Pharmaceutical Research, Vol. 26, No. 6, June 2009 (© 2009)
DOI: 10.1007/s11095-009-9852-z

Research Paper

Utility of Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) for Initiation and Maintenance of Drug Supersaturation in the GI Milieu

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Received December 3, 2008; accepted February 6, 2009; published online March 10, 2009

Purpose. To identify materials and processes which effect supersaturation of the GI milieu for low solubility drugs in order to increase oral bioavailability.
Methods. A variety of small and polymeric molecules were screened for their ability to inhibit drug precipitation in supersaturated solutions. The best polymeric materials were utilized to create spray-dried dispersions (SDDs) of drug and polymer, and these were tested for drug form and homogeneity. Dispersions were tested *in vitro* for their ability to achieve and maintain drug supersaturation, for a variety of drug structures.
Results. Of the 41 materials tested, HPMCAS was the most effective at maintaining drug supersaturation. Drug/HPMCAS SDDs were consistently more effective at achieving and maintaining drug supersaturation *in vitro* than were SDDs prepared with other polymers. Drug/HPMCAS SDDs were effective *in vitro* for eight low solubility drugs of widely varying structure. Drug/HPMCAS SDDs were more effective at achieving and maintaining supersaturation than were rotoevaporated Drug/HPMCAS dispersions or physical mixtures of Drug and HPMCAS. The degree of achievable drug supersaturation increased with increasing polymer content in the SDD. The drug in Drug /HPMCAS SDDs was amorphous, and the dispersions were demonstrated to have a single glass transition and were thus homogeneous.
Conclusion. HPMCAS has been identified as a uniquely effective polymer for use in SDDs of low solubility drugs, with broad applicability across a variety of drug structures and properties.

KEY WORDS: bioavailability improvement; dispersions; hydroxypropylmethylcellulose acetate succinate; HPMCAS; low solubility drugs; supersaturation; spray-dried dispersions.

INTRODUCTION

It is well-known that oral absorption of a drug depends upon the drug's solubility in the gastrointestinal (GI) milieu and upon its GI wall permeability. While there are numerous complex factors which may enter into the degree of absorption of a drug, a simple conceptual approach is to consider that the maximum absorbable dose (MAD) of a drug in humans is roughly:

$$\mathrm{MAD} = S \times \mathrm{Ka} \times \mathrm{SIWV} \times \mathrm{SITT}$$

where S is the drug solubility at intestinal pH, Ka is the transintestinal absorption rate constant (related to permeability), SIWV is the small intestinal water volume available for dissolution of the drug (generally taken to be ~250 ml), and SITT is the small intestinal transit time (generally taken as ~4.5 h) (1,2). The permeability or absorption rate constant is a function of the drug's molecular weight and hydrophobicity, and generally cannot be easily altered without changing the chemical structure of the drug, likely affecting efficacy. The drug solubility is a factor which can be potentially manipulated by initiating and maintaining supersaturation in the GI tract, ideally for approximately 4.5 h, or until the drug is completely absorbed.

The issue of low drug solubility, relative to dose, is an old one which has been exacerbated by modern high throughput *in vitro* screening methodology which generally eliminates solubility as a selection factor (2,3). Many drug candidates in development in recent years have not possessed sufficient solubility to be adequately absorbed without the aid of solubility-enhancing formulations.

The most common formulation approach has been to dissolve the drug in an oil or in low molecular weight liquid polyethylene glycol (PEG), and to encapsulate the solution in a soft gelatin capsule. For example, the angina drug nifedipine (Procardia®) was originally marketed as a PEG softgel, and oil soluble vitamins are commonly marketed as triglyceride oil solutions in softgels. In recent years, advances in softgel-formulation have resulted in more efficient self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS), and in more detailed understanding of the behavior of these systems in the GI tract (4–7). However, considerable practical constraints are that (a) many potential drugs do not have sufficient solubility in softgel-compatible

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solvents and (b) many potential drugs are chemically unstable in solution. Thus formulation scientists have searched for decades for a practical approach to create a solid oral dosage form which is capable of transiently and reproducibly supersaturating the GI lumen with a low solubility drug.

In the 1960s and 1970s, a variety of reports described the use of solid solutions and dispersions of drugs with polymers and small molecules to improve drug dissolution rate and bioavailability. In an early report, Sekiguchi and Obi presented data (in a single human subject) indicating that a eutectic mixture of sulfathiazole and urea gave higher blood levels than sulfathiazole alone (8). Goldberg and colleagues described the use of solid solutions of sulfathiazole with urea, and chloramphenicol with urea, to improve dissolution rate (9). Goldberg *et al.* also reported the use of eutectic mixtures for this purpose (10). Stoll *et al.* reported dissolution and bioavailability improvements utilizing coprecipitates with bile acids (11,12). Early reports on dispersions and coprecipitates with polymers focussed on polyvinylpyrrolidone (PVP) (13–15). The mechanism of dissolution enhancement with PVP was somewhat uncertain because of reports on specific drug–PVP complexes designed to slow drug release in solution (16,17). Chiou and Riegelman demonstrated enhanced canine oral absorption of griseofulvin in dispersions prepared by fusion comprising the drug and polyethyleneglycol 6000 (18). Many subsequent reports of drug–polymer dispersions have been published, and some have been summarized in excellent reviews by Serajuddin (19) and by Leuner and Dressman (20). Regardless, the fact remains that these approaches have been utilized in very few marketed drug formulations. It is our belief that this is a result of a lack of demonstration of broad applicability of any one polymer, a lack of mechanistic understanding of reproducible supersaturation in the GI milieu, and perhaps most importantly a lack of confidence that a dispersion or coprecipitate will not crystallize into a non-bioavailable form on storage.

We set out to identify high energy dispersion formulations which would meet four criteria: (A) form an amorphous molecular dispersion of the low solubility drug in a solid material to facilitate supersaturation of the drug when dissolved, (B) provide precipitation inhibition to maintain supersaturation in the GI tract, (C) provide a bioavailability-enhancing material which can be further formulated in a solid dosage form, preferably a tablet, and (D) provide a formulation in which the drug form is stable, neither crystallizing nor phase separating on storage. In this report, we present studies aimed at identifying excipients with the capacity to both initiate and maintain supersaturation.

MATERIALS AND METHODS

Drugs and Drug Candidates. The drugs and drug candidates studied are presented in Table I. All were synthesized by Pfizer Global Research and Development, except for griseofulvin, nifedipine, and phenytoin, which were obtained from Aldrich or similar sources**.** Compounds 1–6, and Compound 9, are low solubility heterocyclic aromatic drug candidates which are no longer in development. Griseofulvin, nifedipine, and phenytoin are low solubility heterocyclic aromatic drugs which are currently marketed. The physical properties of these compounds, determined in the authors' laboratories or from the literature, are presented in Table II.

