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A Novel Cyclodextrin-containing Glass Thermoplastic System (GTS) for Formulating Poorly Water Soluble Drug Candidates: Preclinical and Clinical Results

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Abstract

We present a novel solid solution/dispersion technology with glass thermoplastic properties that provide good dissolution rates and oral bioavailabilities for poorly water-soluble weak bases. In this process, a thermoplastic gum was prepared by mixing a polyhydroxy acid such as citric acid or tartaric acid with a weakly basic drug, hydroxypropyl-β-cyclodextrin (HP-β-CD) and a cellulose polymer such as hydroxypropylmethylcellulose (HPMC) in a protic solvent. Removal of the solvent gave a material which could be loaded into hard gelatin capsules. Several model compounds were processed in this manner including methylene blue and itraconazole. The resulting data indicated that dissolution properties of GTS's based on methylene blue was pH independent and rapid with ~80% dissolved within 30 min. Three GTS formulations of itraconazole containing 100 mg of the drug and 500 mg of citric acid as well as various concentrations of HP-β-CD and HMPC were found to dissolve rapidly (~100% in 45 min). One of these formulations was selected for human pharmacokinetic evaluation and demonstrated significant oral bioavailability relative to unmanipulated drug. The studies suggest that the components of the GTS provide for solubilization through complexation and reduced pH and that the cellulose polymer acts to inhibit recrystallization of the supersaturated solution formed. The rational development of the GTS dosage form can be useful for generating acceptable formulations for poorly water-soluble drug candidates.

Introduction

A limiting factor in the configuration of useful pharmaceutical dosage forms is often the water solubility of the drug substance [1]. This property as well as intestinal permeability and metabolic stability are the most important criteria in determining the oral bioavailability of a potential new drug. A number of possible manipulation are available to increase the apparent solubility and thus oral bioavailability. These methods are generally derived from the Noyes–Whitney equation [2]:

$$dC/dt = (DA/hV) \cdot (C_s - C_t),$$

where the dissolution rate (dC/dt) is determined by D, the diffusion coefficient, h, the diffusional layer thickness at the solid-liquid interface, A, the surface area of drug exposed to the dissolution media, V, the volume of the dissolution media, C_s, the saturation solubility of the drug and C_t, the drug concentration at time, t. That is, dissolution rate can be increased by increasing the surface area of the drug (via micronization or nanosizing), decreasing the diffusional layer thickness (through improving wettability by, e.g., the addition of surfactants) and by altering the solubility of the drug (through formation of supersaturated drug solution via solid solutions/dispersions, complexation approaches or by manipulation of the solid form to give salts, polymorphs or amorphous material).

Earlier studies showed that itraconazole [3, 4], a useful antifungal agent with ng/ml solubility at neutral pH, could be formulated either as a solid solution in HPMC using both solvent casting and hot melt extrusion [5–7] or as an aqueous solution in HP-β-CD [8]. Such formulations were significantly bioavailability relative to unmanipulated itraconazole. Based on the success of these itraconazole formulations, further modification were attempted. In particular, a general method for preparing solid oral dosage forms for poorly water-soluble weak bases was considered wherein a three component formulation was developed. The components included a solubilizing element (HP-β-CD), a pharmaceutically compatible acid to provide for an acidic microenvironment to enhance solubility (such as citric or tartaric acid) and an element to stabilize the formed supersaturated solution by inhibiting crystallization (HPMC).

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Experimental

Materials

Hydroxypropyl-β-cyclodextrin (HP-β-CD) was obtained from Roquette (Lestrem, France) and was characterized by a degree of substitution of 4.2 based on an FT-IR method. Itraconazole was obtained from Janssen Pharmaceutica, Beerse, Belgium. Other excipients were commercially obtained and all conformed to EP or USP specifications. The hydroxypropylmethylcellulose (HPMC) grade used was characterized as 2910 5 mPa's.

