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Supersaturating drug delivery systems: effect of hydrophilic cyclodextrins and other excipients on the formation and stabilization of supersaturated drug solutions

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Supersaturating drug delivery systems (SDDS) utilize two important design elements in their preparation including converting the drug of interest into a high energy state or other rapidly dissolving form to facilitate the formation of supersaturated drug solutions and providing a means for stabilizing the formed supersaturated solution such that significant drug absorption is possible from the gastrointestinal tract. This has been referred to as a "spring" and "parachute" approach. The current effort is designed to assess materials which may affect properties in SDDS. To this end, a series of excipients was tested in a co-solvent/solvent quench method to assess their ability to attain and maintain supersaturation for a group of 14 drug development candidates. The approach focussed on hydrophilic cyclodextrins including hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutyl-β-cyclodextrin (SBEβCD). Various rheological polymers and surfactants were also included in the study. Consistent with previous investigations, the pharmaceutical polymers, as a class, had minimal effects on the extent of supersaturation but tended to be good stabilizers while the surfactants tended to provide for the greatest degree of supersaturation but the formed systems were poorly stable. This study found that hydrophilic cyclodextrins, especially SBEβCD, gave superior results in terms of attaining and maintaining supersaturation. A knowledge of the behavior and performance of excipients in this context can be useful in designing solid oral dosage forms for difficult-to-formulate drugs and drug candidates.

1. Introduction

The inability to adequately formulate poorly water-soluble drug candidates is a significant impediment to their development. Unfortunately contemporary drug pipelines are often highly populated with compounds manifesting these physicochemical limitations in large part because of the methods by which drugs candidates are selected. Within the pharmaceutical industry the nature of drug screening has evolved over the years such that high throughput screening techniques have become routine. This hit identification strategy put a type of evolutionary pressure on emerging drug candidates, which has led to a systematic increase in molecular weight, lipophilicity and a decrease in water solubility of lead compounds over time (Lipinski et al. 1997; Lipinski 2001; Prentis et al. 1988; Kola and Landis 2004). As a result, the number of formulation options has been increased to address the larger number of challenges presented. These methods include the use of wetting and complexing agents, particle size reduction and co-solvents (Liu 2000). An interesting approach in this context are supersaturating drug delivery systems (SDDS) in which a drug is incorporated in the dosage form as either a high energy form such as an amorphous phase or a co-crystal (Gao and Morozowich 2006; Guzmán et al. 2004). In the case of the amorphous material, a dispersion in a hydrophilic polymer can be completed to increase its solid state stability through vitrification, Fox behavior and by interactions of the drug with the polymer (Serajuddin 1999; Leuner and Dressman 2000). The system exhibits carrier-controlled dissolution providing for the formation of supersaturated drug solutions. The metastable drug solution then has to be stabilized physically so that significant absorption can occur. This can be accomplished by adding material to the formulation that inhibits nucleation and crystal growth. Excipients that may serve this role include rheological polymers, surfactants and cyclodextrins (Vandecruys et al. 2007).

A practical example of a SDDS 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 HPMC polymeric matrix. 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).

The aim of the current investigation was to gain insight into which excipients may be best suited to provide functionality in the SDDS. Thus, a group of drug candidates was screened in a co-solvent/solvent quench assay to assess which materials had the best effect on supersaturation extent and stability.

2. Investigations, results and discussion

Excipients which stabilize formed supersaturated solutions may be important additives to solid formulations (Vandecruys et al. 2007). A method developed in our laboratories was applied to screen excipients based on a co-solvent approach. Fourteen developmental candidates were examined using this assay. Table 1 gives the solvent systems used as well as the dissolution media and initial supersaturation associated only with adding the solvent to the dissolution media (without an excipient). 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.

Materials that may inhibit nucleation or crystal growth have been reported (Macie and Grant 1986; Rodriguez-Hornedo and Murphy 1999). 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; 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 in-

Table 1: Solvent systems and concentrations, dissolution media, initial and final concentrations of the compounds in the media and the percent change over time

Compound	Solvent	Concentration	Media	C(5 min) mg%	C(120 min) mg%	Delta%
1	DMF	50 mg/mL	0.01 H HCl	1.6	1.7	0
2	DMSO	30 mg/mL	0.01 H HCl	14	14	0
3	DMF	100 mg/mL	0.01 H HCl	41	8	−80
4	DMF	100 mg/mL	0.01 H HCl	0.05	0.03	−40
5	DMF	50 mg/mL	pH 6.8 USP	5.5	0.21	−96
6	DMA	50 mg/mL	0.01 H HCl	34	10	−71
7	DMF	100 mg/mL	0.01 H HCl	0.05	0.03	−40
8	DMF	100 mg/mL	0.01 H HCl	41	7.6	−81
9	DMSO	30 mg/mL	0.01 H HCl	14	13.8	−1
10	NMP	50 mg/mL	0.01 H HCl	<0.01	<0.01	0
11	DMF	100 mg/mL	pH 6.8 USP	10.6	0.9	−92
12	DMF	100 mg/mL	0.01 H HCl	<0.01	<0.01	0
13	DMSO	25 mg/mL	0.01 H HCl	<0.01	<0.01	0
14	DMF	100 mg/mL	0.01 H HCl	0.45	0.44	−2