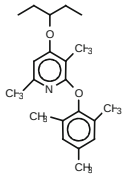
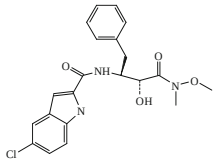
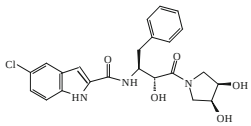
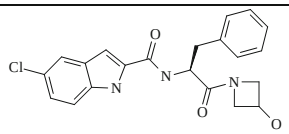
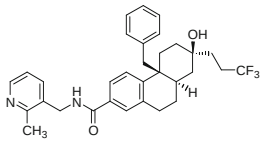
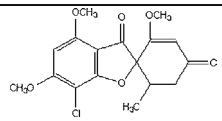
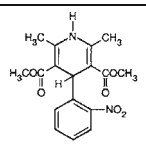
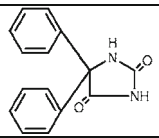
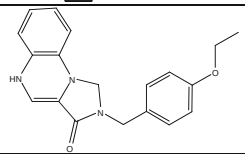
Preparation of Spray-Dried Dispersions (SDDs). SDDs were made at labscale, using the following method exemplified for a dispersion of Compound 2. A solution of Compound 2 and polymer was made by dissolving 133.0 mg of [R-(R*,S*)]-5-chloro-N-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl]-1-H-indole-2-carboxamide (Compound 2, Table I) and 67.0 mg of HPMCAS-MF (Shin Etsu, containing 23.4% methoxyl, 7.2% hydroxypropyl. 9.4% acetyl, 11.0% succinoyl, MW=8.0×10^4, Mn=4.4×10^4) in 10 g of HPLC grade acetone (Burdick & Jackson). The compound/polymer solution was then placed in a 20 mL syringe that was then inserted into a syringe pump. Solvent was rapidly removed from the above solution by spraying into a small spray-drying apparatus called a "Mini" spray drier, which was built in our laboratories and is described below. The resulting 2:1 Compound 2:HPMCAS-MF SDD was a dry, white, substantially amorphous powder. In the text and figures, Drug/Polymer SDD composition is expressed as % drug in the SDD. Thus a 67% SDD contains 2:1 (*w*/*w*) Drug/Polymer.

Dissolution Studies—Syringe/Filter Method. This method is exemplified by the following description of its use for study of the dissolution of a dispersion of Compound 2. Test solution is held in a syringe from which samples are expelled through a filter at pre-determined time points. Between expelling samples from the syringe, the syringe is rotated (50 rpm) on a wheel held in an oven at 37°C. For example, 7.5 mg of the 67% Compound 2:HPMCAS-MF material described above was placed in an empty disposable 10 mL syringe (Aldrich, Fortuna). A 20 ga hypodermic needle was attached to the syringe, and 10 mL of model-fasted duodenal fluid (MFDF) at 37°C was drawn into the syringe.

The needle was then replaced with a 13 mm, 0.45 μm polyvinylidine diflouride syringe filter (Scientific Resources, Titan), and the syringe was vigorously shaken for 30 s. After 30 s, six drops of the solution were expelled and a subsequent 13 drop sample was delivered to a test tube. After expelling the sample, the syringe plunger was drawn back to pull an air bubble into the syringe to aid in subsequent mixing and the syringe placed back on the rotating wheel in a 37°C oven. The sample was diluted 1:1 with a solution containing 60/40 1.7 wt.% ammonium ascorbate/acetonitrile, and the concentration of Compound 2 was determined by HPLC (Hewlett Packard 1090 HPLC, Phenomenex Ultracarb ODS 20 analytical column, absorbance measured at 215 nm with a diode array spectrophotometer). The remaining solution in the syringe was mixed by rotating on the wheel at 50 rpm in the 37°C oven. Samples were taken at various times as described above, analyzed, and compound concentrations calculated.

Dissolution Studies—Microcentrifuge Method. This method is exemplified by the following description of its use for study of the dissolution of a 50% Compound 2:HPMCAS-MF SDD. In a 37°C controlled temperature box, 1.8 mg of solid SDD was weighed into an empty microcentrifuge tube (polypropylene, Sorenson Bioscience Inc.). 1.8 mL of Model Fasted Duodenal Fluid (MFDF) was added to the tube. The theoretical maximum concentration of compound in solution (e.g., if all compound dissolved) was 500 μgA/ml [(1.8 mg

Table I. Drug Structures and Names

Compound	Structure	Chemical Name
Compound 1		3,6-dimethyl-4-(3 -pentoxy)-2-(2 ,4 ,6 -trimethylphenoxy)pyridine
Compound 2		[R-(R*,S*)]-5-chloro-N-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl]-1H-indole-2-carboxamide
Compound 3		5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl-)-3-oxypropyl]amide
Compound 4		5-chloro-1H-indole-2-carboxylic acid [(1)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide
Compound 5		2-Phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-,(4bS,7S,8aR)-
Compound 6 Griseofulvin		(1ʻS,6ʼR)-7-C hloro-2ʼ,-4,6-trimethoxy-6ʼ-methylspiro[benzofuran-2(3H),1ʼ-[2]cyclohexane]-3,4ʼ-dione
Compound 7 Nifedipine		3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester
Compound 8 Phenytoin		5,5-diphenyl-2,4-imidazolidinedione
Compound 9		2-(4-ethoxybenzyl)-1,2-dihydroimidazo[1,5-a] quinoxalin-3(5H)-one

dispersion) (1,000 μg/1 mg) (0.5 μg compound/μg dispersion) / 1.8 ml=500 μgA/ml]. This value is the theoretical maximum supersaturated concentration. The centrifuge tube was closed and a timer was started. The tube was then mixed continuously at the highest speed on a vortex mixer (Fisher Vortex Genie 2) for 60 s. The tube was transferred to a centrifuge (Marathon, Model Micro A), allowed to stand undisturbed for 6 min, then centrifuged at 13,000×*g* for 60 s. A 25 μL sample was removed from the solids-free supernatant in the centrifuge tube via pipette (Gilson Pipetman P-100) 10 min after the timer was started. Solids in the centrifuge tube were resuspended by mixing the sample continuously on the vortex mixer for 30 s. The centrifuge tube was returned to the centrifuge and allowed to stand undisturbed until the next sample was taken. Each sample was centrifuged, sampled and resuspended as described previously. Each sample was

Table II. Drug Properties

Compound	Water solubility (μg/mL)	T_m (°C)	CLog P	pK_a
1	<0.2	76	6.76	3.5
2	1	192	3.68	None
3	80	238	3.10	8.5; 12.9
4	14.6	175	4.06	None
5	0.0038	255	6.24	None
6 Griseofulvin	14.6	220	2.2	None
7 Nifedipine	6	173	3.12	None
8 Phenytoin	26	295	2.47	8.3
9	0.35	267	2.89	9.2

diluted 1:1 with a solution containing 60/40 1.7 wt.% ammonium ascorbate/acetonitrile, and the drug concentration was determined by HPLC (Hewlett Packard 1090 HPLC, Phenomenex Ultracarb ODS 20 analytical column, absorbance measured at 215 nm with a diode array spectrophotometer). Samples were taken at various times as described above, analyzed, and compound concentrations were calculated.

Model Fasted Duodenal Fluid (MFDF). The MFDF solution was composed of phosphate-buffered saline solution (82 mM NaCl, 20 mM Na_2HPO_4, 7.3 mM KH_2PO_4, pH 6.5, 290 mOsm/kg) containing 7.3 mM sodium taurocholate (Fluka) and 1.4 mM 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids). The MFDF solution was prepared using the following procedure. Into a 100 mL round bottom flask was weighed 0.788 g of the sodium taurocholic acid, which was then dissolved in 5.0 mL of ambient HPLC methanol (Burdick & Jackson). To this solution was added 0.212 g of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine in chloroform, supplied by Avanti Polar Lipids as a 20 mg/mL solution. Following thorough mixing by vortex mixer (Fisher Vortex Genie), the solvent was removed rapidly by rotoevaporator (Rotavapor RE121, Büchi), leaving a dry white surface powder coating the flask. The powder was then reconstituted with 200 mL of 37°C phosphate buffered saline.

Simulated Gastric Fluid. Simulated gastric fluid consisted of 0.1 N HCl in deionized water (pH 1).

Japan-2 Dissolution Fluid. Japan-2 Dissolution Fluid consisted of 0.2 M KH_2PO_4 and 0.2 M NaOH adjusted to pH 6.8.

Spray Dryers. Spray-drying was carried out in three different scale spray-dryers.

