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Use of a screening method to determine excipients which optimize the extent and stability of supersaturated drug solutions and application of this system to solid formulation design☆

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Abstract

Assessing the effect of excipients on the ability to attain and maintain supersaturation of drug-based solution may provide useful information for the design of solid formulations. Judicious selection of materials that affect either the extent or stability of supersaturating drug delivery systems may be enabling for poorly soluble drug candidates or other difficult-to-formulate compounds. The technique suggested herein is aimed at providing a screening protocol to allow preliminary assessment of these factors based on small to moderate amounts of drug substance. A series of excipients were selected that may, by various mechanisms, affect supersaturation including pharmaceutical polymers such as HMPC and PVP, surfactants such as Polysorbate 20, Cremophor RH40 and TPGS and hydrophilic cyclodextrins such as HPβCD. Using a co-solvent based method and 25 drug candidates, the data suggested, on the whole, that the surfactants and the selected cyclodextrin seemed to best augment the extent of supersaturation but had variable benefits as stabilizers, while the pharmaceutical polymers had useful effect on supersaturation stability but were less helpful in increasing the extent of supersaturation. Using these data, a group of simple solid dosage forms were prepared and tested in the dog for one of the drug candidates. Excipients that gave the best extent and stability for the formed supersaturated solution in the screening assay also gave the highest oral bioavailability in the dog.

Keywords: Supersaturation; Excipient; Cellulosic polymers; PVP; Surfactants; Cyclodextrins; Co-solvents

1. Introduction

The ability to generate formulations with relevant orally bioavailability depends on a number of factors including solubility, permeability and metabolic stability. Absorbability is related to the first two factors whose importance has been recognized in the guise of the biopharmaceutical classification system (BCS) (Dressman et al., 1998; Amidon et al., 1995). This approach bins drugs and drug candidates into four categories based on their solubility and permeability properties. The manner in which new drug candidates are selected often relies on high throughput screening techniques. These immobilized receptor techniques tend to sub-select for compounds with undrug-like attributes including high lipophilicity, poor aqueous solubility and high molecular weights (Lipinski et al., 1997; Lipinski, 2001). Retrospective analysis completed in the late 1980s suggested that many drug failures (∼40%) were related in some way to the poor biopharmaceutical properties (Prentis et al., 1988). Reanalysis of drug candidate failures in 2004 indicated that some progress had been made with regard to screening out drug candidates with poor drugability elements but poor drug solubility and, by virtue of the Noyes–Whitney relationship, poor dissolution rates continue to be an important consideration in drug candi-

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date attrition (Kola and Landis, 2004). Numerous methodologies have been suggested and practically applied to improve the ability to market drug candidates whose development is limited by drug solubility, dissolution rate and by virtue of Fick's First Law, absorbability. These include the use of particle size manipulation via micronization and nanonization, the use of wetting agents, the use of complexing agents such as cyclodextrins and the preparation of high energy drug states related to polymorphic or amorphic transformations (Liu, 2000; Kim and Park, 2004; Merisko-Liversidge et al., 2003; Forster et al., 2002; Humberstone and Charman, 1997; Davis and Brewster, 2004).

One suggested path forward is the use of a spring and parachute approach wherein a technique such as solid dispersions or self-emulsifying systems allow rapid dissolution of the poorly water-soluble drug at supersaturated concentration. A formulation component which hinders nucleation or crystal growth then acts as a parachute to stabilize the metastable supersaturated systems (Guzmán et al., 2004; Gao and Morozowich, 2006; Gao et al., 2004). An example of this stratagem is the capsule-based dosage form for the antifungal compound, Sporanox (itraconazole) (Peeters et al., 2002). Itraconazole is associated with very poor formulation properties including a low aqueous solubility (estimated at ∼1 ng/mL at neutral pH), a log $P > 5$ and a melting point of 167 °C. The successful preparation of an oral formulation was based on the development of a solid solution of the drug in a polymeric matrix based on HPMC. This system was prepared by a solvent method in which the drug and polymer were dissolved in a common solvent and coated onto an inert sugar sphere. In this formulation, dissolution of the water-soluble HPMC phase was associated with release of the itraconazole at concentrations above its saturation solubility. The co-dissolving HPMC acted as an inhibitor of drug nucleation and crystal growth such that supersaturated concentrations were maintained long enough for significant absorption and oral bioavailability. The maximum fraction absorbed for this formulation was ∼85% and oral bioavailability as high as ∼55% (Brewster et al., 2004). Other examples are available for solid dispersions prepared by melt extrusion and spray drying (Kohori et al., 1999; Crew et al., 2005; Appel et al., 2006). In addition, nanoparticulate systems can give supersaturated systems based on the greater solubility of small versus large particles (Müller et al., 1999; Lindfors et al., 2006; Wu and Nancollas, 1998).

