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ORIGINAL ARTICLE

Formulation design and pharmaceutical development of a novel controlled release form of azithromycin for single-dose therapy

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Abstract

Background: Azithromycin's long serum half-life (~68 hours) allows for a short 5-day, 3-day, and now 1-day course therapy with a large 2-g dose. Although the single-dose, 1-day therapy offers the advantage of 100% patient compliance, tolerance of such large dose becomes an issue. *Methods*: The dosage form discussed in this article employed a melt-congealing process to produce matrix microspheres with a 3-hour, first-order release. The vehicle blend included alkalizing agents to minimize GI side effects, minimize loss of bioavailability, and mask the bitter taste of azithromycin. *Results*: Azithromycin microspheres are small (~200 μm) with a narrow particle size distribution. Drug release was optimized by controlling the amount of dissolution enhancer in the microspheres and by the addition of proper amount of alkalizing agents in the vehicle blend. The final formulation was selected based on a balance between bioavailability and tolerability. *Conclusions*: Drug release from the microspheres was shown to occur via diffusion through the larger pores formed by dissolution of azithromycin crystals and the smaller interconnected pores formed by dissolution of poloxamer. Several clinical studies have been conducted with the formulation to evaluate its pharmacokinetics and to demonstrate its safety and efficacy. The combined suspension formulation for a 2-g dose of azithromycin provided taste-masking and good tolerability.

Key words: *Azithromycin; controlled release; microspheres; single dose; spray congealing*

Introduction

Azithromycin is a macrolide antibiotic that has been used for more than a decade to treat various infections, particularly those of the urinary tract, bronchial tract, lungs, sinuses, and the middle ear. The unique pharmacokinetics of azithromycin—rapid oral absorption, extensive distribution into tissues, and a long serum half-life of ~68 hours[1]—allows for a short 3-day (500 mg/day for 3 days) or 5-day (500 mg on day 1 followed by 250 mg on days 2–5) course of therapy. Preclinical studies have shown that azithromycin efficacy is related to AUC/MIC ratio and that improved efficacy could result if the therapeutic courses were given all at once as a single dose (i.e., 'front loading' or one dose only)[2]. A single-day therapy would also have the advantage of improved patient compliance. However, side affects, such as nausea, vomiting, and diarrhea, limit the maximum dose of azithromycin that can be administered. Thus, the objective of this work was to develop a new formulation of azithromycin that would allow administration of a full course of therapy in a single dose without compromising toleration.

Three factors were considered in the design of the 2-g single-dose azithromycin formulation: (i) improving gastrointestinal (GI) toleration, (ii) minimizing loss of bioavailability because of an absorption window, and (iii) masking the bitter taste of azithromycin. The GI side effects associated with azithromycin increase with the increase in dosage, and previous studies with intravenous administration have indicated that they are not related to systemic drug levels but to the local concentration of drug in the GI tract[3], possibly because of the

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action of azithromycin on motilin receptors located in the upper GI tract. Intubation studies suggested that improved toleration would result when azithromycin was delivered directly to the ileum versus the duodenum[3]. Preclinical models indicate that azithromycin may have poor colonic absorption[4]. Clinical studies with formulations having very long delivery durations confirmed that azithromycin had an absorption window, that is, poor absorption in the colon leading to low relative bioavailability compared to an immediate release formulation (Data on file, Pfizer, Inc., 1997). Thus, a 2-g dose of azithromycin delivered over a relatively short duration could result in improved toleration without significantly lowering the relative bioavailability. Particle size has an effect on palatability (bitterness, mouth feel, and texture)[5], and to have acceptable palatability, azithromycin release in the mouth has to be minimized and the particle size of the microspheres has to be small to prevent a gritty mouth feel.

Conventional sustained release tablets and capsules were eliminated from consideration as the 2-g dose could not be formulated in a single unit of reasonable size. Consistent with dose-solubility map for technology selection[6], sustained release multiparticulates given as an oral powder for constitution were selected because they provide a means for delivering a large dose as well as other components such as flavors, sweetener, and buffers. Furthermore, multiparticulates have the advantage of being rapidly emptied from the stomach, thereby minimizing drug release in the upper duodenum. The delivery duration would be designed such that the drug would be absorbed prior to the multiparticulates reaching the colon.