Table 2: Extent of supersaturation as defined by a supersaturation ratio (Sat. ratio) observed for various compounds in the presence of 2.5% w/v of various excipients

Compound	HPC Sat. Ratio	HPMC E5 Sat. Ratio	PolyOx Sat. Ratio	PVP-VA64 Sat. Ratio	PVPK30 Sat. Ratio	Cremophor RH40 Sat. Ratio	Polysorbate 20 Sat. Ratio	TPGS Sat. Ratio	HPβCD Sat. Ratio	SBEβCD Sat. Ratio	PEG4000 Sat. Ratio
1	1.2	1.2	0.94	2.4	1.1	3.9	25	91	48	107	1.3
2	1.2	1.4	1.1	1.6	1.3	1.9	1.4	3.4	16	15	1.4
3	1.5	1	0.29	2	1.4	2.6	1.8	2.9	2.1	5.8	1
4	8	18	0.8	6	6	36	28	48	2	80	1.4
5	1.8	1.8	1.5	4.9	2.7	7.5	3.6	16	8.4	31	2.5
6	7	3.8	3.2	7	5.1	2.7	2.4	3	7.2	3.6	1.4
7	8.4	17.8	1	6	5.4	36	29	48	2.8	80	1.4
8	1.5	1	1	2	1.4	2.1	1.8	2.9	2	5.8	1
9	1.2	1.4	1.1	1.6	2.9	1.9	1.4	3.4	18.3	15	1.4
10	1	25.4	1	1	1	400	240	276	1	34	1
11	1.5	1.4	1.7	1	2.2	1.2	1.9	2.2	1	2.6	1
12	1	2.1	1	1	1.7	1540	485	1790	1	1.6	1
13	1	1	1	1	1	1165	369	880	400	660	1
14	2.1	2.7	1.1	1	1.3	11	8.2	10.2	1.9	2.1	1.4

Supersaturation Ratio:

0 to 4.9
5 to 9.9
10 to 99
100 to 1000
>1000

Table 3: Stability of formed supersaturated solution as defined by the delta % in the presence of 2.5% w/v of various excipients

Compound	HPC Delta%	HPMC E5 Delta%	PolyOx Delta%	PVP-VA64 Delta%	PVPK30 Delta%	Cremophor RH40 Delta%	Polysorbate 20 Delta%	TPGS Delta%	HPβCD Delta%	SBEβCD Delta%	PEG4000 Delta%
1	0	0	0	0	0	−95	−98	−93	0	0	0
2	−12	−5	−7	−9	−6	−62	−42	−70	−2	−12	−21
3	−68	−14	−8	−75	−81	−7	−7	−12	−79	0	−16
4	−75	−67	0	−73	−67	−17	−21	−8	0	−25	−14
5	−90	−70	−88	−93	−93	−56	−30	−73	−91	0	−93
6	−93	−78	−93	−78	−85	−74	−65	−14	−82	−5	−80
7	−76	−66	0	−73	−48	−13	−21	−8	−21	−27	−14
8	−68	−16	−8	−75	−80	−7	−7	−12	−79	0	−17
9	−10	−2	−4	−7	−5	−61	−45	−71	−13	−11	−19
10	0	−100	0	0	0	−12	−8	−97	0	0	0
11	−89	−89	−88	−42	−88	−36	−63	−42	−35	−36	0
12	0	−43	0	0	−60	−75	−73	0	0	0	0
13	0	0	0	0	0	−73	−41	0	100	100	0
14	−33	−7	−10	0	−10	−58	−67	−55	−4	−12	0

Delta%:

−25%
−26% to −75%
>−75%

cluding 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 (Strickley 2004). Surfactants can solubilize materials via micelle formation but can also alter the surface tension at the crystal-medium interface. Cyclodextrins can solubilize material through the formation of dynamic inclusion complexes (Loftsson and Brewster 1996; Davis and Brewster 2004). 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. 2007; Torres-Labandeira et al. 1990; Uekama et al. 1992). PEG4000 or Polyox may affect supersaturated solutions through various mechanisms.