The optimisation of system features that will allow for sustained supersaturation and by extension improved oral bioavailability is the stimulus for the current study. A number of research efforts have pointed to methods for solubilizing, that is increasing the saturation solubility, of poorly water-soluble drugs and drug candidates. Some of these have lead to marketed products (Strickley, 2004). Supersaturation approaches to enhance topical and transdermal therapies have been widely reported (Raghavan et al., 2001, 2003; Davis and Hadgraft, 1991; Moser et al., 2001a,b; Hadgraft, 1999). Less information is available on techniques to stabilize formed high energy solutions intended for oral application especially in a manner which could be useful in early formulation design and screening. Armed with such data the selection of excipient may be optimized. Herein we suggest an approach for testing excipients with regard to their ability to attain and maintain supersaturation. This approach was implemented and results on a number of early drug candidates are discussed. Finally, a case study is described where early solid formulations are generated based on excipient behaviour in the supersaturation tests.

2. Materials and methods

Research compounds were obtained from Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium. All compounds demonstrated a purity of >95%. The log P and pK_a of the drug candidates were determined experimentally while other parameters (topological polar surface area (TPSA) and molecular volume (MolVol)) were calculated using the ADME Predictor software package (Simulations Plus, Lawrenceville, CA). The following excipients were used in the studies: hydroxypropyl cellulose (HPC) 150–700 mPa s (Aquelon Belgium N.V., Doel-Beveren, Belgium), hydroxypropylmethyl cellulose (HPMC) 2910 5 mPa s (Aqualon, Hercules, Zwijndrecht, The Netherlands), Polyox NF 100k (Dow Chemical Company, Midland, MI, USA), polyvinylpyrrolidone-*co*-vinyl acetate (PVP VA)64 (BASF AG, Ludwigshafen, Germany), polyvinylpyrrolidone (PVP) K30 (BASF AG, Ludwigshafen, Germany), Cremophor RH40 (BASF, Hamoir, Belgium), Polysorbate 20 (Codibei NV, Zaventem, Belgium), α-tocopherol polyethylene glycol succinate (TPGS) (Eastman Chemical Company, Anglesey, UK), PEG4000 (Sigma–Aldrich, Bornem, Belgium). 2-Hydroxypropyl-β-cyclodextrin (HPβCD) was obtained from Roquette (Lestrem, France) and was characterized by a degree of substitution of 4.2 based on an FT-IR method (Michaud and Icart, 2001). Additionally, for the solid dosage forms the following excipients were used: lactose (DMV International, Veghel, The Netherlands), citric acid (Merck, Darmstadt, Germany), sodium lauryl sulfate (SLS) (Cognis Benelux, Hoofddorp, The Netherlands), silicone dioxide (Degussa, Frankfurt, Germany), PEG400 (Functional Chemicals, Muttenz, Switzerland), PEG20000 (Sigma–Aldrich, Bornem, Belgium), sugar spheres (Hans Werner, Tornesch, Germany), microcrystalline cellulose (MCC) (FMC, Philadelphia, USA), crosscarmellose sodium (FMC, Philadelphia, USA), magnesium stearate (Univar Benelux, Brussels, Belgium). Other materials and solvents were obtained from Sigma–Aldrich (Bornem, Belgium) or Janssen Pharmaceutica (Beerse, Belgium).