Methods

For dissolution studies, a USP II apparatus was used. In general, 300–600 mL of a 0.01 to 0.1 N HCl solution served as the dissolution media stirring at between 50 and 100 rpm equilibrated at 37 °C. At various times after introduction of the dosage form, a sample of dissolution media was taken and filtered through a 0.45 μ polyvinylidene difluoride membrane (Nihon Milipore). Samples were then diluted with 0.01 N HCl and analysed by UV at 254 nm using a Hewlett Packard 8450A diode array spectrophotometer.

Human clinical studies were completed under GCP guidelines. Pharmacokinetic studies were completed using a validated bioanalytical method for itraconazole and its major metabolite, hydroxyl-itraconazole [9]. Volunteers received one 100 mg itraconazole GTS capsule after a standard breakfast. At various times thereafter, blood was drawn and the concentration of itraconazole and hydroxyl-itraconazole determined. Pharmacokinetic parameters were then derived from the plasma concentration time profile. Historical data was available for non-optimized itraconazole formulation (i.e., simple drug-in-capsule) and indicated that these systems were not orally bioavailable.

Results and discussion

Three studies were included in this assessment including the justification for inclusion of each component of the system, the development of a model GTS using methylene blue and the development of a prototype formulation for itraconazole. The usefulness of the solubilizing element and the pharmaceutical polymer in stabilizing the formed supersaturated solution was assessed as follows: A solution of itraconazole was prepared in dimethylformamide (50 mg/mL). The solution was then added dropwise into the dissolution media until a precipitate formed. Dissolution was completed using 300 mL of 0.1 N HCl equilibrated at 37 °C. The solution is stirred at 150 rpm. At 5, 30, 60 and 120 min after addition of the solution, a small volume of the suspension is removed from the vessel, filtered and the concentration determined by UV. Results are given in Figure 1.

As shown, the low pH environment (pH 1), provides for useful solubility with initial values of 75 mg% solubilized in the presence of HP-β-CD and ~40 mg% in the presence of methocel. Importantly, the itraconazole concentrations are not stable in the presence of HP-β-CD alone and decrease through precipitation if HPMC is not present. Thus, optimal performance is obtained when both the solubilizer and the starch are present.

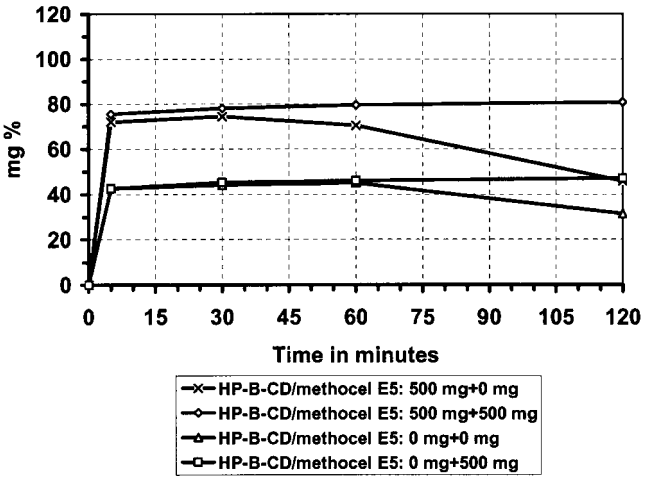

Figure 1. Effect of HPMC (methocel) or HP-β-CD on the physical stability of a supersaturated solution of itraconazole.

Based on these data, systems were prepared containing a drug or model compound plus the three additional excipients using the following procedure: the drug and citric acid monohydrate were dissolved in hot ethanol after which HP- β-CD and HPMC were added. The solvent was then removed. Interestingly, the product of these experiments was not a powder but a gum, which could best be described as a glass thermoplastic. These glass thermoplastic systems (GTS) could be manipulated using a number of techniques to form a variety of shapes and pharmaceutical forms.

