively.

It should be noted that the exponential coefficient of a power function is essentially an index of the curvature of the profile it defines (or, in the present case, the rate of change in work of compaction as a function of applied force). Accordingly, one would typically expect larger values of the above coefficient to signify improved bonding

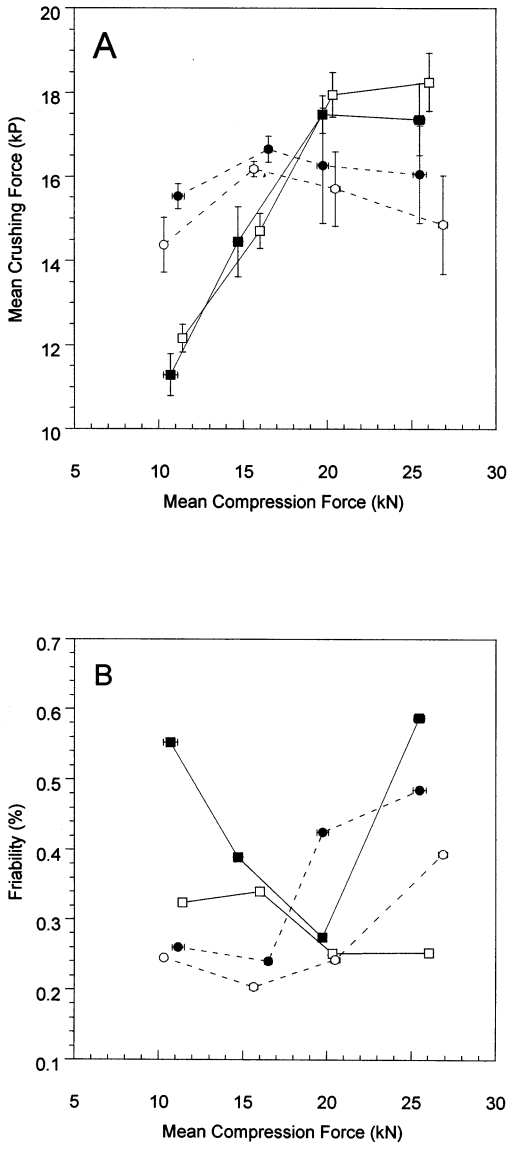

Fig. 5. Physical properties of surfactant-enriched, L-733,725 10-mg potency tablets formulated with Pearlitol™ SD200 and varying levels of microcrystalline cellulose (Avicel® PH-102): ■, 35% w/w; □, 40% w/w; ●, 45% w/w; ○, 50% w/w. Each data point represents the mean of ten determinations. Error bars denote the standard deviation.

and greater densification in the case of a porous, heterogeneous material subjected to viscoelastic deformation under applied stress. However, values of total work that arise from integration of entire force-displacement profiles represent both the energy utilized to create the compact as well as that required to overcome die wall friction. Moreover, such values fail to distinguish between energy consumed by the irreversible processes of consolidation, fragmentation and plastic deformation and by reversible (elastic) deformation that may occur on relaxation of the compact upon decompression (Ragnarsson, 1996).

Nevertheless, simple force-displacement data can be utilized successfully to gain important insight into various aspects of the compaction process and to establish basic relationships between total work of compaction and the mechanical strength of compressed tablets. In the present context, those compaction processes resulting in viscoelastic deformation and improved internal bonding would be characterized both by large values of the exponential coefficient and by improved mechanical strength of the compacted material under increasing stress. In contrast, those compaction processes characterized by large values of the exponential coefficient and measurable decreases in mechanical strength would indicate considerable elastic recovery within the tablet matrix secondary to poor internal bonding.