2.1. Supersaturation assay

A co-solvent/solvent quench-based approach was used to generate the drug in a supersaturated state. In most cases, the drug of interest was dissolved to a concentration of 100 mg/mL in *N*,*N*-dimethylformamide (DMF). Dimethylacetamide (DMA) was also used in a few experiments and in isolated incidences, a 50 mg/mL solution was applied based on the limited solubility of the drug candidate. In the majority of cases the final organic content in the dissolution media ranged between 1% and 5% (v/v) although there were a few compounds where the final media contained >5% (v/v) of the organic component. A dissolution vessel

was prepared using a 20 mL glass vial with stopper. Into the vial was placed 10 mL of the media of interest (0.01N HCl, USP pH 4.5 buffer, USP pH 6.8 buffer or water) with or without 2.5% (w/v) of the excipient of interest. The vial was equilibrated at 37 °C in a water bath (Variomag Telemodule 20P) and stirred at 600 rpm using a magnetic stir bar (2 cm × 0.55 cm). The organic solution of the compound was added drop-wise using a small volume pipet into the stirring solution until a precipitate was just noticeable visually. At 5, 30, 60 and 120 min post-drug addition, a small volume of the dissolution medium was withdrawn, filtered through a 0.5 μm Millex-LCR (Millipore Corp.) filter and the concentration determined using Beer's Law with an Agilent 8543 UV spectrophotometer. The pH of the systems was measured throughout the sampling exercise (Sentron type pH meter (Titan)). In assessing the excipients, a supersaturation index was defined based on the ratio of the initial drug concentration in the excipient-based dissolution vessel as a function of that in the dissolution media that did not contain the excipient. In addition the physical stability of the solution was assessed over time with a $\Delta\%$ defined at the extent to which the drug precipitated from C(5 min) to C(120 min). In addition, initial supersaturation associated with addition of the drug-containing organic solvent to media without excipients was inferred based on the initial concentration values as well as the change in concentration of these systems over time.

2.2. Formulation based on the supersaturation studies

Six simple formulations were used in the animal studies including (1) a simple drug blend in a gelatin capsule, (2) a PEG400 solution, (3) a drug dispersion in HPMC E5 coated onto sugar spheres and placed in a gelatin capsule, (4) an HPβCD coprecipitate pressed into a tablet, (5) a mixture of the drug and Cremophor RH40 with additional excipients filled into a gelatin capsule, (6) a mixture of TPGS and other excipients filled into a gelatin capsule. In all cases red cap-red body capsules from Capsugel (Belgium) were used. The amount of drug in the formulations was adjusted to the weight of the dogs. In the descriptions, generic preparation methods for either 50 mg (1 unit per dog) or 25 mg (2 units per dog) nominal weight formulations are given. For the drug blend in capsule, 25 mg drug, 0.59 mg sodium lauryl sulfate, 0.59 mg silicon dioxide and 300 mg granulated lactose were mixed and filled into a size 1 capsule. The PEG400 solution contained 40 mg of Compound 1 in 1.0 mL of PEG400. The bead-based concept contained 25 mg Compound 1, sugar spheres (25–30 mesh, 236 mg), 75 mg of HPMC E5 and 13.5 mg of PEG20000 used as a seal coat. Drug and HPMC were dissolved in a mixture of 2040 mg of dichloromethane and 360 mg of ethanol. The solution was sprayed on the sugar beads using an Uni-Glatt coater with 6 in. Wurster insert (Uni-Glatt, Glatt, Germany) at a spraying rate of 15–20 g/min and an inlet temperature of 50–60 °C. In a second step, PEG20000 was dissolved in a mixture of 72.9 mg dichloromethane and 48.6 mg ethanol and sprayed on top of the first layer. The total batch size was approximately 1600 g. The coated sugar beads were filled in the hard gelatin capsules (size 0) by hand. The HPβCD-based formulation contained 25 mg of Compound 1, 75 mg of HPβCD, 14 mg of citric acid monohydrate, 243 mg of granulated lactose, 60 mg of microcrystalline cellulose, 30 mg of crosscarmellose sodium and 2.3 mg of magnesium stearate. The drug, cyclodextrin and citric acid were mixed in acetone and ethanol after which the solvent was removed. The co-precipitate was blended with the other listed excipients and hand pressed into a tablet. For the concept based on Cremophor RH40, the drug (50 mg), the surfactant (250 mg) and citric acid monohydrate (500 mg) were dissolved in ethanol after which the solvent was removed and the residue manually loaded into a size 00 capsule. The last concept was similarly prepared by blending the drug (50 mg), TPGS (250 mg) and 25 mg of HPMC E5 in ethanol, removing the solvent and then loading the residue into a size 0 capsule. The latter two concepts are based on a glass thermoplastic approach (Brewster et al., 2003). The dissolution of the capsules was assessed using a USP II apparatus using 600 mL of 0.01N HCl medium equilibrated at 37 °C. The paddle stirred at 75 rpm and data are given as the average of two units.

