Osmotic capsules: A universal oral, controlled-release drug delivery dosage form

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An osmotic, oral, controlled-release capsule is described. This capsule provides drug delivery at fixed delivery rates (T80% = 6 or 14 h) independent of drug properties (e.g., solubility) or drug loading, thereby allowing rapid development of investigational or commercial drugs, especially for proof-of-concept type clinical studies. The capsule body and cap are prepared with cellulose acetate and polyethylene glycol in acetone and water using high density polyethylene molds as templates and a conventional tablet pan coater. After the shells are removed from the molds manually, a laser hole is drilled in the end of the capsule body. The drug is introduced as a shaped tablet admixed with polyethylene oxide. A “push” tablet consisting of high molecular weight polyethylene oxide, microcrystalline cellulose, and sodium chloride is also inserted into the capsule body. The capsule halves lock together due to ridges, alleviating the need for a banding operation.

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1. Introduction

By metering active pharmaceutical ingredient (API) delivery over some period of time, oral controlled-release (CR) dosage forms can provide significant advantages over their immediate-release (IR) counterparts. Among these advantages are the ability to reduce dosing frequency and the ability to moderate a drug’s maximum and minimum characteristics of the dosage form along with its stability and manufacturability. In the development of a CR dosage form, a number of considerations come into play. These can be broadly divided into two groups: (1) factors related to the manufacture and performance of the dosage form, and (2) factors related to the performance of the API when metered out throughout the gastrointestinal (GI) tract. To develop a dosage form, there are a number of technologies that can be considered, each with its advantages and challenges. Among the oral CR dosage form options are hydrophilic matrix tablets, hydrophobic matrix tablets, CR beads, and osmotic dosage forms [1–8]. The selection of which option to develop depends on the desired performance characteristics of the dosage form along with its stability and manufacturability. When an API is delivered slowly in vivo, its absorption behavior depends on the API release rate, its transit through the GI tract and factors affecting regional API absorption. The latter factors include API solubility in different GI regions, the presence of transporters (both for uptake and for efflux), and intestinal metabolism. In some cases, excipients can be added to a dosage form to improve API solubility or inhibit efflux.

Because of the complexity of the issues involved, both in terms of dosage form performance and API behavior in the GI tract, it is often difficult to predict the in vivo pharmacokinetics of an API. The result is that clinical trials are often performed to determine the optimal dosage form, optimal delivery rate and whether the desired pharmacokinetics and medical benefit can be achieved. These trials can involve multiple formulation options in parallel studies or sequential studies based on results.

In the present work, an oral CR drug delivery technology platform was designed that could be used for rapid development of different release profiles and additives for an API with minimal formulation optimization. While it was recognized that this rapid demonstration technology could be supplanted with other technologies for commercialization, the overall time to market could be shortened by rapidly defining the drug-related factors before spending the time and resources on development of the eventual commercial dosage form. For this technology to be most useful, it was designed to have the following features: (1) API-independent drug delivery, (2) wide range of drug loading, (3) easily prepared without specialized equipment, (4) good correlation between in vivo and in vitro dissolution behavior, and (5) simple formulation (i.e., requiring minimal development work). As will be discussed, these needs are met with the development of an osmotic capsule. Osmotic dosage forms are well established and exhibit good in vitro–in vivo correlation for API dissolution performance [1–3,6]. The osmotic capsule in this product concept is prepared generically, and then filled with the appropriate API. As will be discussed, by specialized development of the capsule, no banding operation is required to ensure that the two capsule components remain intact throughout the GI tract, making for simple capsule preparation without the need for specialized equipment.
Osmotic capsules have been prepared previously [9–17] using controlled porosity from asymmetric membranes. These capsules provide an osmotic CR option; however, they can only deliver drugs with sufficient solubility such that the entire dose dissolves in the capsule from the osmotic water influx (about 1 mL). Because of this limitation, we developed an osmotic capsule adapted from the bilayer (push–pull) osmotic tablet technology that is capable of delivery independent of API properties [18–22]. In the bilayer osmotic tablet technology, two tablet layers are coated with a semipermeable membrane that permits water influx but does not allow internal components to leave. The coating over the active tablet layer has a hole drilled through it, which allows a stream of material to be extruded from the core. One of the tablet layers (the “push” layer) contains an osmotic active agent (an osmogen) and a high molecular weight, water-soluble polymer that swells as water imbibes through the semipermeable membrane. The other layer contains an API mixed with a suspending, water-soluble polymer. This suspension is sufficiently viscous to suspend the API, but flows under the shear created by the combination of osmosis and pressure from the swelling layer to allow extrusion out of the hole in the coating. In the present work, a coated tablet is replaced by a capsule. In this case, two capsule shells and a push-layer tablet are used generically (i.e., independently of the specific API used). An active tablet is produced from the API and a suspending polymer. This tablet is inserted into the capsule along with the push tablet. The capsule cap is snapped over the double-locking ridges located along the capsule body. The result is a functional osmotic capsule that can deliver the API with a predetermined profile; that is, a release rate that is independent of the nature of the API, or drug loading within the range of 1–300 mg.

