Evaluating a New Quality Control Test for Soft Gelatin Rectal Capsules

Yasvanth Ashokraj, Swati Laud, Kalpesh Sawant, Prashant Modak, and Praveen Date

Soft gelatin capsules (SGC) are popularly used pharmaceutical dosage forms, whose critical quality attributes are efficient opening/rupture, disintegration, and dissolution. Unlike oral capsules, however, rectal capsules must dissolve in minimal fluid and hydrodynamics, without digestive enzymes to break down the crosslinking of gelatin, if any. Therefore, a reliable biomimetic method is needed to characterize SGC rupture/disintegration during rectal administration. This article demonstrates how qualitative physical attributes testing, a method that has recently been approved for use by the World Health Organization, can be used to achieve these goals.

Soft gelatin capsules (SGC) are popularly used pharmaceutical dosage forms, wherein the active ingredient is delivered in a non-aqueous vehicle, either as solution, suspension, or semisolid, through various routes of administration. SGC offers unique advantages of filling high doses of poorly water-soluble drugs, loading of ultra-low dose drugs accurately (e.g., cardiac glycosides and vitamin D analogs), and providing the option of filling excipients that inhibit P-glycoprotein for better bioavailability (1).

Quality control of SGC is crucial to ensure the product's intended *in-vivo* performance, and a variety of quality control tests are available to use for evaluation (2, 3). The critical quality attributes are efficient opening/rupture, disintegration, and appropriate dissolution in biological fluid.

Table I (4,5,6) lists methods that assess the disintegration or rupture of SGCs. However, these tests are best suited to orally administered SGCs because they require a large volume of fluid (e.g., 500 mL). Rectal SCGs are exposed to very different conditions (i.e., limited fluid volume [7] and hydrodynamics). Hence, a suitable test that is biorelevent in terms of media, volume, hydrodynamics, and capability to quantify the disintegration or rupture events of SGC for rectal use is essential.

Artesunate SGCs were developed as a pre-refferal treatment option for malarial infection in children under six years of age living in remote tropical areas with limited access and to provide a standard care of treatment (intramuscular artesunate) in hospitals (8). Suppositories hold an advantage over oral therapy when treating severely ill children who are vomiting and who may be weak or losing consciousness, because they act faster than the oral dosage forms.

The authors tested a new apparatus and method, termed qualitative physical attributes testing (QPAT), which was developed to address this need. The results of the test using artesunate SGCs are summarized in this article.

Materials and methods

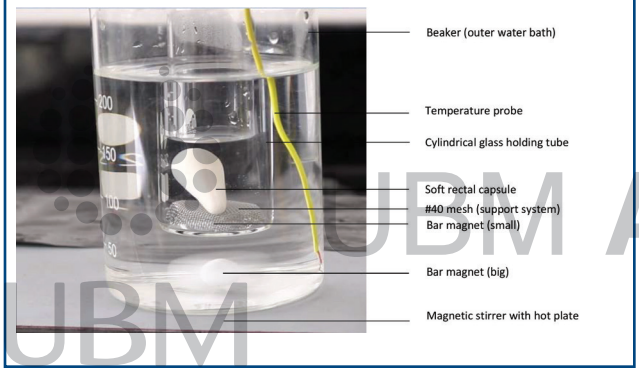
Materials. For buffer preparation, potassium dihydrogen phosphate (analytical reagent [AR] grade, S.D.Fine Chem), sodium hydroxide (AR grade, S.D.Fine Chem), orthophos-

Submitted: Sept. 4, 2018
Accepted: Oct. 16, 2018

Table I. Disintegration test/rupture test for soft gelatin capsules described in pharmacopeia.

Test	Method
<2040> Disintegration and dissolution of dietary supplements–rupture test for soft shell capsules (4)	• Medium–water; 500 mL • Apparatus & rpm–USP II & 50 • Time–15 min • The capsule shell is considered ruptured if breached, exposing or allowing the fill contents to escape
Disintegration test for oral soft capsules *(Ph. Eur. Method 2.9.1)* (5)	• Medium–water. (When justified and authorized, 0.1 M hydrochloric acid or artificial gastric juice may be used.) • Apparatus–disintegration apparatus. • Time–30 min • All of the dosage units have disintegrated completely.
Disintegration Test for Suppositories and Pessaries–rectal or vaginal gelatin shell (*Ph. Eur. Method 2.9.2*) (6)	• Medium–water • Apparatus–specially designed setup • Method–rupture of the gelatin shell of rectal or vaginal capsules occurs allowing release of the contents • Time–30 min • Rupture of the gelatin shell of rectal or vaginal capsules occurs allowing release of the contents

Figure 1. A prototype setup to observe the physical events of artesunate soft gelatin capsule.



phoric acid (laboratory reagent (LR) grade, Rankem), cetyltrimethyl ammonium bromide (CTAB) (extrapure AR grade, Sisco Research Laboratories), and purified water were used.