Micro Spray Dryer. This small-scale spray dryer consisted of a two-fluid atomizer (a NIRO Aeromatic, 2.7 mm ID air cap, 1.0 mm ID fluid cap) mounted on top of a vacuum flask (21). The spray solution, which was maintained at 40°C, was delivered to the atomizer using a peristaltic pump, while drying gas (nitrogen) was delivered to the atomizer at 20 psig (1.4 barg). The SDD was collected in a microporous cellulose extraction thimble mounted in a vacuum trap. The vacuum flask was maintained at 400 mbar pressure to aid in solvent evaporation and drying of the SDD.

Mini Spray Dryer. This bench-top spray dryer consisted of an atomizer in the top cap of a vertically oriented 10-cm diameter stainless steel pipe (21). The atomizer was a two-fluid nozzle (Spraying Systems Co. 1650 fluid cap and 64 air cap). Atomizing gas (nitrogen) was delivered to the nozzle at 100°C at a flow rate of 15 g/min, and the spray solution was delivered to the nozzle at room temperature and at a flow rate of 1.0 g/min using a syringe pump (Harvard Apparatus, Syringe Infusion Pump 22). Filter paper attached to a supporting screen was clamped to the bottom end of the pipe to collect the solid spray-dried material and allow the nitrogen and evaporated solvent to escape.

PSD-1 Spray Dryer. This spray drying apparatus consisted of a type XP Portable Spray-Dryer with a Liquid Feed Process Vessel Model No. PSD-1 (Niro A/S, Soeborg, Denmark). The PSD-1 was equipped with a two-fluid spray nozzle. Heated drying gas (nitrogen, typically at 120°C) was delivered to the drying chamber through an inlet duct that surrounded the 2-fluid nozzle. The resulting SDD exited the chamber with the drying gas through transport ducts and into a cyclone. At the top of the cyclone was an exhaust vent that allowed the nitrogen and evaporated solvent to escape. The SDD was collected in a canister.

Particle Size Measurement. The volume-weighted mean diameter of the SDD particles was measured by laser light scattering using a Malvern Mastersizer 2000. A dry powder feed method was used, and samples were taken at a rate of three measurements per aliquot with a delay time of 7 s. Volume-weighted mean diameter was calculated from the light scattering data assuming a Gaussian size distribution, with approximately 85% of the particle volume being within about 30% of the reported size.

Scanning Electron Microscopy. Scanning Electron Microscopy (SEM) was performed using a Hitachi model S-3400N.

Powder X-Ray Diffraction. Powder x-ray diffraction (PXRD) was carried out using a Bruker AXS D8 Advance diffractometer. Samples (approximately 100 mg) were packed in 0.5 mm deep shiny bottom zero background holder sample cups. Samples were spun in the ϕ plane at a rate of 30 rpm to minimize crystal orientation effects. The x-ray source (KCu_α, λ=1.54 Å) was operated at a voltage of 45 kV and a current of 40 mA. Data for each sample were collected over a period of 30 min in continuous detector scan mode at a scan speed of

2 s/step and a step size of 0.04°/step. Diffractograms were collected over the 2θ range of 4° to 40°.

Differential Scanning Calorimetry. Sample pans were equilibrated at <5%RH, crimped dry, and loaded into the furnace of a Perkin-Elmer Pyris 1 DSC with a robotic arm. The samples were heated from 0°C to 200°C at 10°C/min.

RESULTS

Screening for Effective Precipitation-Inhibiting Excipients

Polymers and small molecules were studied for their ability to maintain the supersaturation of a drug solution. This screening was carried out by dissolving Compound 9 in dimethylacetamide (DMAC) and adding this organic drug solution to model fasted duodenal fluid (MFDF) at 37°C to produce a total concentration (dissolved plus undissolved drug) of ~100 μg/ml (~33-fold greater than saturation), in a 10 ml syringe. The syringe was rotated in a 37°C oven as described in Materials and Methods. The dissolved drug concentration was determined periodically by pushing an aliquot of the suspension through a filter, and measuring the dissolved drug concentration by HPLC. Samples were collected at 0.5, 5, 30, 60, 90, 120, 180, and 1,200 min. This experiment was carried out with a variety of small molecules and polymers dissolved in the MFDF at 0.62 mM or 0.2 mg/ml, respectively, to determine whether these small molecules or polymers had the ability to maintain supersaturation of Compound 9. Data on 41 potential precipitation inhibitors are presented.

Table III presents the peak dissolved drug concentration, the drug concentration at ~20 h post-mixing, and the area under the *in vitro* concentration *vs.* time curve (AUC) for the first 60 min and 180 min after addition of drug in DMAC. On each day on which a test was run, a control precipitation determination was run in the absence of test precipitation inhibitor. An AUC Enhancement Factor was calculated for each test precipitation inhibitor by dividing the test AUC-180 min by the AUC-180 min for the control run concurrently. Table III also presents average peak drug concentration, drug concentration at ~20 h, AUC-60 min, and AUC-180 min for seven separate control determinations to provide a perspective on the variability of these values from day to day.

In all cases, including controls, supersaturation was achieved on adding a DMAC solution of Compound 9 to MFDF plus and minus experimental precipitation inhibitors. The AUC Enhancement Ratios indicate that none of the small molecules tested were effective precipitation inhibitors. On the other hand, a number of the polymers were effective in maintaining supersaturation. The polymers which gave an AUC Enhancement Ratio of 2.0 or greater (an arbitrary cutoff) were hydroxybutylmethylcellulose (HBMC), hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose phthalate (HPMCP), and polyvinylalcohol (PVA). Of these, HPMCAS gave the highest AUC Enhancement Ratio. In addition, HPMCAS also provided the highest drug supersaturation at ~20 h post mixing (drug concentration of 13.4 and 14.6 μg/ml).

Spray-Dried Dispersions (SDDs) of Drugs and Polymers

Various approaches were studied for combining a drug and a precipitation inhibitor to make a practical bioavailability-enhanced formulation. Work was carried out using hot melt extrusion, solutions/suspensions in gelatin capsules, and co-spray-drying of drug and precipitation inhibitor to form spray-dried dispersions (SDDs), in addition to other approaches**.** The SDD approach was studied extensively, with four goals: (A) form an amorphous molecular dispersion of the low solubility drug in a solid polymeric material to facilitate supersaturation of the drug when dissolved, (B) provide a precipitation inhibitor to maintain supersaturation in the dissolution medium, (C) provide a bioavailability-enhancing formulation which can be further formulated in a solid dosage form, preferably a tablet, and (D) provide a formulation in which the drug will not crystallize on storage of the final dosage form. Results with SDDs are presented here.

SDDs were prepared, as described in Materials and Methods, utilizing a variety of low solubility drug candidates and marketed drugs, presented in Table I. These compounds ranged in aqueous solubility from 3.8 ng/ml to 80 μg/ml (Table II). SDDs were prepared with HPMCAS-MF or -LF. SDDs prepared on the "Micro", "Mini", and "PSD-1" spray dryers were prepared at the approximate scale of <2 g, 0.02 to 1 g, and 1 g to 2 kg, respectively. In each case, a dry free-flowing powder was obtained. Fig. 1 presents a scanning electron micrograph and the particle size distribution for a 50% Compound 3:HPMCAS-MF SDD. (50% indicates a 1:1 (*w*/*w*) Drug/Polymer SDD.) The particle size distribution generally appears to be biphasic, with a group centered at about 100 μm and a group centered at about 20 μm. The particles generally appear to be hollow spheres, and this is generally the morphology for a variety of SDDs properly prepared with a variety of drugs and drug candidates.