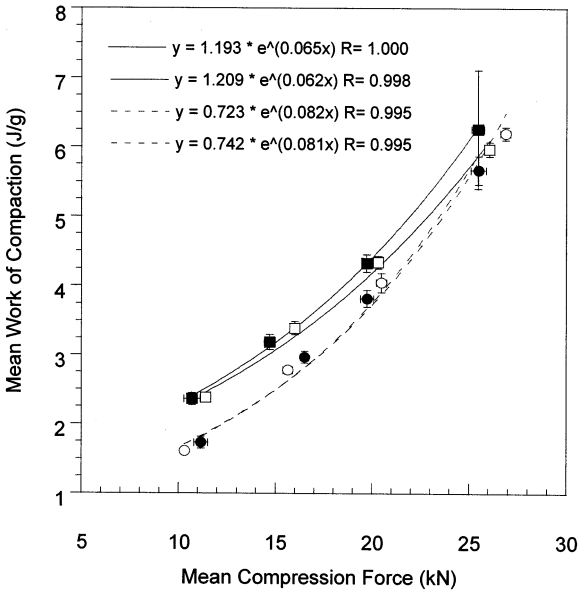

Fig. 6. Compaction profiles of L-733,725 precompression blends containing Pearlitol™ SD200 and varying levels of Avicel® PH-102: ■, 35% w/w; □, 40% w/w; ●, 45% w/w; ○, 50% w/w. Each data point represents the mean of ten determinations. Error bars denote the standard deviation.

Based upon tablet hardness and friability data, it was determined that maximum mechanical strength of L-733,725 tablets could be achieved by incorporating MCC into the formulation at a level of approximately 40% and subjecting the precompression blend to forces of approximately 20 kN. This conclusion was further supported by the physical appearance of compressed tablets following 400-rev (16-min) friability testing, for compacts prepared under these conditions revealed little to no evidence of chipping or edge wear. Although the effects of compression speed and dwell time were not addressed in the present work, it is acknowledged that such studies would need to be performed in order to confirm selection of an optimal tablet composition during formulation and process optimization studies.

3.2. Influence of bulk drug particle size and applied compression force on the dissolution of L-733,725 in vitro

Based upon the poor aqueous solubility of L-733,725, it was anticipated that bulk drug particle size would play a major role in the rate of drug release from compressed tablets. Bulk drug particle size was also expected to affect the extent of release since the contact time between crystalline drug particles and a locally high concentration of SLS micelles would be limited due to continuous erosion of the tablet matrix and attendant diffusion of SLS into the surrounding aqueous environment. The importance of bulk drug particle size on release behavior was initially confirmed following dissolution testing of two batches of 10 mg L-733,725 film-coated tablets prepared with milled and unmilled bulk drug (Fig. 7). Tablets containing milled drug resulted in the dissolution of more than 80% of the dose within 30 min, while tablets of identical composition prepared with unmilled drug resulted in the dissolution of

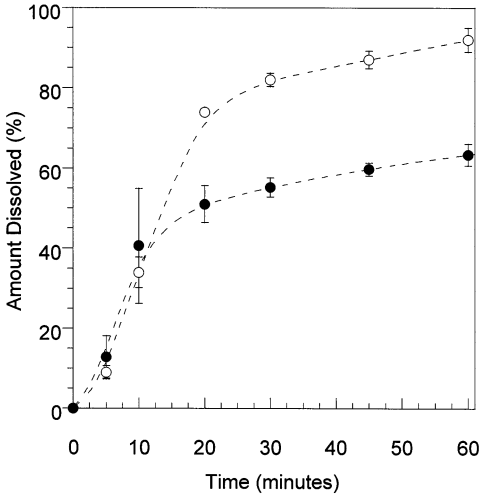

Fig. 7. Profiles of L-733,725 release from 10-mg potency film-coated tablets in 250 ml of modified simulated gastric fluid at 37°C (USP paddle method at 50 rpm): ●, unmilled bulk drug; ○, milled bulk drug. Each data point represents the mean of three determinations. Error bars denote the standard deviation.

only 50% of the dose over the same period. Although unmilled bulk drug was shown to possess a primary particle size distribution equivalent to that of milled drug (mean = 10 μm, 95% < 50 μm), microscopic examination of unmilled material revealed the presence of agglomerates that had formed during the bulk drug crystallization and drying processes. Accordingly, the observed differences in release behavior in vitro were attributed to the larger effective particle size and reduced specific surface of the agglomerated material. A milling procedure (single pass through a cone mill equipped with a 300 μm screen) was subsequently adopted to deagglomerate the bulk drug.