2.3. Bioavailability in the dog

All animal studies were completed according to relevant Belgium Law (18 October 1991) as approved by the European Convention on the protection of vertebrates that are used for experimental and other scientific purposes, Annex A and B as drawn up in Strasbourg (18 March 1986) and the Royal Decree of 14 November 1993 covering the protection of laboratory animals. All experiments were planned and completed under the auspices of the Institutional Animal Care and Use Committee (IACUC). Male Beagle dogs were obtained from Harlan, Germany and maintained in the resident Jansen Pharmaceutica dog colony. Their body weight ranged from 11 to 13.4 kg at the start of the study. Dogs were healthy as judged from routine blood examinations (haematological and biochemical parameters) and certified by the attending veterinarian. All animals were observed prior to, at the time of dosing and up to 24 h post-dosing. Dogs had free access to water and food through the experimental period. Fed animals were dosed using a cross-over design with a washout period of 14 days. Solid formulations were dosed orally. Oral solutions were administered by gavage using a stomach tube. The IV arm of the study was completed using a dose of 1.25 mg/kg and a vehicle containing 75:25 PEG:water. Blood samples were obtained from the jugular vein (3 mL collected onto EDTA) just prior to dosing and at the following time points thereafter: 0.5, 1, 2, 4, 6, 8, 24, 32, 48, 72 and 96 h. Blood samples were centrifuged at room temperature at 1900 × g for 10 min to separate the plasma. The plasma was transferred to a second test tube and frozen within 2 h of sampling at −20 °C. Samples were analysed using a validated LC–MS/MS method. Plasma samples (0.1 mL) were subjected to solid phase extraction (Bond Elut solid phase columns, 130 mg, SPE (Varian Corp)). Columns were conditioned with 3 mL methanol, 3 mL water and 1 mL acetic acid (1 M). Plasma was applied to column and washed with subsequent aliquots of water, acetic acid and methanol. The compound was eluted from the column with 3 mL methanol/ammonium

hydroxide (25% aqueous) at a ratio of 98:2. The extract was evaporated to dryness and reconstituted with 150 μL of a 50:50 mixture of ammonium formate (0.01 M) and methanol. Twenty microliters of the sample was then applied to a 10 cm × 4.6 mm i.d. reversed phase HPLC column (3 μm Hypersil C18 BDS) and eluted with a mobile phase containing 40% 0.01 M ammonium formate and 60% methanol flowing at 0.8 mL/min (before splitting). LC–MS/MS analysis was completed using an API-3000 system (Applied Biosystems) which was dedicated to the HPLC (Agilent). The lower limit of quantification was 1 ng/mL. Individual plasma concentration–time profiles were subjected to a non-compartmental pharmacokinetic analysis using WinNonlin software (Pharsight Corp., Mountain View, CA, USA). The area under the plasma curve (AUC) from time 0 to 24 or 96 h was calculated using the linear up/down trapezoid rule. Oral bioavailability was reported as the ratio of $(AUC_{oral}/AUC_{IV}) \times 100$.

3. Results and disscusions

Excipients which stabilize formed supersaturated solutions may be important additives to solid formulations. A method was developed to screen for such excipients based on a co-solvent approach. Twenty-five developmental candidates were screened using this assay. Physicochemical properties including molecular weight, TPSA, log *P*, pK_a and molecular volume for the screened materials are presented in Table 1. The compounds cover a reasonable chemical space with MW ranges between 327 and 721, TPSAs between 46 and 198 Å^2, log *P*s between 1.76 and >5 and molecular volumes between 273 and 602 Å^3. The effect of various excipients on the extent of supersaturation is given in Table 2 while the stability of the formed supersaturated solution in the presence of the specified excipient is given in Table 3. The excipients were selected based on a variety of potential mechanisms which may impact the ability of the material to nucleate or to arrest crystal growth. The exact mechanisms associated with nucleation and crystal growth are not well-described. Crystal growth is believed to take place in three steps (Macie and Grant, 1986; Rodriguez-Hornedo and Murphy, 1999; Raghavan et al., 2001):

- diffusion of the molecule from the bulk media to the solid crystal interface;
- the adsorbed molecule, through a surface reaction, becomes part of the crystal lattice and the heat of crystallization is released;
- the heat of crystallization is conducted to the bulk media.