Several methods exist to prepare multiparticulates including extrusion–spheronization[7], balling (spherical agglomeration), spray congealing, and cryopelletization[8]. The small particle size of microspheres from spray congealing offers the advantage in formulating a suspension. In this process, microspheres were formed by suspending azithromycin dihydrate in a molten carrier matrix. This suspension was sprayed using a spinning-disk atomizer to form droplets, which congealed into solid microspheres upon cooling. Typical low melting point matrix materials that have been mentioned in the literature are waxes, fatty acids, glycerides, stearic acid, and stearyl alcohol, and other materials are solids at room temperature and melt without decomposition[9].

In addition to the microspheres, the final powder for oral suspension also contained a vehicle blend containing taste-masking components (sweetener and flavors), colorants, and suspending agents. Additionally, the vehicle also contained alkalizing agents, which were designed to keep a high pH of the constituted suspension to prevent drug release while in suspension and for taste masking. The alkalizing agents also reduced the frequency of GI side effects by increasing the gastric pH for a short period of time and further reducing the rate of drug release in the stomach[10]. The choice and quantity of alkalizing agents were optimized in a clinical study.

The final formulation is conveniently administered after constituting with 60 mL of water; the entire contents are orally administered as a single dose. It should be used within 12 hours of mixing and taken 1 hour before or 2 hours after a meal[11]. The formulation was approved in the United States by the FDA in June 2005 and is commercially available as Zmax™ (Pfizer Inc., New York, NY, USA). Several clinical studies have been conducted with this novel formulation to evaluate its pharmacokinetics and tolerability[12,13] and to demonstrate safety and efficacy in a variety of indications, for example, respiratory tract infections[14–16], community-acquired pneumonia[17–20], acute bacterial rhinosinusitis[20–22], and chronic bronchitis[23].

Materials

Azithromycin dihydrate was obtained from Pfizer Inc.; glyceryl behenate (Compritol® 888 ATO) was obtained from Gattefosse Corp. (Paramus, NJ, USA); poloxamer 407 (Lutol® F-127) was obtained from BASF Corp. (Mount Olive, NJ, USA); anhydrous trisodium phosphate (TSP) was obtained from Astaris LLC (Webster Groves, MO, USA); sucrose was obtained from American Sugar Refining Co. (Brooklyn, NY, USA); magnesium hydroxide and titanium dioxide were obtained from Whittaker, Clark & Daniels, Inc. (South Plainfield, NJ, USA); hydroxypropyl cellulose was obtained from Aqualon (Hopewell, VA, USA); xanthan gum was obtained from CP Kelco Inc. (Chicago, IL, USA), colloidal silicon dioxide was obtained from Cabot Corp. (Alpharetta, GA, USA); and cherry and banana flavoring were obtained from International Flavors & Fragrances Inc. (Shrewsbury, NJ, USA).

Methods

Preparation of melt-congealed microspheres

The microspheres were made using a melt-congealing process, shown schematically in Figure 1. Azithromycin dihydrate, glyceryl behenate, and poloxamer 407 were blended and fed into a twin-screw extruder (B & P Process Equipment and Systems, LLC, Saginaw, MI, USA) to form a molten mixture of the components. The molten mixture was then fed into the center of a custom-made spinning-disk atomizer to form azithromycin microspheres. The spinning-disk atomizer consisted of a bowl-shaped stainless steel disk (10.1 cm in diameter) that was heated to about 90°C by a thin-film electric-resistance