The delivery performance of the GTS was initially assessed using Methylene Blue. The dye was incorporated into a model GTS such that a 900 mg dosage form contained 600 mg citric acid, 250 mg HP-β-CD, 50 mg HPMC and 2.63 mg Methylene Blue. The dissolution of the capsules was completed according to the USP (II) using 600 mL of the various media stirred at 100 rpm. The dissolution baths were maintained at 37 °C. The dissolution of release of the dye is given in Figure 2. As suggested in Figure 2, the release of the model substance (methylene blue) is independent of pH.

Itraconazole is a useful antifungal compound with challenging formulation properties [3, 4, 8]. The chemical structure of itraconazole is given in Figure 3 with attendant preformulation data for the crystalline material given below:

Log P: >5
pKa = 4
Aqueous Solubility at Neutral pH ~ 1 ng/mL
Solubility in 0.1 N HCl ~ 4 μg/mL
Solubility in 20% w/v HP-β-CD (pH 7) ~ 0.5 mg/mL

The preparation of drug-containing GTS was possible using the following exemplary procedure [10]: 20 g of itraconazole and mixed with 100 g of citric acid in 100 mL of ethanol. The

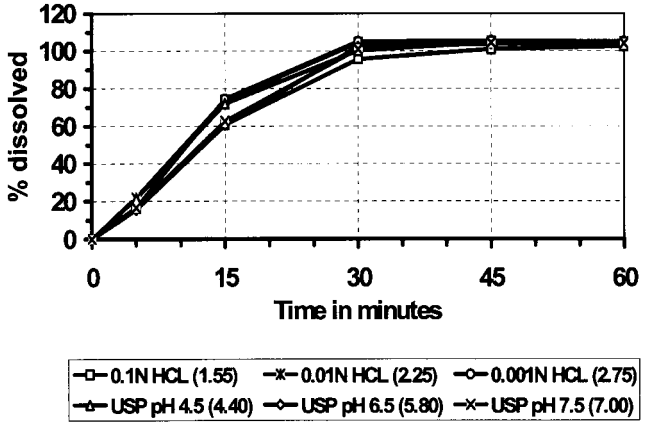

Figure 2. Effect of media pH on release of methylene blue from a prototype GTS. PH values are given parenthetically in the legend.

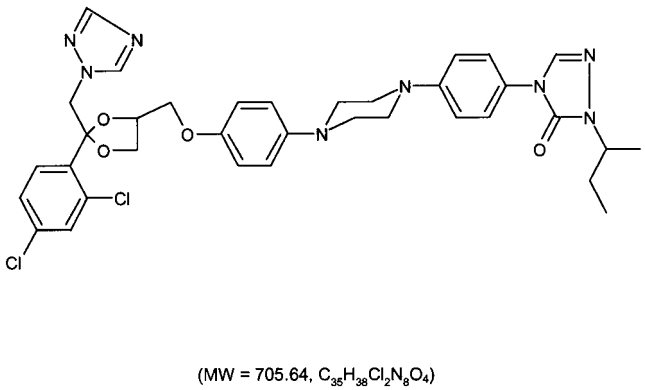

Figure 3. Chemical structure of itraconazole.

system was heated to 70 °C until the acid and drug were dissolved at which point 50 g of HP-β-CD and 10 g of HPMC were added. These elements were then dissolved while stirring at 70 °C. The solution was then poured on stainless steel plates, which were placed in a vacuum oven and dried for 2 h at 80 °C. The plates were withdrawn from the vacuum oven and the gel residue removed, formed into 900 mg cylinders and placed into No. 0 hard gelatin capsules. Similar systems were prepared as described in Table 1.

Dissolution profiles for the GTS are provided in Figure 4. Capsules were placed in a USP II apparatus containing 300 mL of 0.1 N HCl equilibrated at 37 °C (100 rpm). As shown, approximately 100% of the dosage form was dissolved by 45 min. Formulation A (which contained the highest amount of HP-β-CD) appeared to dissolved the fastest with 15 min values of ~80% compared to values of ~60% for systems B and C. Itraconazole itself does not dissolve to any appreciable extent under these circumstances (the solubility of itraconazole in 0.1 N HCl is 4 μg/mL).