The cellulosic, PEO/PEG and PVP-based polymers had variable effects on the formed supersaturated solution. HPC gave generally poor results with two compounds (**4** and **7**) providing solubility increases in the 5–10 fold range. HMPC was somewhat more conductive for the formation of supersaturated solutions with 3 hits in the range of 5 to 25-fold (Compounds **4**, **7**, **10**). The povidones were similar in behavior to the HPC polymeric system. Polyox and PEG4000 were the worst excipients in forming supersaturated solutions in that there was not a single example of a concentration increases above 3-fold or so. The surfactants, as a class, better supported the formation of supersaturated solutions. There were 7-hits in the case of both Cremophor RH40 and Polysorbate 20 and 9-hits for TPGS. TPGS also tended to give a higher average supersaturation compared to the other two detergents. HPβCD also provided for useful values with 6 of the 14 compounds demonstrating supersaturation ratios >5. Data on the SBEβCD was even more impressive with 10 compounds out of 14 showing supersaturation ratios of greater than 5.

An indication of the stability of the formed supersaturated systems is provided in Table 3. The data suggest that HPC provides stable solution in 6 out of 14 instances while there were 7 hits for HMPC. Polyox and PEG4000 provided stable solutions in 11 and 13 cases, respectively. Again the properties of the povidones were similar to that of HPC. The surfactants could be stratified based on stability with TPGS > Polysorbate 20 ≈ Cremophor RH40. The cyclodextrin also proved to be an interesting excipient as solution stabilizer. HPβCD inhibited precipitation in 8 out of 14 drug systems while the SBEβCD generated 11 hits (<25% precipitation) and two addition compounds that gave extents of precipitation of 27% and 36% during the 2 h time course of the experiment.

An interesting observation is also available by comparing Tables 1 and 3. Specifically, those compounds which show the greatest physical instability in solution after addition of the drug solution into the dissolution media without an excipient also tended to produce compounds that show poor stability in the presence of an excipient. Having said that, compounds which showed the highest extent of supersaturation in media that did not contain an excipient were not correlated to excipient-containing systems with regard to the extent of supersaturation (Tables 1 and 2).

These data on cyclodextrins are interesting in that some published data suggest that cyclodextrins were poor excipients in supporting supersaturation and, in some cases, accelerated crystallization while others point to cyclodextrin as being a useful supersaturating excipient (Dias et al. 2003; Ma et al. 1996; Iervolino et al. 2000). Xiang and Anderson (2002), for example, found that the generation of supersaturated solutions of a novel anti-cancer agent (Silatecan) was possible by converting a precursor to the lactone at an appropriate pH in a SBEβCD solution. In addition, Torres-Labandeira et al. (1990) found that supersaturated solutions of pancratistatin could be prepared in HPβCD solutions. In their preparation procedure, the drug was treated with ammonium after which the aqueous ammoniac solution was removed by freeze-drying. Reconstitution of the powder allowed for solutions as high as 9 mg/mL to be prepared. While precipitation was observed in these samples, the use of polyethylene containers as well as HPγCD provided for significantly prolonged latency periods prior to precipitation.

In conclusion, the ability to attain and maintain supersaturation is a significant added-value in designing orally available dosage forms for difficult-to-formulate drug candidates. By using these techniques, it is possible to provide useful formulations for materials which manifest so-

lubility at neutral pH of < 1 ng/mL as illustrated by the Sporanox® dosage form for itraconazole. Constructing these SDDS required a knowledge of the behaviour of certain pharmaceutically acceptable excipients with regard to their participation in increasing the extent of supersaturation of how they might support the stability of the formed metastable systems. The current report adds to the body of data in this context and identifies the hydrophilic cyclodextrins, particularly SBEβCD, as useful formulation components. While certainly factors related to dosage form bulk should be assessed, these material at reasonable relative amounts demonstrated desirable properties on supersaturation over a number of chemotypes and physical properties as provided in the test set. This suggests that they may be useful excipient for SDDS.

3. Experimental

3.1. Materials

Research compounds were obtained from Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium. All compounds demonstrated a purity of >95%. 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 VA64) (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). Sulfobutyl-β-cyclodextrin (SBEβCD) was purchased from Cydex Corp. (Lawrence, Kansas). Other materials and solvents were obtained from Sigma-Aldrich (Bornem, Belgium) or Janssen Pharmaceutica (Beerse, Belgium).

3.2. Supersaturation assay

A co-solvent/solvent quench-based approach was used to generate the drug in a supersaturated state (Vandecruys et al. 2007). Table 1 gives details on the water-miscible organic solvent used. In the majority of cases the final organic content in the dissolution media ranged between 0.01% and 5% v/v. 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 (0.01 N HCl or USP pH 6.8 buffer) 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 after 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.

A preliminary account of this work has been presented: Brewster, M. "Screening Methods to Identify Excipients which Increase the Extent and Stability of Supersaturated Drug Solutions and Application of this System to Solid Formulation Design." Sixth Retrometabolic Based Drug Design and Targeting Conference, Göd, Hungary, June 3–6, 2007.

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