The influence of effective particle size on drug release was further demonstrated by preparing uncoated tablets containing bulk L-733,725 obtained by sieve fractionation of unmilled drug. Six fractions of agglomerated drug were investigated, ranging in size from 38 to 250 μm. Following mixing and manual compression with a hydraulic Carver press, dissolution profiles of resulting tablets were determined in modified SGF as before. As shown in Fig. 8, minor differences in both rate and extent of drug release were observed after 5–10 min, and were found to be inversely related to the extent of agglomeration. Differentiation of overall dissolution behavior became increasingly apparent with time, yielding differences in amount released of up to 30% after 60 min. As expected, tablets containing the smallest agglomerates (38–53 μm) afforded more rapid and complete drug release, while the opposite was true for tablets containing the largest fractions of agglomerated drug (180–250 μm). Tablets containing intermediate size fractions behaved accordingly, with higher rates of drug release corresponding to smaller effective particle size.

Utilizing tablets of identical composition, a second dissolution study was conducted to determine the influence of applied compression force on the rate and extent of drug release from tablets containing milled bulk drug. Powder blends were prepared as before and subjected to forces ranging

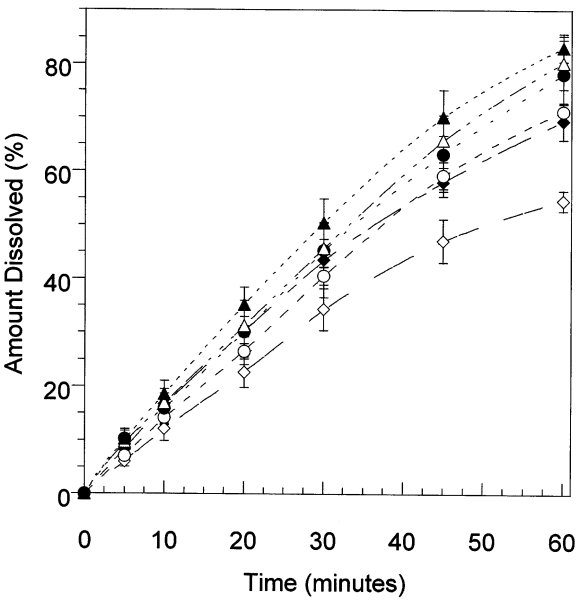

Fig. 8. Profiles of L-733,725 release from 10-mg potency uncoated tablets in 250 ml of modified simulated gastric fluid at 37°C (USP paddle method at 50 rpm) as a function of effective drug particle size: ▲, 38–53 μm; △, 53–75 μm; ●, 75–90 μm; ○, 90–150 μm; ◆, 150–180 μm; ◇, 180–250 μm. Each data point represents the mean of three determinations. Error bars denote the standard deviation.

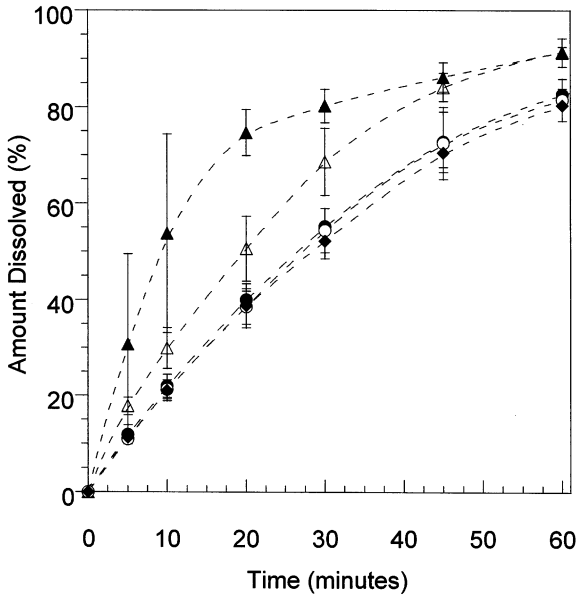

Fig. 9. Profiles of L-733,725 release from 10-mg potency uncoated tablets in 250 ml of modified simulated gastric fluid at 37°C (USP paddle method at 50 rpm) as a function of applied compression force: ▲, 5 kN; △, 10 kN; ●, 15 kN; ○, 20 kN; ◆, 25 kN. Each data point represents the mean of three determinations. Error bars denote the standard deviation.

from 5 to 25 kN. As shown in Fig. 9, the rate of drug release was fastest from tablets compressed to applied forces of 5–10 kN. Under these conditions more than 90% of the drug was released within 60 min. By way of comparison, compacts subjected to 15, 20 and 25 kN demonstrated slower overall release behavior, resulting in the release of only 80% of the dose over the same time period. Interestingly, mean dissolution profiles for the latter three sets of tablets were remarkably similar, despite considerable differences (up to 67%) in the amount of force used to prepare them. These findings suggest that the porosity of the L-733,725 tablet matrix reached a critical value under a load of 15 kN that was not significantly reduced upon application of larger forces. Such behavior is highly consistent with that of a non-swellable polymeric matrix that releases drug primarily by an erosion-based mechanism.