Materials that may inhibit nucleation or crystal growth have been reported. These materials have several potential actions including:

- altering bulk properties such as surface tension or saturation solubility;
- changing the adsorption layer at the crystal-medium interface;
- selectively adsorbing to the crystal interface thereby blocking crystal growth;
- being adsorbed into growth layers and thereby disrupting growth layers across the surface;
- adsorbing into surface imperfections causing rough surfaces to become flat;

Table 1
Compound properties, dissolution media and initial and final concentrations in the dissolution media

Compound	MW	TPSA (Å^2)	log *P*	pK_a	MolVol (Å^3)	Media	*C*(5 min) (mg%)	*C*(120 min) mg%	*Δ*%
1	366.4	97	4.8	5.6	352	0.01N HCl	18	16	−11
2	373.4	80	1.58	1.86	306	0.01N HCl	14	14	0
3	436.5	107	4.97	4.9	392	0.01N HCl	41	8	−80
4	453.5	150	3.9	3.53	385	0.01N HCl	0.05	0.03	−40
5	558.7	108	3.9	Multiple	559	pH 6.8	5.5	0.21	−96
6			1.76	3.68		0.01N HCl	34	10	−71
7	547.4	109	4.49	6	375	pH 6.8	0.3	<0.001	–
8	441.4	131	3.05	10.12	340	0.01N HCl	7.3	1.8	−75
9	353.4	82	2.13	2.2; 8.9	308	0.01N HCl	92	9	−90
10	413.5	47	2.72	8.18	322	0.01N HCl	0.23	<0.001	–
11	327.5	49	4.27	–	336	Water	38	38	0
12	573.7	198	3.29	2.2	490	pH 6.8	71	4	−94
13	504.5	101	5.03	5.72	410	0.01N HCl	<0.05	<0.05	–
14	686.8	47	4.43	7.2; 3.1	602	pH 6.8	9	4	−56
15	573.7	198	3.29	2.2	490	0.01N HCl	17	18	6
16	720.9	108	4.94	Multiple	686	0.01N HCl	3	7	130
17	676.7	130	4.88	7.5; 3.6	585	pH 4.5	13	3	−77
18	427.5	97	2.4	8.26	303	0.01N HCl	397	–	–
19	344.4	94	2.9	–	306	0.01N HCl	<0.01	<0.01	–
20	371.4	54	2.9	2.1; 8.5	343	0.01N HCl	0.4	0.4	0
21	499.4	50	5.11	2.8	424	0.01N HCl	<0.001	<0.001	–
22	555.5	46	5.14	9.1	466	0.01N HCl	351	364	4
23	572.6	59	>5	6.3	487	pH 6.8	<0.001	<0.001	–
24	394.4	154	2.15	3; 9	273	0.01N HCl	5	5	0
25	639.8	84	>5	8.5	609	0.01N HCl	<0.001	<0.001	–

Table 2
The extent of supersaturation observed for various compounds in the presence of 2.5% (w/v) of various excipients