2. Methods

2.1. Chemicals and Materials

The materials used in preparing the capsules and conducting the testing were obtained from the following sources:

- Polysorbate 80: Tween™ 80 NF, ICI Americas Inc
- Polyethylene glycol (PEG) 3350; polyethylene oxide coagulant grade (PEO coag.); polyethylene oxide N80 grade (PEO N80); microcrystalline cellulose, Avicel™ PH102 (MCC): Dow Chemical Company
- Cellulose acetate (CA) 398-10: Eastman Chemical Company
- FD&C blue number 2 lake dye: Colorcon Inc
- Magnesium stearate: Mallinckrodt Inc
- Acetaminophen: MP Biopharm for capsules; Sigma-Aldrich or USP for reference standards
- Sodium chloride: EMD Chemicals Inc
- Sildenafil citrate: prepared as described in [23]
- Carbamazepine: Sigma-Aldrich
- HPLC grade 1 N hydrochloric acid (HCl), concentrated phosphoric acid (H₃PO₄), acetonitrile (ACN) and methanol (MeOH): J.T. Baker (Phillipsburg, NJ) or Burdick & Jackson (Muskegon, MI)
- HPLC grade trifluoroacetic acid (TFA) and triethylamine (TEA): Sigma-Aldrich
- Purified water: obtained using a Milli-Q® Gradient A10® or Elix® 5 water purification system from Millipore Corp.
- Sodium dodecyl sulfate (SDS): Bio-Rad Laboratories, Inc
- Simulated Intestinal Fluid (without enzymes) [0.05 M potassium phosphate buffer, pH 6.80] (SIF): Chata Biosystems, Inc.

2.2. Capsule Shell Preparation

High density polyethylene (HDPE) molds were prepared for both the capsule caps and bodies by automatic lathing of polyethylene rods by Isco Inc (Columbus, OH). For the short-duration capsules (i.e., faster drug releasing), a solution was prepared by dissolving 12 g of Tween 80 in 1200 g of acetic acid. This solution was sprayed in an LDCS tablet coater (Vector Corp.; 1.5 L pan, Schlick 970/Vector hybrid nozzle, Liquid Tip 10W44019 with a 1.0 mm orifice, Air cap 27w44183 anti-arching) charged with 500 g each of HDPE cap and body molds resulting in an ~1% weight gain. Coatings were carried out using 10 psi atomizing air pressure, 5 psi pattern air pressure, a target flow rate of 20 g/min, 18 rpm pan speed, 40 °C exhaust temperature, and 40 cfm inlet air flow. The Tween 80 coating was found to make removal of the capsule shells from the molds easier and with fewer defects. Another solution was prepared by dissolving 93.8 g of PEG3350 in 293 g of water, adding this solution to 11.2 kg of acetic acid, then adding 140.6 g of CA. This solution was sprayed onto the molds previously coated with Tween 80 until a weight gain of 12.5% was achieved. After the coating was completed, the coated molds were dried in an oven at 40 °C/30% relative humidity (RH) for 24 h (ES2000 Mini-Tray Dryer). The capsule shells were trimmed using a mounted razor blade, and then removed from the molds using positive air pressure through a hole in the center of the molds. The capsule bodies were placed in holders, and then a 2-mm hole was drilled at the tip of each using a Lumnolics Phase I laser (GSI Group Ltd).