A mathematical comparison of mean dissolution profiles from the above studies was performed utilizing the model-independent approach of Moore and Flanner (1996) in which individual profiles are compared as a whole in lieu of a point-by-point comparison. The model-independent method employs a difference factor (f_1) that represents the relative error between two dissolution profiles based upon an aggregate of percent difference at each time point, and a similarity factor (f_2) that represents the similarity in percent released based upon a logarithmic transformation of the sum of squared error. For dissolution profiles to be considered similar, values of f_1 should be close to 0 (range: 0–15), while values of f_2 should be close to 100 (range: 50–100). Using the mean dissolution profile for tablets containing the smallest agglomerates of L-733,725 (38–53 μm) as the basis for comparison, values of f_1 and f_2 were calculated for each of the five mean profiles pertaining to larger fractions of agglomerated bulk drug. A similar comparison was performed for mean dissolution profiles obtained from compression force studies. In the latter case, the mean dissolution profile for tablets compressed under a force of 20 kN was employed as the reference profile. Results of both analyses are summarized in Table 3.

Table 3
Calculated parameters for release of L-733,725 from 10-mg potency uncoated tablets as a function of effective drug particle size and applied compression force based upon the model-independent approach of Moore and Flanner (1996)

Formulation parameter	Difference factor (f_1)	Similarity factor (f_2)
Particle size range (μm)[a]		
38–53	–	–
53–75	6.8	72.5
75–90	9.4	65.7
90–150	18.3	52.6
150–180	15.6	53.8
180–250	34.0	37.8
Applied compression force (kN)[b]		
5	52.2	29.7
10	25.5	46.2
15	3.8	83.3
20	–	–
25	2.2	89.1

[a] Compressed under a force 20 kN.
[b] Prepared with milled drug.

Table 4
Derived parameters for release of L-733,725[a]

Parameter	Release constant (k)	Release exponent (n)	Regression coefficient (R)
Particle size range (μm)[b]			
38–53	32.0	0.86	0.999
53–75	34.0	0.86	0.999
75–90	31.7	0.85	0.998
90–150	44.4	0.94	0.999
150–180	31.2	0.86	0.998
180–250	37.2	0.91	0.998
Applied compression force (kN)[c]			
5	5.3	0.42	0.954
10	15.2	0.68	0.995
15	26.7	0.80	0.997
26.7	28.8	0.82	0.996
0.80	25.9	0.80	0.997

[a] From 10-mg potency uncoated tablets as a function of effective drug particle size and applied compression force based upon a model of Fickian and non-Fickian drug release from polymeric matrices (Korsmeyer et al., 1983; Peppas, 1983, 1985; Ritger and Peppas, 1987a,b).
[b] Compressed under a force 20 kN.
[c] Prepared with milled drug.

The model-independent analysis of dissolution behavior as influenced by effective bulk drug particle size confirmed the importance of this parameter on the release of L-733,725 from compressed tablets. Based upon mean dissolution data for the 38–53 μm fraction (i.e. the reference profile), calculated values of f_1 and f_2 revealed an overall lack of similarity in dissolution behavior for those fractions exceeding 90 μm. Dissolution profiles of tablets containing the 53–75 μm and 75–90 μm fractions were shown to be similar, although calculated values of f_1 and f_2 in the latter case were considerably closer the limiting values of 15 and 50, respectively. A similar analysis of mean dissolution data for tablets compressed under increasing force confirmed the importance of this parameter on drug release, but only for the lowest values studied. Based upon mean dissolution data for tablets compressed at 20 kN, values of f_1 and f_2 revealed a significant lack of similarity when compared to values for tablets compressed at 5 and 10 kN. Such a difference is readily apparent upon visual inspection of the data. Recall, however, that tablets of suitable mechanical strength were only achieved when powder blends were subjected to applied forces of 15 kN and greater. Given the extremely low values of f_1 and high values of f_2 for tablets compressed at 15 and 25 kN, it was therefore concluded that compression force plays little practical role in the rate and extent of L-733,725 release from the surfactant-enriched tablets in vitro.