Compound	HPC	HPMC E5	PolyOx	PVPVA	PVPK30	RH40	Poly20	TPGS	HPβCD	PEG4000
1	2.1	12.3		2.2	0	3.2	3.6	5.1	1.6	1.4
2	1.2	1.4	1.1	1.6	1.3	1.9	1.4	3.4	16	1.4
3	1.5	1	0.29	2	1.4	2.6	1.8	2.9	2.1	0.43
4	8	18	0.8	6	6	36	28	48	2	1.4
5	1.8	1.8	1.5	5	2.7	7.5	3.6	16	8.4	2.5
6	7	3.8	3.2	7	5.1	2.7	2.4	3	7.2	1.4
7	4.3	5	2	57	20	57	37	1217	20	0.7
8	1.4	1.8	2.5	2.6	1.9	73	46	84	15	2.3
9	1.3	1.2	0.96	10	1.4	7.7	10	10	6.7	0.14
10	1	5.7	3	3	1	35	22	70	91	1
11	1.2	1.6	1.1	1.3	1.1	5.6	5.3	6	11	1.2
12	1.7	1.7	1.3	1.4	2.1	0.2	0.2	0.42	1.5	1.2
13	4	6.6	2.6	1.4	2	5000	3200	5420	260	1
14	1.6	1.3	1.2	2.1	1.9	48	34	45	11	0.9
15	1.1	1.2	0.9	1.5	1.4	24.5	19	42	10	1.6
16	4.7	4.7		6	6.3	9.2	51	123	18	4.3
17	1.5	1.3		1.5	1.4	3.4	29	31	14	1.9
18	1	1	0.9	1.1	1	1	1	1	0.8	0.9
19	1	9	1	1	1	32	34	180	1	1
20	2.3	4	1.4	6.4	7.5	55	45	85	60	2.2
21	1	280		1	1	>10000	>10000	>10000	3000	1
22	1	1		1	1	2	1.5	1.7	1.4	1.3
23	1	1	1	1	1	>10000	>10000	>10000	2000	1
24	2	3.2		4.2	18.6	93		38	4	1.2
25	>10000	1		>10000	2500	>10000	>10000	>10000	>10000	1

Supersaturation ratio: ( ) 0–4.9; ( ) 5–9.9; ( ) 10–99; ( ) 100–1000; ( ) >1000.

- altering the surface energy of the crystal face which may change the level of solvation.

Rheological polymers such as HPMC and PVP are thought to interact through a number of mechanisms including adsorbing to the crystal (via hydrogen bonding) and collecting at the growing crystal-bulk media interface and thereby providing diffusion resistance (Raghavan et al., 2001). Some reports also suggest that these polymers can form complexes with the drug of interest, increase their saturation solubility and therefore reduce the extent of supersaturation (Rodriguez-Hornedo and Murphy, 1999; Strickley, 2004). Surfactants can solubilize materials via micelle formation but can also alter the surface tension at the crystal-medium interface (Constantinides et al., 2006; Rangel-Yagui et al., 2005). Cyclodextrins can solubilize material through the formation of dynamic inclusion complexes (Loftsson et al., 2004; Loftsson and Brewster, 1996; Thompson, 1997; Rajewski and Stella, 1996). Additional data suggest that cyclodextrins can also inhibit nucleation and crystal growth through non-complex based mechanisms which may be similar to those associated with the pharmaceutical polymers described above (Brewster et al., 2006; Torres-Labandeira et al., 1990; Uekama et al., 1992). PEG4000 or Polyox may affect supersaturated solutions through various mechanisms (Li et al., 2006; Urbanetz and Lippold, 2005).

The cellulosic, PEO/PEG and PVP-based polymers had variable effects on the formed supersaturated solution. HPC gave generally poor results with two compounds (Compounds 4 and 6) giving solubility increases in the 5–10-fold range and one compound (Compound 25) providing a significant increase over the baseline. In this case, the absolute value of the drug concentration in the supersaturated solution was small (11 mg%). HMPC was somewhat more conductive for the formation of supersaturated solutions with 7 hits, 4 in the range of 5–10-fold (Compounds 7, 10, 13 and 19), 2 in the range of 10–20-fold (Compounds 1 and 4) and in one instance the excipient provided for a 280-fold increase in concentration (Compound 21). Again in this case, the absolute values of the formed solution was low (0.5 mg%) and the enhancement was related to the very poor solubility of the compound in the dissolution media without excipients. Polyox and, not unexpectedly, PEG4000 were the worst excipients in forming supersaturated solutions in that there was not a single example of a concentration increases above three-fold or so. The surfactants, as a class, better supported the formation of supersaturated solutions. There were 17-hits in the case of both Cremophor RH40 and Polysorbate 20 and 20-hits for TPGS. TPGS also tended to give a higher average supersaturation compared to the other two materials. Compounds that gave the highest absolute values in the supersaturation test for TPGS included Compound 9, 885 mg%, Compound 17, 710 mg% and Compound 8, 614 mg%. HPβCD also provided for useful values with 18 of the 25 compounds demonstrating supersaturation ratios >5. The highest ratios were obtained for Compounds 13, 21, 23 and 25 while the highest absolute values were available

Table 3
The stability of formed supersaturated solution in the presence of 2.5% (w/v) of various excipients