Differential scanning calorimetry data are presented in Fig. 2 for a 67% Compound 2:HPMCAS-MF SDD. The SDD exhibited a single broad glass transition at T_g=~100°C, intermediate between the two T_gs of a physical mixture of the pure amorphous drug and the polymer. This indicates that the dispersion is entirely or almost entirely a homogeneous amorphous dispersion of Compound 2 in HPMCAS-MF. This observation was typical of SDDs properly prepared with other drugs and drug candidates.

Fig. 3 presents powder x-ray diffraction data for SDDs of HPMCAS and Compounds 2, 3, and 5. In each case, only broad featureless peaks are observed, indicating that the dispersions are amorphous. These relatively featureless PXRD patterns were typical of SDDs properly prepared with other drugs and drug candidates.

Dissolution of SDDs prepared with Compounds 1 through 8 was studied using the centrifugation method or the syringe/filter method described in MATERIALS AND METHODS. SDD compositions and dissolution details are presented in Table IV, and dissolution results are presented in Fig. 4. Control dissolution studies are also presented in Fig. 4, utilizing crystalline drug or amorphous drug, or both. In every case, the HPMCAS SDD provided a higher peak drug concentration, and maintained the concentration above

Table III. Screening for Excipients Which Inhibit Precipitation of Drug 9 in Model Fasted Duodenal Fluid

Candidate precipitation inhibitor	Source/grade	Peak drug concentration (μg/ml)	Drug conc. at ~20 h (μg/ml)	*In vitro* AUC-60 min (μg min/ml)	*In vitro* AUC-180 min (μg min/ml)	AUC-180 enhancement factor
Control (none)	–	85.1±4.3	3.7±1.8	3,406±521	4,625±698	1.0
Polymers						
Carboxymethylcellulose	Aldrich (300–6,000 cps)	55	5.6	2,533	3,418	0.7
Celluloseacetate phthalate	Eastman	95	6.4	3,792	5,664	1.2
Hydroxybutyl methylcellulose	Aldrich	94	4.6	4,920	9,461	2.0
Hydroxyethyl cellulose	Aqualon (99–250 M)	92	4.3	4,189	5,931	1.3
Hydroxyethyl cellulose	Aqualon (99–250 M)	87	5.1	3,878	6,023	1.3
Hydroxypropyl cellulose	Aqualon Klucel EFF	82	5.9	3,918	6,057	1.3
Hydroxypropyl cellulose	Aqualon Klucel EFF	90	5.9	3,981	6,700	1.4
Hydroxypropyl methylcellulose	Dow Methocel K100	82	6.1	4,495	7,363	1.6
Hydroxypropyl methylcellulose	Dow Methocel K100	94	7.0	5,982	9,137	2.0
Hydroxypropyl methylcellulose	Shin-Etsu	98	6.7	4,632	11,385	2.5
Hydroxypropyl methylcellulose acetate succinate	Shin-Etsu MF	87	13.4	5,661	14,557	3.2
Hydroxypropyl methylcellulose acetate succinate	Shin-Etsu MF	96	14.6	4,489	12,692	2.7
Hydroxypropyl methylcellulose acetate succinate	Shin-Etsu MF	94	NM	4,302	11,982	2.6
Hydroxypropyl methylcellulose phthalate	Shin-Etsu 50	92	12.2	5,220	11,590	2.5
Hydroxypropyl methylcellulose phthalate	Shin-Etsu 50	84	7.4	4,759	8,108	1.8
Hydroxypropyl methylcellulose phthalate	Shin-Etsu 50	90	9.4	5,018	7,501	1.6
Polyacrylamide	Aldrich	100	4.5	3,366	7,287	0.9
Polyacrylic acid	Aldrich	79	5.1	2,532	3,540	0.8
Polyethylene glycol	Dow 300NF	92	5.5	3,518	4,630	1.0
Polyethylene imine	Polysciences	90	5.1	5,220	7,322	1.6
Hydroxyethyl polyethylene imine	Polysciences	89	6.0	5,197	7,424	1.6
Polyethylene oxide	Union Carbide 200K	87	4.8	3,431	4,464	1.0
Polyvinylacetate phthalate	Colorcon	92	6.6	4,966	7,074	1.5
Polyvinyl alcohol	Elvanol 51–05	93	8.9	4,940	12,040	2.6
Polyvinylpyrrolidone	BASF; Kolloidon 90F	98	5.4	4,234	6,761	1.5
Polyvinylpyrrolidone	BASF; Kolloidon VA64	89	5.9	5,541	8,644	1.9
Dextrin type IV	Sigma	77	5.6	3,224	4,327	0.9
Microcrystalline cellulose	Mendell; Emcocel	87	4.6	3,914	5,198	1.1
Gelatin (porcine)	Sigma	94	7.0	3,545	5,009	1.1
Sodium alginate	Grindsted	89	5.7	3,346	4,395	1.0
Starch	Colorcon; NF 1500	93	5.2	4,122	6,156	1.3
Pluronic F68LF	BASF	92	1.2	3,984	5,689	1.2
Pluronic L35	BASF	91	1.2	3,245	4,244	0.9
Pluronic L101	BASF	93	4.3	3,392	4,323	0.9
Surfactants						
Hexadecyltrimethyl-ammonium bromide	Sigma	70	5.2	2,940	4,254	0.9
n-Octyl-D-glucopyranoside	Fluka	86	4.3	3,605	4,752	1.0
Sodium lauryl sulfate	Aldrich	89	3.1	4,387	6,793	1.5
Tween 20	ICI	78	4.9	3,263	4,850	1.0
Sodium taurocholate	Fluka	92	4.9	4,221	6,793	1.5

Amino acids/peptides						
Phenylalanine	Aldrich	35	4.8	2,738	4,971	1.1
Tyrosine	Aldrich	47	4.7	2,730	4,837	1.0
Phenylalanylalanine methyl ester	Prepared in our laboratories	68	4.6	3,571	5,294	1.1
Methionyl-tyrosyl-glycyl-glycyl-glycyl-phenylalanine methyl ester	Prepared in our laboratories	100	4.8	4,031	5,275	1.1
Phenylalanyl alanine methyl ester, trifluoroacetate salt	Prepared in our laboratories	96	4.4	4,608	5,869	1.3
Phenylalanyl histidine methyl ester	Prepared in our laboratories	96	4.6	3,694	4,689	1.0
Carboxylic acids						
Benzoic acid	Matheson	73	4.9	3,107	4,448	1.0
Phthalic acid	Aldrich	82	5.0	3,369	4,550	1.0
Miscellaneous						
Benzoin	Aldrich	79	4.5	3,710	5,073	1.1
Phenol	Aldrich	99	4.6	3,687	4,892	1.1
Sorbitol	Sigma	73	4.9	2,975	4,547	1.0

See text for details

control for about 100 to 200 min. (Measurements were generally made out to 90 or 180 min.) In almost all cases, supersaturation was achieved very quickly, and the drug concentration remained at or near the peak concentration. In the case of the dispersion of Compound 6 (griseofulvin), the concentration fell to about one-half the peak value by 180 min (Fig. 4f). The physical properties of griseofulvin in Table II, relative to those of the other studied compounds, do not provide an explanation for why supersaturation was not maintained as well as for the other compounds. It is particularly striking to note that an HPMCAS dispersion works well for an extremely low solubility compound such as Compound 5, which has an aqueous solubility of 3.8 ng/ml (Fig. 4e).

The dissolution plots for Compound 1 also demonstrate that the HPMCAS SDD gave higher supersaturation than was observed for a physical mixture of Compound 1 and HPMCAS at the same drug/polymer ratio as in the SDD (Fig. 4a).

The dissolution plots for Compound 2 demonstrate that predissolution of the HPMCAS in the dissolution medium before addition of amorphous Compound 2 powder results in less supersaturation than that provided by the SDD (Fig. 4b). The SDD provides the drug in a molecularly dispersed form, which facilitates initial high supersaturation, which is then maintained by the HPMCAS.