For the long-duration (i.e., slower-releasing) capsules, the same process was used except that the coating solution was prepared by dissolving 48 g of PEG3350 in 293 g of water, adding this solution to 11.2 kg of acetic acid, then adding 175.8 g of CA and 10.5 g of triethylicitrate. This solution was sprayed onto molds previously coated with Tween 80 until a weight gain of 12.5% was achieved. After trimming and removal from the molds, the capsule shells were weight sorted to 80–105 mg for the caps and 85–110 mg for the bodies.

2.3. Push Tablet

Push tablets were prepared by blending 2163.0 g of polyethylene oxide coagulant grade, 1461.6 g of sodium chloride, 546.0 g of MCC and 8.4 g of FD&C blue number 2 lake dye in a bin blender for 10 min at 12 rpm. Prior to blending, the polyethylene oxide coagulant grade and sodium chloride were delumped by passing the material through a Comil™ U10 (Quadro Engineering) using a 055R round impeller at 800 rpm. During blending, the material was passed through the Comil using the 055R round impeller at 1000 rpm. Magnesium stearate (21.0 g; Mallinckrodt Inc) was added to the blend, and the mixture was blended for an additional 5 min. This mixture was tableted using a 7.75-mm diameter tooling (flat faced beveled edge lower punch and modified ball upper punch). Tablets were prepared using a Kilian T100 (Ima Kilian GmbH) tablet press (9 station rotary press) to give tablets of 300 mg each (tablet thickness 6.65 mm; tablet hardness 4.5 kp).

2.4. Active Tablets

Tablets of actives were prepared in each case by weighing the unit dose of the API plus sufficient PEO Polyox™ N80 to make 594 mg of material into a vial, then adding 6 mg of magnesium stearate. The formulations used in each figure are shown in Table 1. The mixture was blended for 5 min using a Turbulata® shaker-mixer (Glen Mills Inc) at 100 rpm. Tablets were prepared using an NP-RD10 single station tablet press (Natoli Engineering Company Inc) with a 7.75-mm deep fill die, flat faced beveled edge lower punch and modified ball upper punch. Tablets were compressed with a force of 0.08 Mton to give tablets with thicknesses of 15–16 mm.

2.5. Analytical Methods—Dissolution Methods

Dissolution testing was performed using USP Apparatus 2 and dissolution media that provide for sink conditions throughout the analysis. Specifically, a VK 7000 dissolution apparatus from Varian, Inc (Cary, NC) or an SR8-Plus™ dissolution test station from Hanson
50 mL of water via oral gavage. Each dog was left on its normal daily drug tablet made up of PEO N80. This was followed by approximately administered an osmotic capsule containing a push tablet and a placebo appropriate P

maintained at 30 °C, a mobile phase of TEA (pH 3.0±0.1 adjusted with column (5 μm; 150×3.9 mm) from Waters Corporation (Milford, MA) maintained at 30 °C, a mobile phase of TEA (pH 3.0±0.1 adjusted with H3PO4; 0.05 M)–MeOH–ACN (58:25:17, v/v/v) with a flow rate of 1.0 mL/min, an injection volume of 20 μL, and UV detection at 290 nm. The total analysis time for this method was 10 min. The acetaminophen samples were analyzed using a Luna C18(2) 100 Å column (3 μm; 150×4.6 mm) from Phenomenex (Torrance, CA) maintained at 30 °C, a mobile phase of 0.05% TFA–ACN (80:20, v/v) with a flow rate of 1.0 mL/min, an injection volume of 5.0 μL, and UV detection at 246 nm. The total analysis time for this method was 6 min.