Compound	HPC	HPMC E5	PolyOx	PVPVA	PVPK30	RH40	Poly20	TPGS	HPβCD	PEG4000
1	-47	-91		-56	-19	-12	-14	-18	-14	20
2	-12	-5	-7	-9	-6	-62	-42	-70	-2	-21
3	-68	-14	-8	-75	-81	-7	-7	-12	-79	-16
4	-75	-67	0	-73	-67	-17	-21	-8	0	-14
5	-90	-70	-88	-93	-93	-56	-30	-73	-91	-93
6	-93	-78	-93	-78	-85	-74	-65	-14	-82	-80
7	-35	0	0	-35	-17	-12	-18	-92	-90	-
8	-30	-69	-78	-11	-21	-90	-59	-60	-80	-82
9	-84	-84	-90	-44	-89	-2	-21	-5	0	-8
10	0	-70	-21	-44	0	-25	-40	-44	-33	0
11	-9	-19	-12	-8	-3	-3	-8	-11	-6	0
12	-97	-74	-96	-93	-95	-27	-27	-63	-80	91
13	-60	-78	-54	-43	-30	-93	-92	-58	0	0
14	-7	0	-98	-63	-82	-94	-94	-90	-84	-75
15	0	0	-6	0	0	-12	-39	0	0	0
16	0	0		0	0	-74	-88	-70	0	0
17	-68	0		-85	-72	-95	-42	-85	-88	-84
18										
19	0	-89	0	0	0	-13	-21	-39	0	0
20	0	-38	-46	0	-57	-41	-22	-29	-17	-43
21	0	0		0	0	-95	-93	-53	0	0
22	0	0		0	0	-28	0	-9	0	0
23	0	0	0	0	0	-89	-87	-75	0	0
24	-10	0		0	0	-77		-23	-21	-33
25	-18	0		-53	0	-56	-4	-13	-18	0

Δ%: ( ) 0–25%; ( ) 26–75%; ( ) >75%.

for Compound 9, 625 mg%, Compound 25, 421 mg%, Compound 11, 414 mg% and Compound 6, 244 mg%. These data are in contrast to other reports which suggest that cyclodextrins were poor excipients in supporting supersaturation and, in some cases, accelerated crystallization (Dias et al., 2003; Ma et al., 1996; Iervolino et al., 2000) Simple correlation between supersaturation ratios and individual physicochemical parameters given in Table 1 was poor suggesting complex interactions between the excipients and the drug candidates.

An indication of the stability of the formed supersaturated systems is provided in Table 3. Taken in isolation, the data suggest that HPC provides stable solution in 12 out of 25 instances while there were 14 hits for HMPC. Polyox and PEG4000 provided stable solutions in 8 and 15 cases, respectively. The surfactants could be stratified based on stability with TPGS > Polysorbate 20 > Cremophor RH40. These data cannot, however, be used in and of themselves and should be combined with the information in Table 2. That is information on both the extent and stability of the supersaturated solutions is needed to select appropriate excipients for subsequent development. To this point, an example may be illustrative.

Compound 1 is a poorly soluble weak base with a water solubility of 0.002 mg% and solubilities in 0.01N HCl of 1.9 mg% and 0.1N HCl of 1.3 mg%. When a DMA solution is added to 0.01N HCl, a supersaturated solution is generated at 18 mg% (i.e., nine-fold higher than the equilibrium solubility in 0.01N HCl) which is maintained through 120 min with an 11% decrease in concentration. Table 4 gives the time versus concentration data obtained in the supersaturation assessments. In evaluating the first line of Tables 2 and 3, the excipient that gave the highest extent of supersaturation was HPMC which gave a 12-fold increase over the solubility generated in the medium without excipient and greater than 100-fold increase over the equilibrium solubility in 0.01N HCl and TPGS where a five-fold improvement over the medium and an almost 50-fold increase over the

Table 4
Concentration (in mg%) of Compound 1 over time in a dissolution media (0.01N HCl) containing 2.5% (w/v) of various excipients

Time (min)	0.01N HCl	HPC	HPMC E5	PVPVA	PVPK30
5	18	38	222	41	16
30	16	24	27	22	14
60	16	20	21	20	13
120	16	20	20	18	13
Final pH	1.99	2.30	2.38	2.29	2.30
Final % organic solvent	3.4	2.9	2.4	3.1	2.9