Table 1. Composition of itraconazole-based GTS's

	Composition in milligrams		
	A	B	C
Itraconazole	100	100	100
Citric acid	500	500	500
HP-β-CD	275	250	225
HPMC	25	50	75

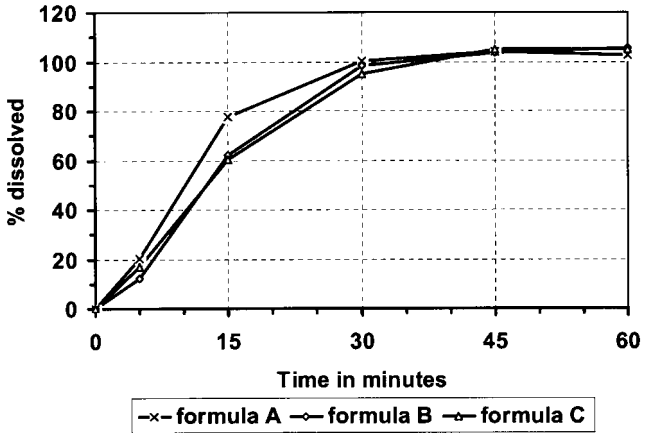

Figure 4. Dissolution profiles for itraconazole incorporated in various GTS's.

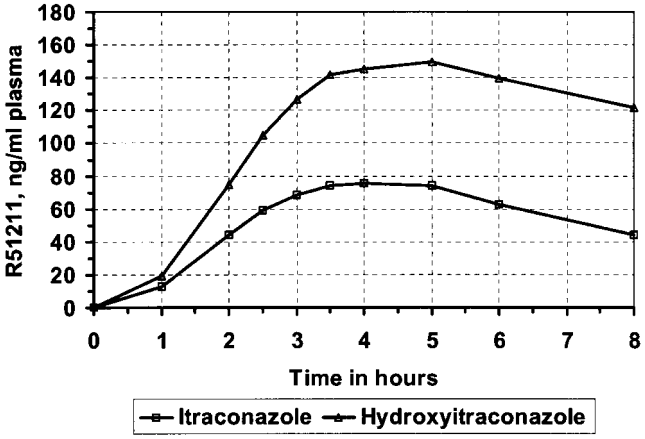

Figure 5. Plasma concentrations of itraconazole and hydroxyitraconazole after dosing with 100 mg of itraconazole incorporated into a GTS (formula A).

The oral bioavailability of itraconazole in a GTS format was assessed in man (Table 2, Figure 5). A 100 mg itraconazole GTS capsule was administered to 8 healthy volunteers after a standard breakfast. Blood was then taken at various times after drug administration (1, 2, 2.5, 3, 3.5, 4, 5, 6 and 8 h) and pharmacokinetic data derived from the plasma/time profiles for both itraconazole and its major (active) metabolite, hydroxyitraconazole. Itraconazole administrated as such exhibits very poor oral bioavailability (<1%). The data demonstrate significant oral bioavailab-

Table 2. Pharmacokinetic analysis in man obtained after oral dosing 100 mg of itraconazole prepared in formula A (see Table 1)

Parameters	Itraconazole	Hydroxyitraconazole
t_{max}, h $\pm$ SD	3.9 $\pm$ 1.4	4.4 $\pm$ 1.6
C_{max}, ng/mL $\pm$ SD	94.4 $\pm$ 31.7	171 $\pm$ 47
AUC_{48h}, ng $\times$ h/mL $\pm$ SD	1077 $\pm$ 476	2385 $\pm$ 914

ility relevant to dosing of an unoptimized dosage form of itraconazole. The bioavailability of itraconazole from the GTS appeared to be similar to that of the marketed Sporanox capsules.

Conclusions

A novel glass thermoplastic system based on citric acid, HP-β-CD and HPMC was found to be a useful modality for solubilizing poorly water soluble weak bases such as itraconazole as well as to increase their dissolution rate. These properties imparted to the dosage form useful oral bioavailabilities and pharmacological potencies. These systems may be generally useful in nature.

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