2.7. Analytical Methods—UV End-Analysis Methods

The amount of dissolved sildenafil citrate and acetaminophen in Figs. 2 and 5 was determined using a HPLC End-Analysis Methods autosampler that was used to draw 5-mL aliquots through a 10-μm HDPE filter from Quality Lab Accessories LLC (Bridgewater, NJ) to rinse the lines and then another 1.5 mL for analysis, an Agilent 1100 series liquid chromatograph with a variable wavelength detector, and external standard solutions of the drug for peak-area quantification. The sildenafil citrate samples were analyzed using a Symmetry C18 column (5 μm; 150×3.9 mm) from Waters Corporation (Milford, MA) maintained at 30 °C, a mobile phase of TEA (pH 3.0±0.1 adjusted with H3PO4; 0.05 M)–MeOH–ACN (58:25:17, v/v/v) with a flow rate of 1.0 mL/min, an injection volume of 20 μL, and UV detection at 290 nm. The total analysis time for this method was 10 min. The acetaminophen samples were analyzed using a Luna C18(2) 100 Å column (3 μm; 150×4.6 mm) from Phenomenex (Torrance, CA) maintained at 30 °C, a mobile phase of 0.05% TFA–ACN (80:20, v/v) with a flow rate of 1.0 mL/min, an injection volume of 5.0 μL, and UV detection at 246 nm. The total analysis time for this method was 6 min.

2.3. Capsule Preparation—Locking

In developing a simple, versatile osmotic oral CR capsule, several aspects must be achieved to assure utility. Because the osmotic capsule is designed to remain intact throughout the GI tract even though the osmotic potential inside the capsule generates a hydrostatic pressure that tends to push the two capsule halves apart, one of the important elements in the design of this dosage form was how the two capsule halves will be kept together. While this problem could potentially be solved by adding a liquid (banding) such as a solvent or wax, in order to maintain the simplicity of use, a design was developed where the two capsule halves lock together mechanically. Ridges allow the capsule halves to lock together thereby keeping the capsule intact throughout the GI tract. In order to produce the capsule walls with the locking ridges, a process was developed where high density polyethylene (HDPE) molds were used as templates. The HDPE molds can be prepared using automatic lathes or injection molding. A standard pan-coating process was used to form the osmotic capsule shells on the molds, with the shells removed from the molds by a combination of positive air pressure and mechanical stripping.

3. Results/Discussion

3.1. Overall Structure

The osmotic capsule for rapid oral CR evaluation consists of four elements, as shown in Fig. 1: a capsule body (which has a laser-drilled hole through the closed end), active tablet, push tablet, and capsule cap. The first steps involved in the use of the osmotic capsules are the manufacturing of the capsule shells and the push tablet. These steps do not involve the API; therefore, they can be carried out as a batch prepared in bulk and stored under suitable conditions. The second steps involve preparing a tablet of the API, then loading all the components into the capsule, and snapping the capsule cap over the capsule body. While manufacturing the capsules can be challenging (as discussed below), once they are prepared, their use with different APIs is relatively straightforward.

3.2. Capsule Preparation—Locking

The animal experiments in this study were conducted in accordance with the “Principles of Laboratory Animal Care” with approval of the appropriate Pfizer governance. Six male beagle dogs were each administered an osmotic capsule containing a push tablet and a placebo drug tablet made up of PEO N80. This was followed by approximately 50 mL of water via oral gavage. Each dog was left on its normal daily consumption of food (high density canine diet, 5L18, which contained 36% fat, 27% protein, and 37% carbohydrate by calories) the day prior to the study. The dogs were fed 10 g of this food 15 min prior to dosing the capsules, then fed normally 6 h post dosing. The capsules were recovered from the feces, one day post-dosing. Examination of all six capsules showed that each remained intact (i.e., the two halves remained snapped together) and that the push tablet (dyed red) had completely displaced the drug tablet (white) within the capsule shell. None of the dogs showed any adverse events associated with the capsules.