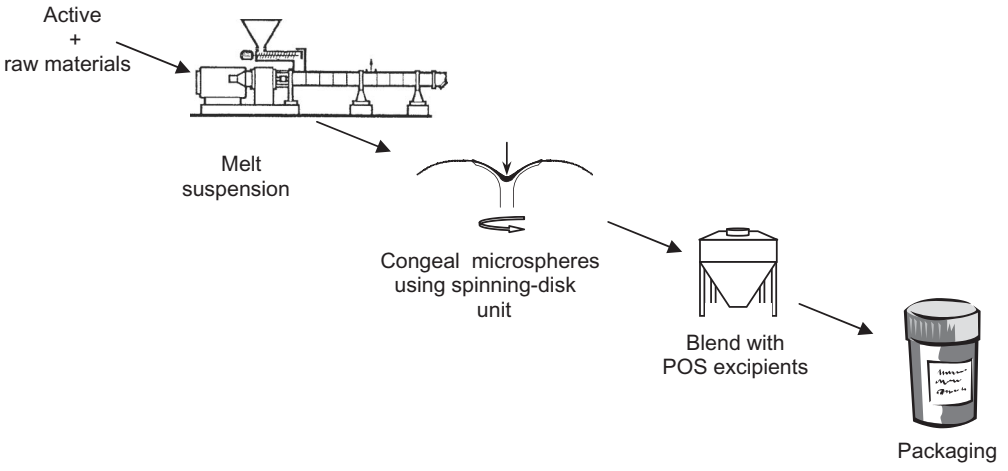

Figure 1. Schematic of the manufacturing process for microspheres.

heater located beneath the disk. The disk could be rotated at up to 10,000 rpm by a motor mounted below the disk. The particles formed by the spinning-disk atomizer were congealed in ambient air and collected.

Particle size
The particle size distribution was determined using a Malvern Mastersizer-S particle size analyzer (Malvern Instrumenets Inc., Southborough, MA, USA).

Scanning electron microscopy
Microspheres were sputter coated under vacuum (100 mtorr) with Au/Pd (Hummer 6.2; Ladd Research, Williston, VT, USA) and examined using the LEO 430 Scanning Electron Microscope (Carl Zeiss SMT, Inc., Thornwood, New York, NY, USA).

Crystallinity
Azithromycin crystallinity was evaluated using powder X-ray diffraction using a Bruker AXS D8 Advance diffractometer (Billerica, MA, USA).

In vitro dissolution
The dissolution test was performed using the USP apparatus 2 (rotating paddles) at 50 rpm in 800 mL of 0.1 M sodium phosphate buffer at the specified pH. The amount of drug release was analyzed by high-performance liquid chromatography with a UV detector at 210 nm.

Titration
Each test formulation and placebo was constituted with 60 mL water and titrated with 0.2–5 mL increments of 0.1 N HCl where the size of the subsequent increment depended upon the pH change associated with the prior increment. Titration curves for suspensions containing magnesium hydroxide or calcium carbonate were allowed to equilibrate for approximately 5 minutes after each acid addition prior to reading pH values.

Gastric pH Study
A human clinical study was conducted to monitor the pH of the stomach (using a pH probe) after dosing test formulations containing alkalizing agents and a control formulation (placebo). Subject pH traces and intermittent pH readings at specified time points were gathered. The test formulations in the titration and gastric pH study were as follows: 176 mg TSP, 352 mg TSP, 352 mg TSP + 500 mg calcium carbonate, 352 mg TSP + 250 mg magnesium hydroxide, 352 mg TSP + 500 mg tromethamine (TRIS), 352 mg TSP + 1000 mg TRIS, and placebo (water only).

Results and discussion

Characterization of microspheres

Microspheres produced by the spray-congealing process were round and smooth (Figure 2) with a relatively narrow particle size distribution (Figure 3). Powder X-ray diffraction data indicated that about 99% of the azithromycin present in the microspheres was in the crystalline dihydrate form (Figure 4) confirming that the form of drug was not changed through the process of making microspheres.

Mechanism and kinetics of drug release

After exposure to water, the surface of the microspheres became porous and a cross section of the microspheres showed interconnected pores (Figure 5a–c). Based on this observation and the known relative particle sizes of azithromycin and poloxamer, we hypothesized that the larger pores (cavities) corresponded to areas that were