The dissolution plots for Compound 7 demonstrate that the SDD provides two-fold higher supersaturation than does a rotovapped and milled dispersion (Fig. 4g). It is likely that the better performance of the SDD is due to formation of a more homogeneous and complete molecular dispersion of the drug in polymer because the preparation of the SDD involves fast evaporation of the solvent in which the drug and polymer are dissolved. In the case of rotovapping, the solvent is removed slowly, allowing time for inhomogeneity to develop, with likely drug-rich and polymer-rich regions in the dispersion. The dissolution plots for Compound 8 also demonstrate the superiority of spray-dried over rotovapped dispersions, although in this case the difference is less pronounced at later time points (Fig. 4h).

Fig. 5 presents an *in vitro* comparison of the effectiveness of the polymers HPMCAS, HPC, and PVAP in dispersions made with Compound 2, tested in MFDF solution. Compound 2 has an aqueous solubility of 1 μg/ml, and a ClogP of 3.68. All three polymers resulted in significant drug supersaturation, with HPMCAS the highest. PVAP was unable to maintain supersaturation for the duration of the experiment (180 min).

Fig. 6 presents an *in vitro* comparison of the effectiveness of the polymers HPMCAS, CAT, CAP, PVP, and HPMC in dispersions made with Compound 4. Compound 4 has an aqueous solubility of 14.6 μg/ml, and a ClogP of 4.06. HPMCAS achieves and maintains the highest level of supersaturation, with the other enteric polymers CAT and CAP also working better than PVP and much better than HPMC. All the polymers tested were able to maintain Compound 4 supersaturation (at varying levels) for 90 min in MFDF solution.

Fig. 7 presents an *in vitro* comparison of the effectiveness of the polymers HPMCAS, CAP, CAT, HPMC, HPMCP, and PVP in dispersions made with the extremely low

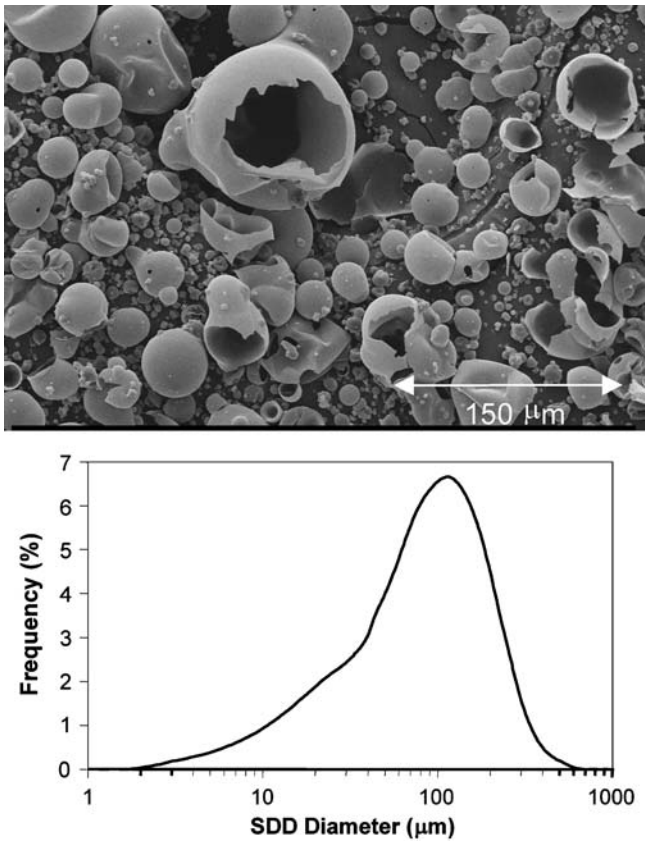


Fig. 1. SEM and corresponding particle-size distribution for a 50% Compound 3:HPMCAS-MF SDD.

solubility, high-melting non-ionizable Compound 5, tested in phosphate-buffered saline. Compound 5 has an aqueous solubility of 3.8 ng/ml, and a ClogP of 6.24. While the three enteric polymers HPMCAS, CAP, and CAT each facilitated a similar high level of supersaturation of Compound 5, only HPMCAS was able to maintain a Compound 5 concentration near the peak value for 90 min. The polymers HPMC, HPMCP, and PVP were not able to maintain Compound 5

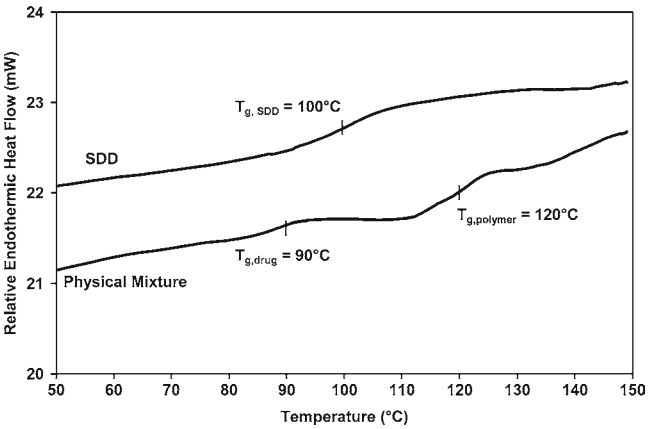


Fig. 2. Comparison between the glass transition temperature T_g of a 67% Compound 2:HPMCAS-MF SDD and that of a physical mixture of the same drug and polymer at the same ratio.

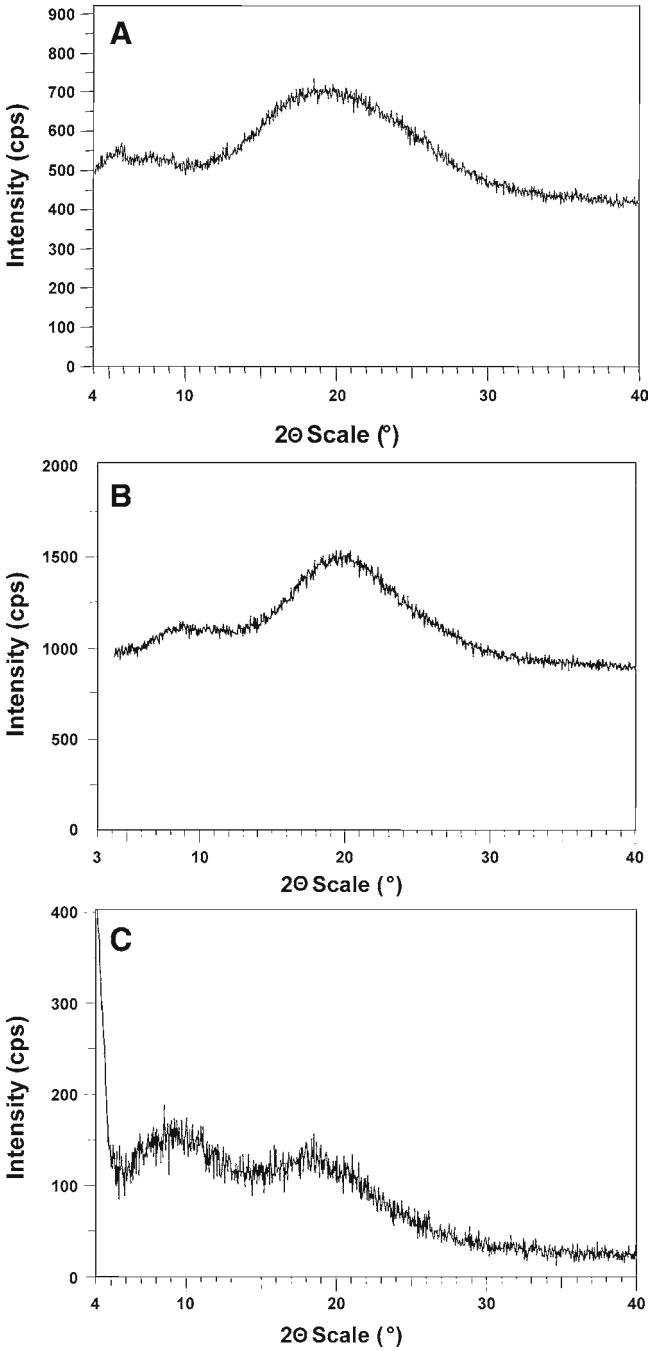


Fig. 3. Powder X-ray diffractograms of **A** 67% Compound 2: HPMCAS-MF SDD; **B** 50% Compound 3:HPMCAS-MF SDD; **C** 25% Compound 5:HPMCAS-MF SDD.