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Table 1

<table>
<thead>
<tr>
<th>Figures</th>
<th>Sildenafil citrate</th>
<th>Acetaminophen</th>
<th>Carbamazepine</th>
<th>Polyox N80</th>
<th>Magnesium stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>160 mg</td>
<td>434 mg</td>
<td>6 mg</td>
<td>544 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>4, 6, 7</td>
<td>50 mg</td>
<td>529 mg</td>
<td>6 mg</td>
<td>394 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>5</td>
<td>65 mg</td>
<td>309 mg</td>
<td>6 mg</td>
<td>219 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>5</td>
<td>200 mg</td>
<td>357 mg</td>
<td>6 mg</td>
<td>219 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>6</td>
<td>30 mg</td>
<td>564 mg</td>
<td>6 mg</td>
<td>564 mg</td>
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</table>
The ridges in the capsule design involve a trade-off between the ability to remove the capsules from the molds (favoring thin ridges) and the need to ensure that the capsule remains intact during use in the GI tract (favoring larger ridges). Based on the limitations for ease of capsule removal, ridges were limited to 0.25 mm in height. The mechanical force needed to pull the two halves of the snapped-together capsules apart was measured for single-ridged and double-ridged (0.25 mm in height) capsules using a texture analyzer. The forces were found to be 318±1 g for the single-ridged capsule and 772±25 g for the double-ridged capsule. The increased force required to pull the double-ridged capsule apart while still allowing removal of the capsule from the mold made it the preferred design.

3.3. Capsule Preparation—Permeability

The rate of drug delivery from the osmotic capsule is controlled by the water permeability of the capsule shell, in much the same way as with the coatings of osmotic tablets. As with osmotic tablets, the osmotic capsule uses the combination of a water-insoluble polymer (cellulose acetate, CA) and a water-soluble polymer (polyethylene glycol 3350, PEG3350). The ratio of these two components determines the water permeability and corresponding rate of drug delivery. The drug delivery rate can be reflected in a time to deliver a fixed amount of drug, which takes into account both any lag in the initial drug delivery and the rate once drug starts releasing from the dosage form. In our case, we use the time to deliver 80% of the drug (T80%) as a convention. Fig. 2 shows the impact of this fraction weight fraction of CA in the coating on the drug delivery rate, at a given capsule thickness. As can be seen, to achieve the desired 6–8 h and 12–14 h T80% values, the CA fractions in the capsule walls are 0.60–0.70 and 0.75–0.80, respectively. The capsule wall thickness also influences the permeability to water and therefore the drug delivery rate; however, the usable thickness range is fairly limited due to the mechanical restraints involved with fitting the two capsule halves together and the need for adequate mechanical strength. The coating process used in the preparation of these capsules is generally within the ratio of CA, PEG, acetone and water that gives dense rather than porous (sometimes referred to as asymmetric) membranes [10–12]. This is borne out in microscope images of cross-sections of the capsule walls which do not show the presence of pores. As stated above, however, it is likely that PEG will leach from the capsule when the capsule is exposed to water. For a discussion of the permeability of CA/PEG coatings with bilayer tablets, presumably similar to our capsules, the reader is referred to Ref. [18].

3.4. Push Tablet

With high solubility APIs, it is anticipated that drug solution can be pumped out the capsule hole in a manner analogous to the behavior seen with elementary osmotic pumps [24]. When the API solubility is somewhat lower, osmotic drug delivery systems have often employed swelling materials to back-fill the space of the drug material as it exits the hole [18–20,25]. This allows for more complete drug delivery even with insoluble drugs. In the present capsule, complete drug delivery of even low solubility API is assured using a push tablet included in the general structure. The push tablet consists of a high molecular weight,
water-soluble polymer (polyethylene oxide, PEO, MW 5,000,000) and an osmotic agent (sodium chloride). This push tablet helps increase the osmotic driving force for water ingress through the semipermeable capsule when the capsule is ingested. The polymer swells as the water enters and pushes on the API-containing suspension. For ease of handling, the smallest size of push tablet used was 300 mg, with 2:1 PEO:NaCl (i.e., while smaller push tablets would probably function effectively, they are difficult to handle). Studies where the weight was varied between 250 and 350 mg did not show any difference in drug delivery rate or residual drug remaining in the capsule after 24 h of testing. While it is possible that optimizing this ratio and absolute amount could result in an increase in the active layer size (and overall amount of API that can be delivered), the ease of handling advantage of the 300 mg push tablet provides little incentive for optimization. Microcrystalline cellulose was added to the formulation to improve powder flow and tablet friability.