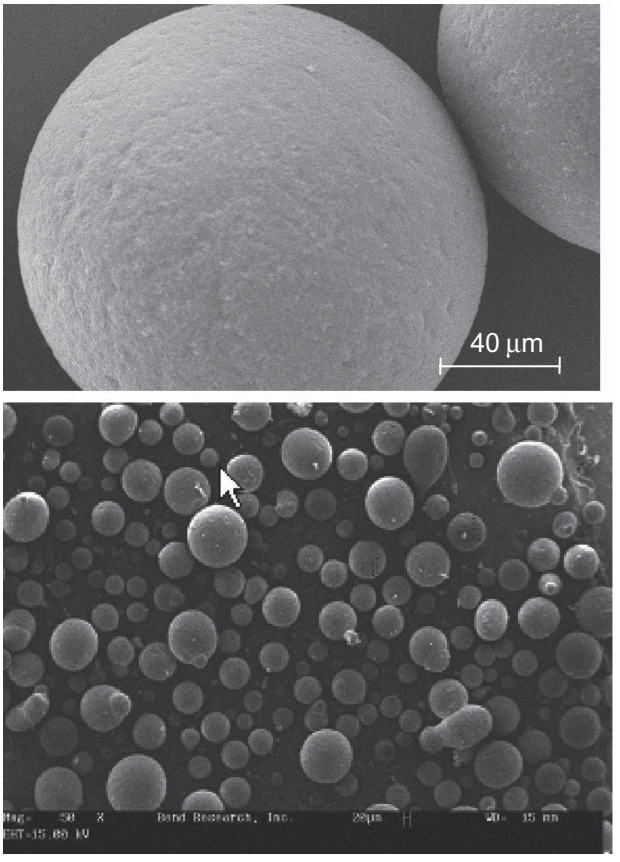

Figure 2. Scanning electron micrograph of intact microspheres.

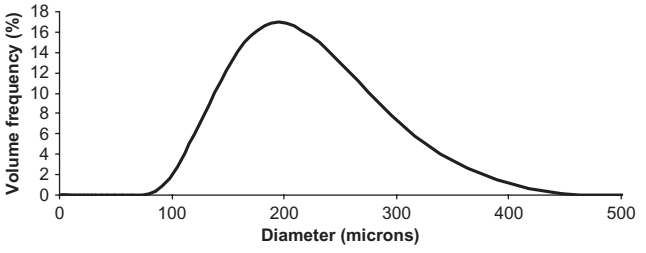

Figure 3. Particle size distribution of azithromycin microspheres as determined by a Malvern particle size analyzer.

occupied by the drug crystals and the interconnected pores were areas occupied by poloxamer, as shown schematically in Figure 5d. Thus, drug release from the matrix occurred via the classic porous diffusion mechanism.

The kinetics of drug release from porous matrix systems has been widely studied and mathematical expressions derived for various matrix geometries[24]. Typical azithromycin release profiles from microspheres could be modeled as a simple first-order process as shown in Equation (1).

$$A_t = A_\infty(1-e^{-kt}), \quad (1)$$

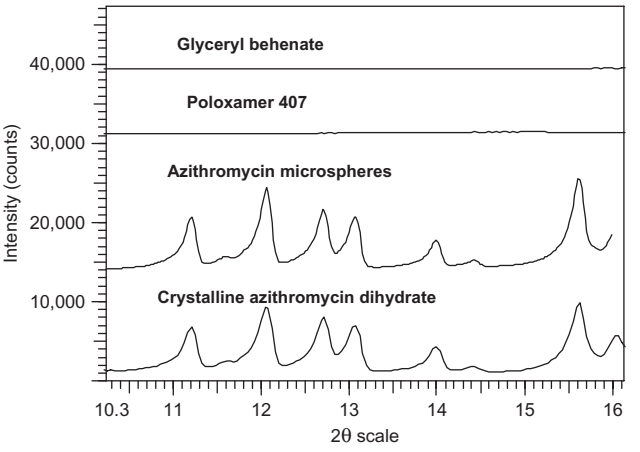

Figure 4. Powder X-ray diffraction comparison of bulk crystalline azithromycin dihydrate and azithromycin dihydrate in microspheres.

where A_t is the amount of drug released, A_∞ is the amount of drug initially present in the microspheres, and k is a first-order release rate constant.

The drug release was dependent on the level of poloxamer incorporated in the formulation and the pH of the dissolution medium (Figures 6 and 7). Consistent with the theory of porous diffusion mechanism, the drug release from the microspheres is a function of the concentration gradient between drug dissolved in the microsphere and the external environment, which is assumed to be 0 (sink conditions). Because azithromycin solubility is higher at a lower pH, the concentration gradient is higher when the pH of the dissolution media is lower. Thus, as shown in Figure 7, the dissolution at pH 6.0 is faster compared to the dissolution at pH 7.5. Figure 8 shows the in vitro release of azithromycin as a function of particle size of the microspheres. Consistent with the theory of a diffusion-based release mechanism, the release rates decreased with increasing particle size.