3.3. Determination of the mechanism of L-733,725 release from compressed tablets

Kinetic parameters of L-733,725 release from compressed tablets were determined by fitting a semiempirical model of Fickian and non-Fickian drug release (Korsmeyer et al., 1983; Peppas, 1983, 1985; Ritger and Peppas, 1987a,b) to individual sets of mean dissolution data. Values of the release exponent (n) and the kinetic constant (k), obtained in each case from the slope and y-intercept of a logarithmic plot of percent released versus time, are summarized in Table 4. Originally proposed to distinguish dissolution-controlled and diffusion-controlled drug release from polymeric matrices, the model was shown to be useful in the present case in determining the relative contribution of matrix erosion to the overall release of L-733,725 from surfactant-enriched tablets. Ac-

cording to the model (Ritger and Peppas, 1987a), a geometry-dependent release exponent of 0.45 indicates release behavior governed solely by diffusion of drug through the tablet matrix (i.e. square root of time dependence). Conversely, a value of 1.0 indicates release behavior governed solely by dissolution kinetics. In the latter case, the drug may be released in pseudo-zero-order fashion, secondary to saturation of drug solubility within the pores of the matrix. Intermediate values of the release exponent (i.e. between 0.45 and 1.0) represent anomalous behavior characterized by a combination of diffusion and dissolution mechanisms.

Given the absence of soluble or swellable polymers in the present dosage form and the comparatively high solubility of the drug in a concentrated surfactant environment, one would not expect the release of L-733,725 to be governed by either of the above mechanisms. This is particularly true since compressed L-733,725 tablets were observed to undergo a process of gradual erosion throughout the dissolution testing period. Accordingly, values of the release exponent in the present case were utilized to distinguish between erosion-controlled release of drug from the tablet surface and diffusion-controlled release from the wax-like tablet matrix. As shown in Table 4, values of n for L-733,725 tablets prepared with different size fractions of agglomerated bulk drug were uniformly large, ranging from 0.85 to 0.94. Such values are consistent with a release mechanism governed by surface erosion that approaches, but does not achieve, exact zero-order release due to a reduction in surface area with time. Values of k were also shown to be large and relatively independent of particle size, although the physical significance of such values is more difficult to interpret in the present context.

A similar analysis of dissolution data as a function of applied compression force provides further evidence that release of L-733,725 from the surfactant-enriched matrix is erosion-controlled. As shown in Table 4, tablets compressed under a force of 5 kN resulted in the smallest value of the release exponent (0.42), which increased to 0.68 under a force of 10 kN, and again to approximately 0.80 at forces of 15, 20 and 25 kN. These results are consistent with a release mechanism that shifts from diffusion control to erosion control as the porosity of the tablet (and thus the ability of drug surface area to influence the rate of drug release) decreases with increasing force of compression. Values of the release constant, k, were also shown to increase with increasing compression force. As before, however, the significance of such changes is difficult to interpret from a mechanism-based standpoint.

4. General conclusions

The preceding results demonstrate the potential utility of compressible solid dosage forms containing significant levels of the surface-active excipient, SLS, for use in oral delivery of poorly water-soluble drugs. They also show that practical selection of excipients and optimization of excipient levels, together with an understanding of the role of specific formulation and process parameters, can provide satisfactory physical properties and reliable in-vitro performance. However, it should not be assumed that all pharmaceutically acceptable surfactants are candidates for incorporation into compressible dosage forms, as such compounds vary considerably in their physicochemical properties. Moreover, certain poorly water-soluble drugs may not be amenable to micellar solubilization or may require excessively large molar uptake ratios. In such cases, a surfactant-based dosage form would offer little advantage over conventional formulation approaches. Nonetheless, the present approach offers an alternative to existing strategies in the design and development of solid dosage forms for oral delivery of certain poorly water-soluble drugs.

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