Time (min)	RH40	Poly20	TPGS	HPβCD	PEG4000
5	57	65	92	28	25
30	52	58	84	25	22
60	51	57	76	24	21
120	50	56	75	24	20
Final pH	2.11	2.10	2.36	2.0	2.29
Final % organic solvent	3.7	3.7	5.3	2.7	2.6

Table 5
Biopharmaceutical properties and oral bioavailability of various early solids concepts for Compound 1

Formulation concept	Dissolution[a] (%)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng h/mL)	Oral BA (%)
Drug-in-capsule	47	21	4	308	1.3
PEG400 solution	–	341	4	8,359	31
HPMC E5 coated bead	94	449	2	11,778	38
HPβCD-based tablet	88	761	6	18,129	58
RH40-based capsule	78	816	3	16,981	58
TPGS-based capsule	98	1145	5	31,008	106

[a] Dissolution at 30 min (see Section 2).

equilibrium solubility was observed. In assessing stability, the worst excipient was HMPC with compound levels falling 90% over the 120 min experiment time course. The concentration of drug obtained using TPGS as the excipients were sustained with an 18% loss between the 5 and 120 min time point.

Solid formulations were prepared to optimize the oral bioavailability of Compound 1 using the dog as a model. The formulations that were prepared included a simple drug blend in capsule, a PEG400 solution, a capsule containing beads onto which was deposited a solid dispersion of the compound in HPMC (Verreck et al., 2004), a tablet based on a co-precipitate of the drug with HPβCD, the compound dissolved in Cremophor RH40 and filled into a gelatin capsule and the drug formulated with TPGS and filled into a gelatin capsule. The amount of drug was adjusted such that dogs received 5 mg/kg of the compound. The oral bioavailability of the drug from each concept was determined by comparing blood levels with those obtained using an IV dose of the compound. The data are presented in Table 5. The bioavailability of the compound out of a simple blend was poor consistent with its high crystallinity (m.p. = 256 °C), low solubility, high log *P* and weakly basic nature. Solubilizing the compound in PEG400 increases the bioavailability to 30% but the poor effect of PEG4000 on supersaturation suggests further improvements might be possible. To that end, a concept based on HPMC E5 was assessed. The oral bioavailability of this concept was slightly better than that associated with the PEG400 solution. That is while HPMC may give a good effect on supersaturation extent, the compound so formulated may rapidly precipitate negating any advantage. The cyclodextrin tablet increased the bioavailability in the dog to almost 60% meaning the modest solubility increase (1.6-fold versus medium without excipient and 15-fold versus equilibrium solubility in 0.01N HCl) together with the stabilizing effect of the excipient combined to give a useful solid formulation. Similar results were obtained with Cremophor RH40 which was comparable to the cyclodextrin with respect to both the extent and stability offered to the formed supersaturated solutions. The solid concept with the best performance was based on TPGS where a bioavailability of 100% was achieved. In this case, it is possible that the combination of the increased extent of supersaturation as well as the resulting stability was optimal with regard to the compound assessed. In this limited sample size, it may be concluded that while generating supersaturated solutions at increased concentrations is important, the stability of the formed systems may be the main driver in this excipient-based formulation approach.

4. Conclusions

The data collected herein suggest that a knowledge of how excipients interact with developmental drug candidates may be useful in designing oral solid dosage forms. Two factors seem to be important including the extent to which the excipient can increase supersaturation and the stability of the formed systems. Such data is useful in preparing systems based on solid dispersions, nanoparticles or the amorphous form of the drug. In all of these cases, the high energy form of the drug may dissolve at supersaturated concentration which may, from both a thermodynamic as well as a concentration point of view, be enabling for difficult-to-formulate materials. In the example cited, information on supersaturating excipients was useful in designing simple solids. The approach described is a useful place to start to generate possible excipients with added value in a solid formulation. It is just a start however. Follow-up information should include assessing synergies between different excipients or excipient types. In addition, it may be possible to select a polymeric carrier which also has good supersaturating properties as in the case of HPMC and itraconazole (Verreck et al., 2003; Six et al., 2003) or HPβCD and itraconazole (Rambali et al., 2003).

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