Additional factors that could affect the in vivo drug release kinetics include the presence of alkalizing agents in the formulation, basal acid and acid secretion rates in the stomach, and the GI transit of microspheres leading to release of drug in a variety of pH environments.

Particle size distribution

For the spray-congealing process, the particle size distribution is defined by the type of atomizer. The atomizer used in this case is a rotary (spinning disk) atomizer in which the liquid feed is introduced at the center of the atomizer and accelerated centrifugally toward the edge; first forming a thin liquid film across the disk surface, then transitioning into a torus at the disk edge. When the centrifugal force exceeds the resisting surface tension, atomization can occur and is typically described in

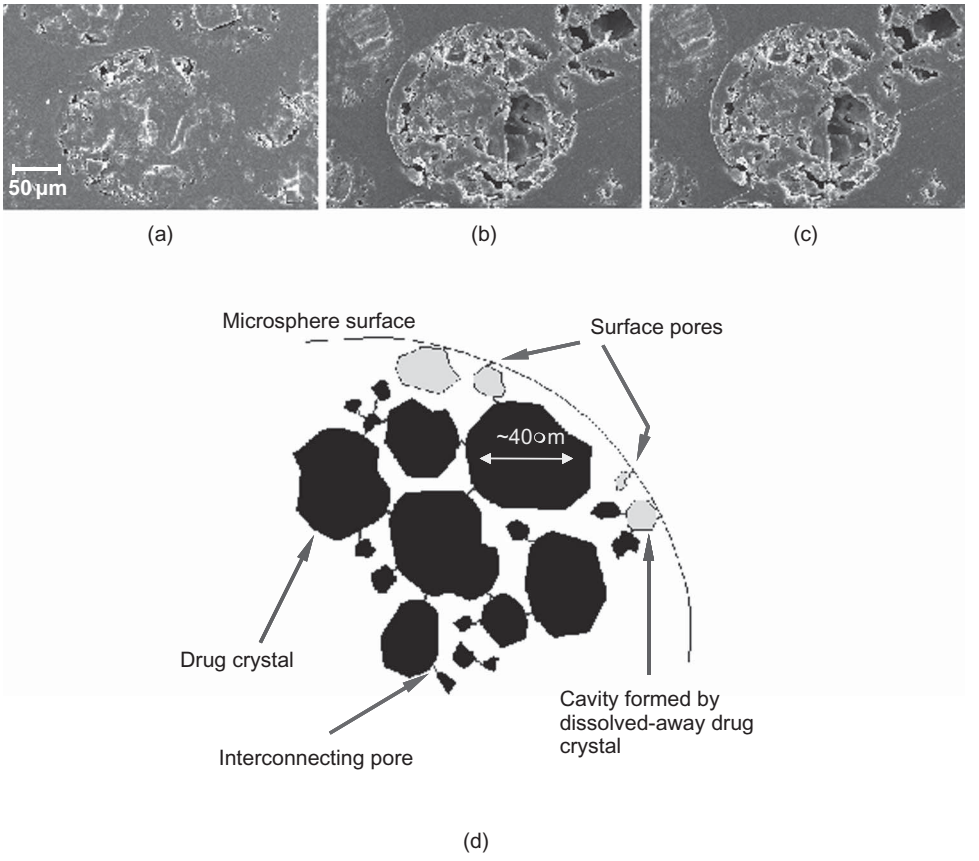

Figure 5. Cross section of microspheres after (a) 5 minutes of exposure to water, (b) 30 minutes of exposure to water, (c) 60 minutes of exposure to water, and (d) schematic showing larger pores corresponding to areas that were occupied by azithromycin and interconnected areas that were occupied by poloxamer.

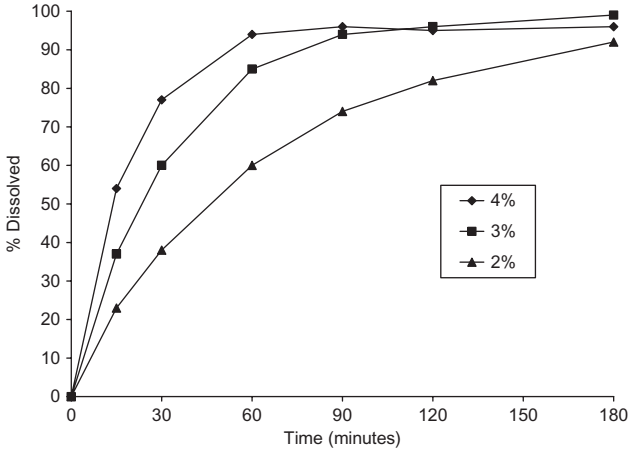

Figure 6. Comparison of dissolution profiles from azithromycin microspheres containing 2%, 3%, and 4% poloxamer (dissolution conditions: USP 2, 50 rpm, 900 mL phosphate buffer, and pH ~ 6.0).