3.5. Active Tablet

The formulation of the tablet containing the API, in general, requires only the API and a suspending aid. The suspending aid is a 200,000 MW PEO (Polyox™ N80). This polymer forms a viscous material as it dissolves in water. Unlike the push tablet, however, this material can flow out of the hole under the shear of the hydrostatic pressure. The overall behavior of the capsules can be seen in Fig. 3 where the drug suspension is extruded out of the capsule hole as the push tablet expands to occupy the entire interior volume of the capsule.

Short- and long-duration osmotic capsules were studied by dissolution to determine the reproducibility of the system. As can be seen in Fig. 4, the individual capsule results exhibit low variability with standard deviations below 7% at every time point. The tightness of the data allows dissolution curve comparisons to be made using the average of only two capsules, as used in the remaining figures in this paper. Fig. 4 also shows that over a wide range of drug delivery, the release behavior is consistent with zero-order behavior. As can be seen, with the short duration capsules, zero-order behavior is seen over a range of 6–95%, while there is more curvature with the long duration capsules such that zero-order behavior is only seen between 13 and 87% release. In practical terms, whether the release is exactly zero order or has some curvature is unlikely to have a measurable effect on the in vivo pharmacokinetics. Another way of looking at these data is that the short-duration capsules have a lag time of about 1.5 h while the lag time for the log-duration capsules is about 4 h. Optimization of the capsule thickness and CA to PEG ratio could potentially allow for a shorter lag time (it is anticipated that lag times would be shorter with thinner capsules of lower permeability than with thicker capsules of greater permeability based on studies of analogous tablet coatings) with slow drug delivery, this was not attempted in the present study since having a constant capsule thickness for both short and long-duration capsules was more convenient to manufacture, and these capsules were adequate to study regional drug absorption.

The drug release was studied with a range of ratios of API to PEO, maintaining an overall weight of 600 mg. As can be seen in Fig. 5, the dissolution of the API is independent of drug loading between 65 and 375 mg of the active being used.

The osmotic capsule was studied using two model drugs of vastly different solubilities to verify that the performance is indeed API-independent. As shown in Fig. 6, the drug dissolution curves for acetaminophen (solubility 17.4 mg/mL at 30 °C in pure water [26]; similar solubility across the gastrointestinal pH range) and carbamazepine (solubility 237 µg/mL at 37 °C in water (2.6 mg/mL in 1% SDS) [27]; similar solubility across the gastrointestinal pH range) are virtually identical. In both cases, the API was simply mixed with PEO (Polyox™ N80) and magnesium stearate, made into the appropriately shaped tablet, combined with the push tablet, and put into the osmotic capsule: no formulation optimization was carried out. These data emphasize the robustness of this CR platform. The fact that these two APIs show very similar CR dissolution curves in spite of...
their solubility differences is also an evidence that any contribution of diffusional drug delivery (as opposed to osmotic delivery) is minimal since diffusional drug delivery is anticipated to show API solubility-dependence.

3.6. Dissolution Medium Dependence

One of the advantages of an osmotic drug delivery system is that the dissolution performance is generally insensitive to the pH of the dissolution medium. This is indeed the case with the osmotic capsule, as shown in Fig. 7. In this case, the dissolution rate was independent of pH in the biorelevant range (2 to 6.8). Again, any contribution of a diffusional component to the drug delivery is probably minimal.

4. Conclusions

An osmotic, oral, controlled-release capsule is described that provides drug delivery at fixed delivery rates (Tons = 6 or 14 h) independent of the drug solubility or loading, thereby allowing rapid development of investigational or commercial drugs, especially for proof-of-concept type clinical studies. The capsule is prepared with cellulose acetate and polyethylene glycol in acetone and water using HDPE molds as templates and a conventional tablet pan coater. The cellulose acetate and polyethylene glycol in acetone and water using proof-of-concept type clinical studies. The capsule is prepared with development of investigational or commercial drugs, especially for independent of the drug solubility or loading, thereby allowing rapid inspiration in the development work; Kazuko Sagawa and Ryan Liese Thombre and Scott Herbig (Pfizer) who conducted the animal studies, Bruce Cathcart (Race Rock Associates LLC) who produced the first molds, Eirinn Ames and Joel Bailie (Bend Research Inc) who conducted development experiments, and Randy Wald (Bend Research Inc) who coordinated development of the scale-up and manufacturing of the capsules.

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