supersaturation as well. The inability of the polymers other than HPMCAS to maintain a high supersaturation level may be due to either or both of (1) the propensity of the very low solubility, high melting Compound 5 to precipitate, and (2) the use of phosphate buffered saline as dissolution medium, which does not have the solubilizing bile salt/lecithin micelles present in the MFDF solution used in Figs. 5 and 6.

Fig. 8 presents the *in vitro* performance of Compound 1: HPMCAS SDDs at various Compound 1 to HPMCAS ratios (10%, 17%, and 33% Compound 1), tested in MFDF

Table IV. *In Vitro* Dissolution Conditions for Dissolution Profiles in Fig. 4

Compound	HPMCAS grade used	SDD composition (wt.% drug)	Dose (μgA/mL)	Dissolution media	Disso method[a]
1	HPMCAS-MF	33	100	MFDF	Microcentrifuge
2	HPMCAS-MF	67	500	MFDF	Syringe/filter
3	HPMCAS-MF	50	1,000	MFDF	Microcentrifuge
4	HPMCAS-LF	50	1,000	MFDF	Microcentrifuge
5	HPMCAS-MF	25	200	MFDF	Microcentrifuge
6 Griseofulvin	HPMCAS-MF	20	200	MFDF	Syringe/filter
7 Nifedipine	HPMCAS-MF	17	200	Japan 2, pH 6.8	Microcentrifuge
8 Phenytoin	HPMCAS-MF	10	100	MFDF	Microcentrifuge

[a] See text for description of dissolution test procedures

solution. Compound 1 has an aqueous solubility of <0.2 μg/ml, and a ClogP of 6.76. It is clear in this case that lower drug loading results in superior performance.

Fig. 9 presents the *in vitro* performance of Compound 3: HPMCAS SDDs at various Compound 3 to HPMCAS ratios (25%, 33%, 50%, and 66% Compound 3). Compound 3 has an aqueous solubility of 80 μg/ml, a ClogP of 3.1, and a high melting point (238°C), and is unionized over the physiological pH range. Dissolution was carried out using the microcentrifuge dissolution test, first in simulated gastric fluid for 30 min, followed by dissolution in a PBS solution. In this case there is a strong dependence on drug loading, with the 25% SDD exhibiting considerably superior performance relative to the 33% SDD. As in Fig. 7, the drug concentration reaches a maximum and then decreases, presumably due to difficulty in maintaining supersaturation in PBS, in the absence of bile salt/lecithin micelles.

DISCUSSION

The current work demonstrates the effectiveness of spray-dried dispersions (SDDs) of low solubility drugs in polymers, and presents data on a variety of polymers, a variety of drugs, and a variety of drug/polymer ratios. The major conclusion of this work is that the cellulosic enteric polymer HPMCAS is clearly superior to other tested polymers in its ability, in spray-dried dispersions, to initiate and maintain drug supersaturation for drugs with a wide variety of structures and physical properties. In the context of this work, the term "supersaturation" refers to an "apparent supersaturation", i.e. increased drug concentration which includes all species that are not removed by centrifugation at 13,000×*g* or that pass through a 0.45 μm filter. The nature of the species in "solution" will be discussed further below.

The efficacy advantage of HPMCAS is primarily due to the polymer's superiority as a precipitation inhibitor, as demonstrated in solutions in which the drug was added as a solvent solution (Table III).

It is particularly interesting that HPMCAS SDDs work well with compounds with very low solubility. In the present work, the lowest solubility compound tested was Compound 5, with a water solubility of ~4 ng/ml. In Fig. 4e, it can be seen that crystalline Compound 5 achieves a maximum concentration of ~5 μg/ml in MFDF, while a 25% Compound 5:HPMCAS SDD achieves an *in vitro* concentration of ~150 μg/ml. Utilizing the observed maximum *in vitro* concentrations in MFDF, and assuming that Compound 5 is well-absorbed and assigning it an estimated Ka of 0.02 min^{-1}, the Maximum Absorbable Dose (MAD) construct predicts a MAD of 6.75 mg and 202.5 mg for crystalline drug and SDD, respectively.

A proposal for the mechanism of supersaturation and bioavailability enhancement for drug/polymer dispersions of the type described here has recently been presented in detail by our group (25). Briefly described, after aqueous dissolution, SDD-derived drug is present in various forms, including (a) nanosized suspended polymer/drug assemblies, (b) drug in bile salt/lecithin micelles, (c) truly supersaturated free drug in solution, and (d) drug in precipitate. For example, dynamic light scattering measurements of a 25% Compound 3: HPMCAS SDD dissolved in PBS, followed by centrifugation at 13,000×*g* to remove precipitated material, demonstrated the presence of colloidal particles with a mean diameter of 79 nm (36). Similarly, dissolution of a 50% Compound 3:HPMCAS SDD in PBS gave colloidal particles with mean diameter 83 nm (36). When HPMCAS alone is dissolved, light scattering reveals particles of approximate diameter 10–20 nm. In addition, NMR measurements of a 25% Compound 3: HPMCAS SDD dissolved in PBS were carried out to measure the concentration of free drug, that is, drug in solution and not in colloidal particles. The NMR-determined concentration of free drug was approximately three-fold the equilibrium solubility of crystalline Compound 3, and approximately two-fold the solubility of amorphous Compound 3 (36). Results for a 50% Compound 3:HPMCAS SDD were similar (36). This is a true, rather than an apparent, supersaturation, and this higher free drug concentration provides a higher driving force for passive diffusional transintestinal absorption. The nanosized polymer/drug assemblies (like the drug-laden bile salt/lecithin micelles) have been demonstrated to be labile, that is, they provide more free drug as free drug is removed from the system (36).

The clear superiority of HPMCAS in increasing the aqueous concentration of low solubility drugs is likely due to two properties. First, above pH 5 the polymer is at least partially ionized, and this charge supports stable nanosized drug polymer aggregates (colloidal particles) which do not merge into larger aggregates which may not be capable of facile release of free drug. Second, HPMCAS is amphiphilic, and hydrophobic regions on the polymer provide sites for drug association, while hydrophilic regions permit the stable