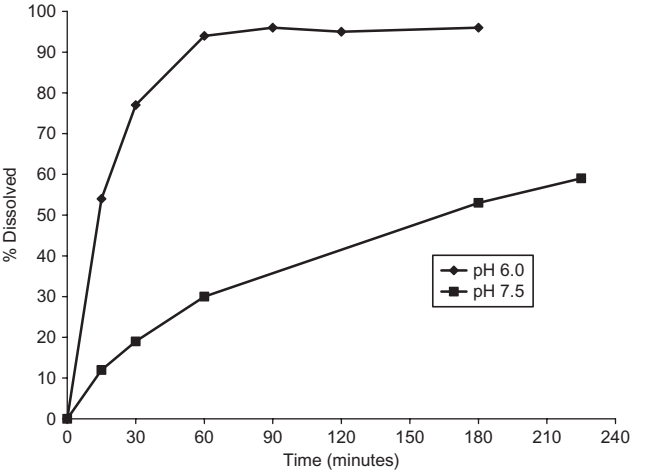

Figure 7. Comparison of dissolution profiles from azithromycin microspheres containing 4% poloxamer as a function of pH of the dissolution media. In the case of dissolution in pH 7.5 media, the paddle speed was increased to 150 rpm after 180 minutes.

three regimes: (i) direct drop formation, (ii) ligament formation, and (iii) sheet formation. The physical properties of the liquid, the liquid flow rate, and the atomizer design and speed primarily determine which of the atomization regimes the atomizer is operating[25].

The droplet size of the rotary atomizers is best characterized by empirical formulas for the specific atomizer design and operation. In the literature, these have best been described by the Weber number, the Reynolds

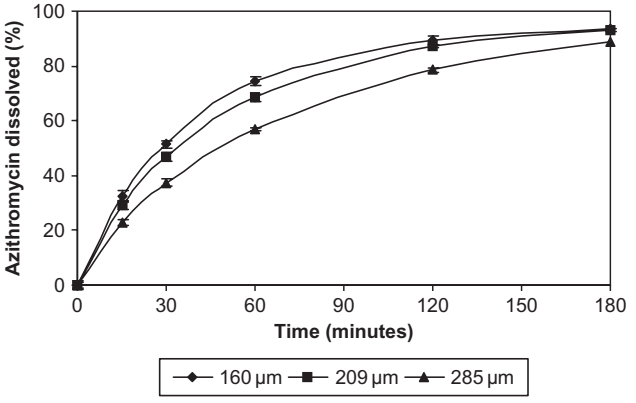

Figure 8. Comparison of dissolution profiles from azithromycin microspheres as a function of the mean microsphere particle size represented by D [4, 3].

number, and a dimensionless flow rate. Although the influence each dimensionless group has on the droplet size varies depending on the atomization regime of operation, the droplet size is directly proportional to the dimensionless flow rate and inversely proportional to both the Weber and the Reynolds numbers. These expressions can be simplified into the following empirical relationship, where the mean diameter of the droplet is directly proportional to the surface tension (σ), viscosity (μ), and feed rate (Q) of the liquid/melt and inversely proportional to the density of the liquid/melt (ρ) and disk diameter (D) and speed (ω)[26]:

$$d\alpha \frac{\sigma^a \cdot \mu^b \cdot Q^c}{\rho^d \cdot D^e \cdot \omega^f}. \quad (2)$$

Once a specific melt formulation has been chosen and the disk design has been selected, this equation can be reduced to the following expression, where C represents the proportionality constant accounting for the physical properties of the melt at the process temperature for a specific disk design:

$$d = C \cdot \frac{Q^c}{\omega^f}. \quad (3)$$

This empirical approach helps improve the understanding of how critical processing parameters may affect the particle size after a formulation has been chosen. This is the type of approach that was taken with the azithromycin microspheres. The disk speed was varied at constant feed rates to evaluate impact on particle size to demonstrate and specify a robust process space.

Optimization of the alkalizing agents

The alkalizing agents were optimized via several in vitro and in vivo studies. Candidate alkalizing agents were as follows: TSP, calcium carbonate, magnesium hydroxide, and TRIS, either alone or in combinations. A typical in vitro titration curve is shown in Figure 9. A clinical study

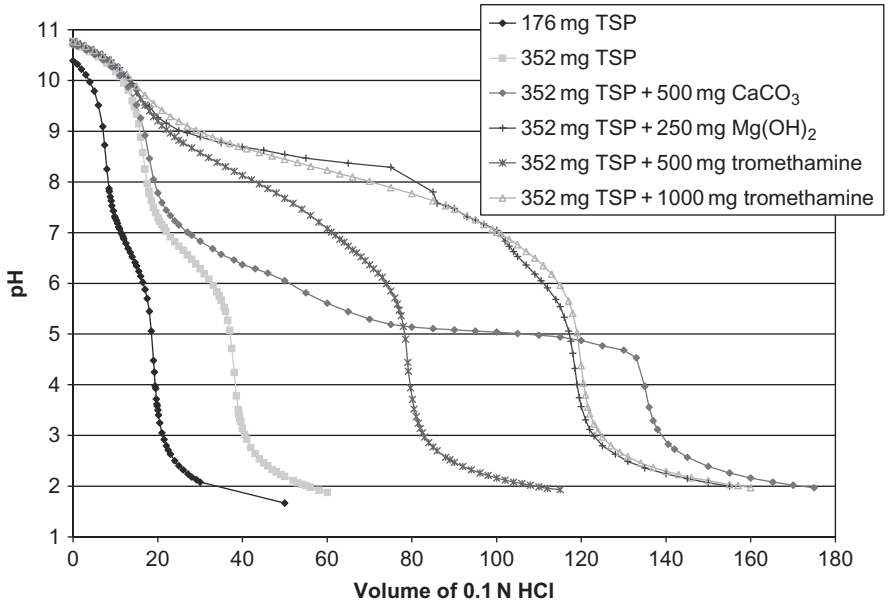

Figure 9. In vitro titration curves of the six formulations. Titration curves for formulations containing magnesium hydroxide or calcium carbonate were allowed to equilibrate for approximately 5 minutes after each acid addition prior to reading pH values. A volume of 60 mL of water was used to constitute suspensions that all contained the sucrose blend (no TSP) in addition to the listed additives.

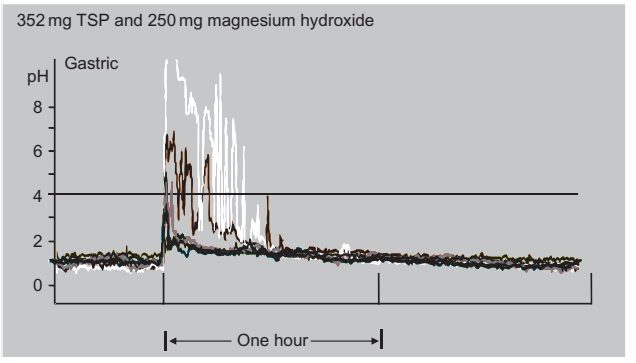

Figure 10. Typical in vivo stomach pH trace from a clinical study to optimize the type and level of alkalizing agents, subjects taking 352 mg TSP and 250 mg magnesium hydroxide.

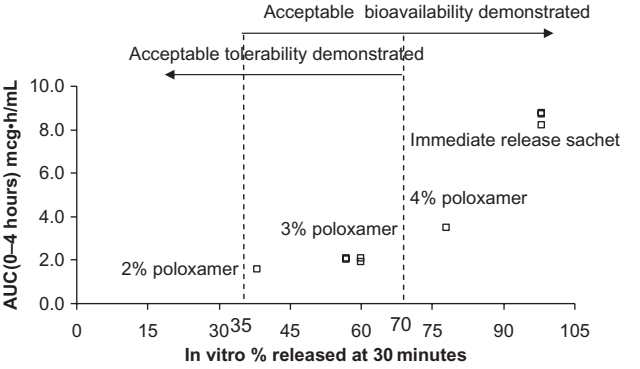

Figure 11. Relationship between AUC (0–4 hours) and in vitro release of azithromycin.