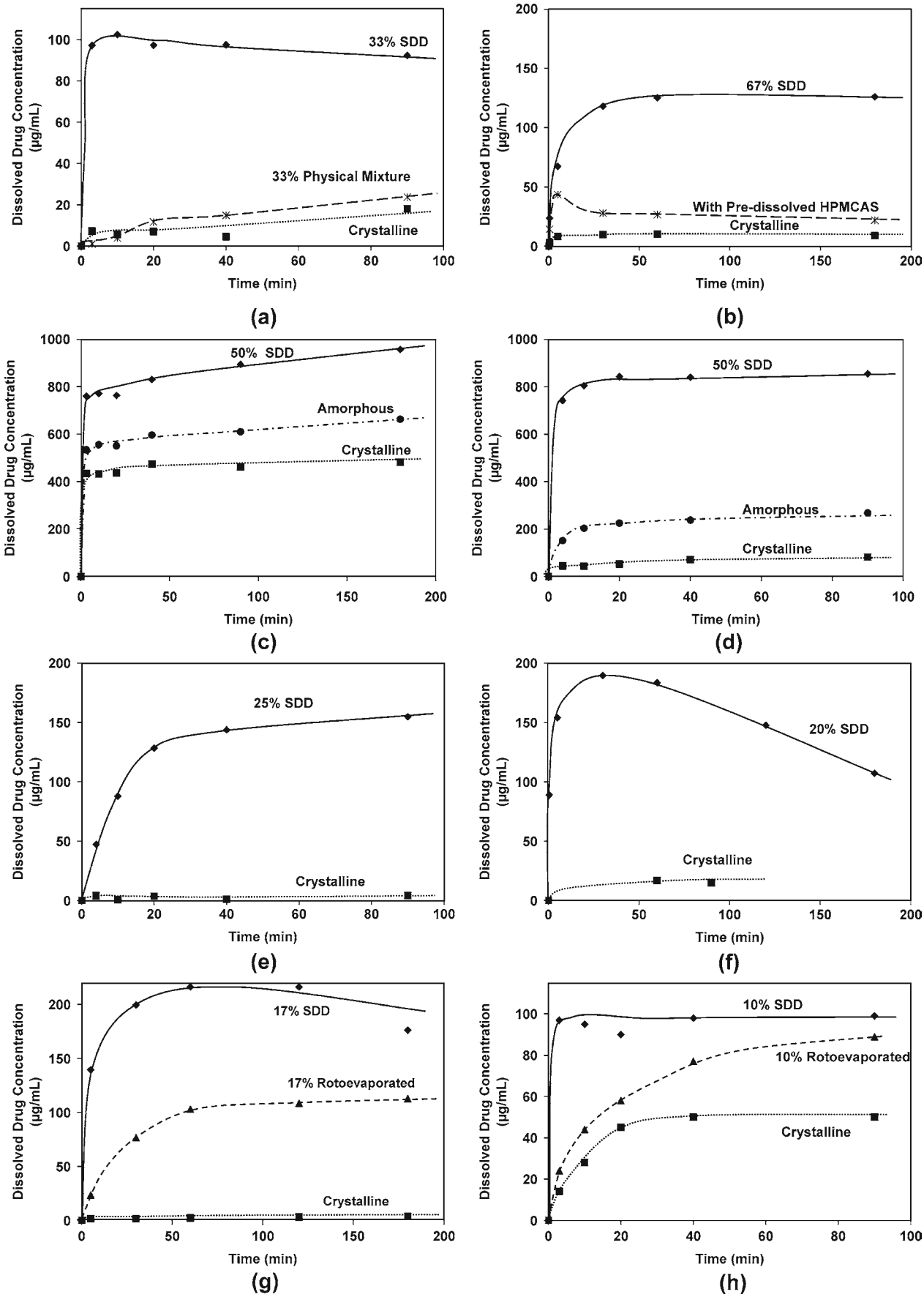


Fig. 4. Dissolution of SDDs made with Compounds 1–8, in **a**–**h**, respectively. See Table IV for SDD composition, and for dissolution details.

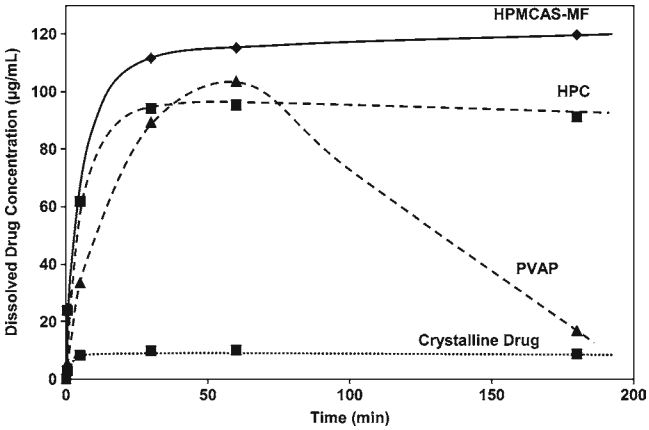


Fig. 5. Dissolution performance of SDDs made with Compound 2 and various polymers, at 50% drug loading. Dissolution was carried out using the syringe dissolution test in MFDF at 37°C, with a 500 µg/ml total concentration (dissolved plus undissolved drug).

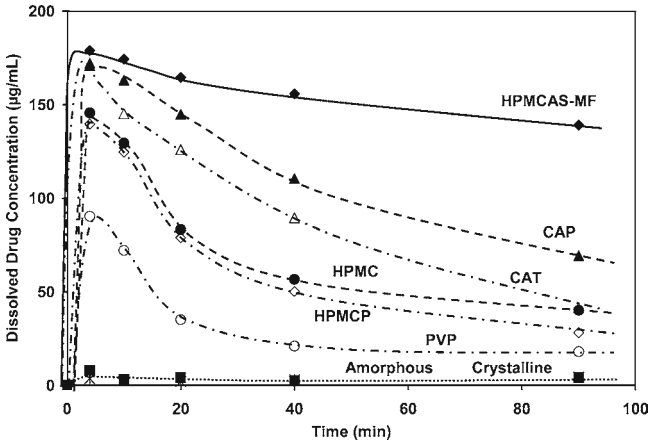


Fig. 7. Dissolution performance of SDDs made with Compound 5 and various polymers, at 10% drug loading. Dissolution was carried out using the microcentrifuge dissolution test in PBS at 37°C, with a 200 µg/ml total concentration (dissolved plus undissolved drug).

formation of hydrated nanosized colloidal structures in aqueous media.

Choice of an appropriate *in vitro* dissolution system which represents the *in vivo* situation is a perennial issue (28–30,37). The lipid content of the milieu of the intestinal lumen is complex and highly variable in the fed and fasted states (31,32). When carrying out *in vitro* studies of low solubility drugs, any attempt at mimicking the *in vivo* intestinal lumenal contents is a compromise, but must minimally involve the presence of one or more bile salts and polar lipids. Admirand and Small reported a mean bile salt/lecithin/cholesterol molar ratio of 74:20:6 for normal gall bladder bile (33). Sjovall reported a range of duodenal/jejunal bile salt concentrations ranging from 2.8–50.2 meq/l (mean 16.4 meq/l) in 29 fasted healthy humans (34). Northfield and McColl reported a mean bile acid concentration of 3.4 mM at the duodenojejunal flexure in seven fasted healthy humans (35). We chose to use a simple "Model Fasted Duodenal Fluid" (MFDF) containing the bile salt sodium taurocholate (NaTC) and the common biliary phospholipid 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine (POPC) at a molar ratio of ~5:1 NaTC/POPC, at a concentration of 7.3 mM NaTC and 1.4 mM POPC, with full recognition that the *in vivo* situation is more complicated. We refer to this *in vitro* medium as "Fasted" because it does not contain the common triglyceride-derived lipids present in the duodenum in the postprandial state, e.g. monoglyceride and diglyceride.

It is interesting that SDDs tested *in vitro* in MFDF generally maintained peak supersaturation for hours (Figs. 5, 6 and 8), while SDDs tested in PBS tended to produce a peak drug concentration which then decreased with time (Figs. 7 and 9). This suggests that biliary bile salt/lecithin micelles may be important *in vivo* for optimal supersaturation maintenance and bioavailability enhancement utilizing dispersions. Regardless, HPMCAS demonstrated clear *in vitro* superiority in both PBS and MFDF.