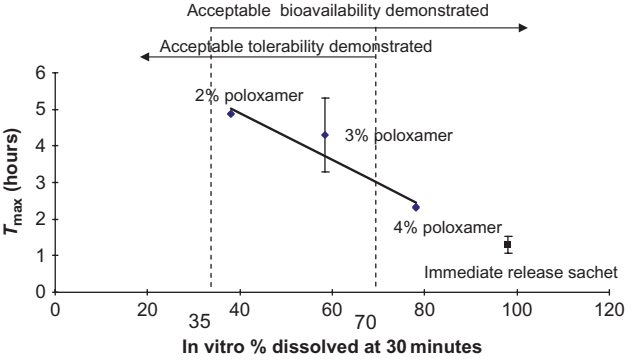

Figure 12. Relationship between T_{max} and in vitro release of azithromycin.

was conducted with six formulations in which subjects were dosed with the formulations or placebo and the pH of the stomach was measured. A typical in vivo gastric pH trace versus time is shown in Figure 10. The data exhibited significant variability from subject to subject for all formulations. The variability could partly be explained because of variability in probe placement in the stomach. Given the subject-to-subject variability for all formulations, the following conclusions were made. TRIS-containing formulations, in general, exhibited the longest duration of pH rise of all formulations. Response by subject to calcium carbonate-containing formulations was equal or greater than that of magnesium hydroxide-containing formulation. Most formulations, on average, raised the pH to 6, or above, for at least 20 minutes.

Balance between bioavailability and tolerability

A key to the development of a new formulation of azithromycin was balancing the drug release rate to have acceptable bioavailability and acceptable tolerability. Through clinical studies with different formulations, a proportional correlation was established between the in vitro dissolution of azithromycin at 30 minutes and the exposure ($AUC_{0–4\ hours}$) (Figure 11). $AUC_{0–4\ hours}$ was selected for the relationship because the GI side effects of azithromycin are related to the exposure of azithromycin early in the GI tract[27]. As shown, 3% of poloxamer in the formulation provided good tolerability and acceptable bioavailability.

The relationship between the in vitro release rate and T_{max} is shown in Figure 12. Faster releasing formulations gave faster absorption. In addition, faster releasing formulations are poorly tolerated because they release higher levels of azithromycin in the upper GI tract where the side effects are triggered. Again, 3% of poloxamer in the formulation offered acceptable tolerability and bioavailability.

It should be noted that the in vitro dissolution methods for azithromycin microspheres were developed to discriminate between drug product batches but not necessarily to be biorelevant. The in vivo release rate of azithromycin from the microspheres is complicated because of the GI transit of the microspheres leading to release in a variety of pH environments coupled with the fact that the release of azithromycin from the microspheres is pH dependent. Thus, the gastric pH, which is influenced by the basal acid and acid secretion rates and the effect of the alkalizing agents included in the formulation, plays an important role in azithromycin released from the microspheres. Thus, a traditional level A in vitro–in vivo correlation was not established for this formulation.

Conclusions

A novel high-dose controlled release formulation of azithromycin was developed for single-dose therapy. The formulation was designed to improve GI toleration while minimizing loss of bioavailability. Because

of the relatively large dose of azithromycin (2 g), the selected dosage form was a powder-for-oral-suspension consisting of drug-containing microspheres, which were manufactured by a melt-spray-congeal process. Drug release from the microspheres was shown to occur via diffusion through the larger pores formed by dissolution of azithromycin crystals and the smaller interconnected pores formed by dissolution of poloxamer. The release could be described by first-order kinetics with complete release within 3 hours at pH 6.0. The rate of drug release was optimized by a combination of microsphere particle size control and selection of the optimum level of the dissolution enhancing agent, namely, 3% (w/w) poloxamer in the microspheres, to provide good tolerability without loss of bioavailability. The formulation also contained a vehicle containing flavors, suspending agents, and alkalizing agents. The alkalizing agents demonstrated their ability to mask the taste of azithromycin and to raise the pH of the stomach above 6.0 for 20–30 minutes. The combined suspension formulation for a 2-g dose of azithromycin provided taste masking and good tolerability.

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