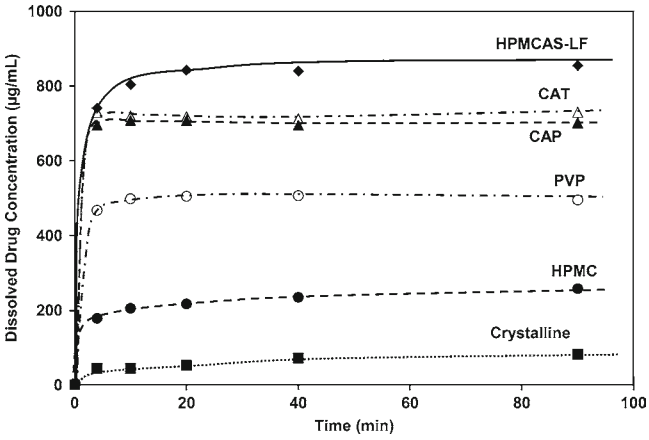


Fig. 6. Dissolution performance of SDDs made with Compound 4 and various polymers. Drug loading was 50% with HPMCAS-LF, CAT, and CAP. Drug loading was 25% with PVP and HPMC. Dissolution was carried out using the microcentrifuge dissolution test in MFDF at 37°C, with a 1,000 µg/ml total concentration (dissolved plus undissolved drug).

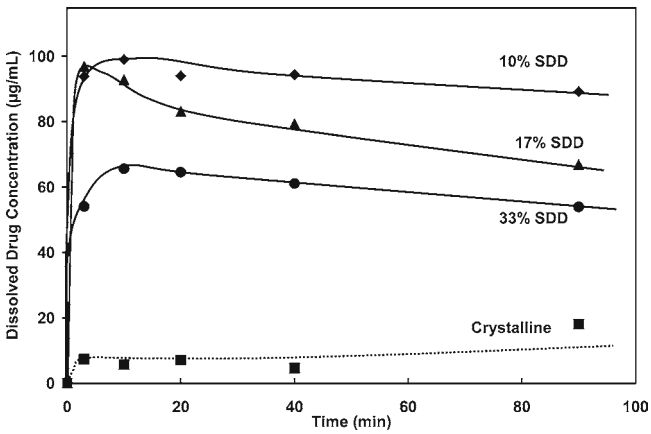


Fig. 8. Effect of drug loading on dissolution performance of SDDs made with Compound 1 and HPMCAS-MF. Dissolution was carried out using the microcentrifuge dissolution test in MFDF at 37°C, with a 100 µg/ml total concentration (dissolved plus undissolved drug).

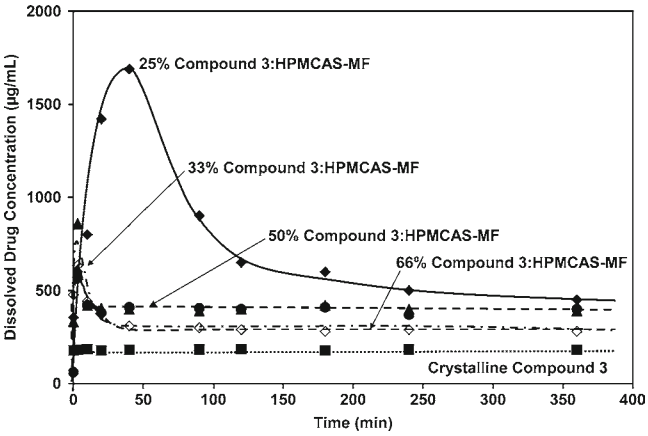


Fig. 9. Effect of drug loading on dissolution performance of SDDs made with Compound 3 and HPMCAS-MF. Dissolution was carried out using the microcentrifuge dissolution test in simulated gastric fluid (30 min) followed by PBS, at 37°C, with a 2,000 µg/ml total concentration (dissolved plus undissolved drug).

In another publication from our group, a dispersion of Compound 3 in HPMCAS, formulated as an aqueous suspension, has been demonstrated to significantly increase the bioavailability of this drug in humans (22). As shown in Table V (from reference 22), the maximum concentration of drug measured in plasma (C_{max}) for the SDD suspension was ~6-fold that for a crystalline drug suspension, and the AUC_{0-24} was ~6-fold higher. The time to achieve maximum drug concentration (T_{max}) was substantially the same for both formulations. Thus the *in vitro* screening and dissolution methodology presented in the current manuscript was effective in identification of materials and processes which resulted in pharmacokinetic improvement.

It is highly desirable that the drug/polymer dispersion be entirely or almost entirely homogeneous and amorphous. The calorimetry data in Fig. 2 and the PXRD data in Fig. 3 demonstrate that properly manufactured dispersions of Compounds 2, 3, and 5 possess these characteristics. This is generally observed for spray-dried dispersions which are prepared under conditions involving fast evaporation of solvent (23,24). We have found that the ability to make a homogeneous amorphous dispersion is generally facilitated by having a lower drug/polymer ratio, and that the optimal ratio range for a given drug depends upon its T_m/T_g and its log P (25).

It is critical that a solid solubilized formulation of a drug possess adequate shelf-life at real-world conditions of temperature and relative humidity. In another publication, we have shown that HPMCAS-MF has a T_g of approximately 95°C at 50%RH (27). In order to maintain a homogeneous solid amorphous dispersion, it is important that the molecular mobility of the dispersion (drug and polymer) be low, to minimize diffusion and crystallization of drug molecules during storage of the solid dispersion formulation. HPMCAS has a relatively high T_g at 0%RH, and a relatively weak dependence of T_g on %RH. PVP, on the other hand, has a higher T_g at 0%RH, but a strong dependence of T_g on %RH, with a T_g of ~50°C at 50%RH. HPMCAS is clearly superior in this respect. Babcock *et al.* (27) proposed that a practical stable dispersion should exhibit a dispersion T_g of 30°C or greater, preferably 50°C or greater, to have sufficiently low mobility to achieve acceptable stability. In order to achieve this, it is important that the dispersion polymer(s) have a high T_g. Because the T_g of a dispersion is related to the T_g and weight fraction of the drug and polymer, via the Gordon–Taylor equation (26), a sufficiently high dispersion T_g may be achieved through choice of a high T_g polymer and by minimizing the drug content of the dispersion (27). There is obviously a practical trade-off in this situation because the quantity of dispersion polymer used cannot be so high that a practically sized oral dosage form can not be achieved.

In addition to the work presented here, we have carried out studies of SDDs with many more drugs (>100), and have recently published a proposal for the relationship between drug properties and SDD physical stability and efficacy (25).

ACKNOWLEDGEMENTS

The following colleagues did much of the initial work on screening, and on development of HPMCAS SDDs (including many of the formulations included in this paper) at Bend Research: Doug Lorenz, Gina Lorenz, Christi Hostetler, and Kathy Colombo Pugh. Initial spray drying apparatus development was done at Bend Research by Christi Hostetler and Doug Millard. We thank Karen Lillebo, Alison Viles, Ann Patten, and Holly Neighbarger of Bend Research for the dissolution tests. We are indebted to Scott McCray of Bend Research for assembling and organizing much of the data in this paper. We are pleased to acknowledge many helpful discussions with Dwayne Friesen and Chris Babcock of Bend Research, and Ravi Shanker of Pfizer. We gratefully acknowledge the enthusiastic support of David Dresback and Timothy Hagen of Pfizer.

Table V. Compound 3 Pharmacokinetics in Fasted Humans after Dosing a 25% Compound 3:HPMCAS-MF Spray-Dried Dispersion (n=4)

Formulation	Dose (mgA)	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-24} (µg-h/mL)
SDD suspension	300	8.4±1.1	2.5±0.6	46±7.6
Crystalline drug suspension	300	1.3±0.3	2.3±1.3	7.4±3.3

From reference (22)

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