Preparation of buffer medium. The buffer solution used as the medium for the QPAT study was prepared by dissolving potassium dihydrogen phosphate and sodium hydroxide in purified water, to which a suitable quantity of CTAB was added to prepare phosphate buffer (pH 7.2, 1.5% CTAB).

Equipment (prototype). The researchers assembled a temperature-controlled glass water bath that consisted of an appropriate cylindrical glass-holding tube (vessel) capable of holding 10 mL or less of selected medium with controlled hydrodynamics and a platform (stainless steel mesh screen) to support the unit dosage form. The glass container had an opening with the required diameter to facilitate the introduction of the unit sample (one rectal SGC). The water bath could hold three glass containers, which facilitated QPAT of three units individually and simultaneously. Additionally, the glass assembly facilitated visual observation of the physical events that each unit dosage form was undergoing during the duration of QPAT. The hydrodynamics of the water bath and medium in the holding tube were controlled by appropriately sized bar magnets in the respective chambers. The whole setup was placed on a magnetic stirrer with hotplate. **Figure 1** depicts the set-up of the equipment.

Experimental procedure. The critical steps of the experiment are described below. These steps will ensure reproducibility and accuracy of experimentation and measurements:

- A large bar magnet was placed at the bottom of the outer water bath.
- The water bath was filled with water to the specified depth at room temperature and placed on a magnetic stirrer with hot plate and heated to 37±2 °C.
- Three cylindrical glass-holding tubes were lowered into the water bath and positioned at specified height.
- A small bar magnet was placed at the bottom of each of the cylindrical glass holding tube.
- Stainless steel mesh screen was placed in each of the cylindrical glass holding tube.
- A suitable volume (10 mL or less) of medium was poured into each of the cylindrical glass holding tube.
- Rotations for the bar magnet were started at the specified settings.
- Temperatures in the outer water bath and the cylindrical glass holding tube were recorded until the temperature was stable at 37±2 °C for at least 5 min.
- One dosage unit (artesunate SGC) was introduced into each of the cylindrical glass holding tubes.
- The time was noted and designated as T=0 min.
- Physical behavior of the dosage unit was observed for any changes (not in any order of significance), such as physical disintegration, first traces of rupture, release of blend from SGC, progressive deformation leading to change in shape, softening (considering gelatin based SGC) of the dosage unit, etc.

SGC are prone to soften over the duration of the test/experiment while disintegrating and releasing the drug contained within. Therefore, the critical events need to be observed over the QPAT, individually and collectively and need to be noted. Accordingly, the critical events noted below were observed during the disintegration process of artesunate SGC and mapped as a function of time:

- A–first sign of physical breakdown of the surface thereby effecting release of the embedded blend of drug product
- B–progressive disintegration of the dosage unit
- C–substantial deformation of the shape of the dosage unit
- D–substantial decrease/change in the size of the dosage unit
- E–near-to-complete disintegration of the dosage unit
- F–physical disintegration of the soft rectal capsule
- G–others relating to the physical structure/character of the dosage unit (soft rectal capsule).

QPAT for artesunate SGC was performed in phosphate buffer (pH 7.2, 1.5% CTAB) on initial and stability samples, whereas only initial samples were evaluated in water. The change in physical nature/appearance at every two-minute interval was recorded as photographs.

Results

The QPAT method was developed using artesunate SGC manufactured during scale-up trials. Because there was no suitable bio-relevant rectal fluid reported in literature, the media recommended for the dissolution testing experiment were phosphate buffer (pH 7.2, 1.5% CTAB) and water. CTAB at a concentration of 1.5% was selected after evaluating several commonly used surfactants in dissolution medium at different concentrations using saturation solubility studies and dissolution trials (these data are yet unpublished and are currently recorded on file). Typically, the complete disintegration of artesunate SGC occurs within 15 minutes. **Figures 2a** and **2b** depict the typical events observed in 10 mL of phosphate buffer (pH 7.2, 1.5% CTAB) and water, respectively, during method development, based on which of the following acceptance criteria was set to assess the quality of the product in routine quality control:

- Not longer than 5 min: first sign of physical breakdown of the surface thereby effecting release of the contained drug/formulation
- Not longer than 10 min: substantial deformation of the shape of SGC
- Not longer than 15 min: near to complete disintegration of SGC.

Accordingly, the data collected on submission batches at initial and stability samples (**Figure 3**) were assessed against the acceptance criteria. A significantly low co-efficient of variation clearly indicates the reproducibility on observation unit-to-unit. The first event of physical breakdown of the surface occurred (event A) consistently within one minute on initial samples and after the storage of the samples in controlled temperature and humidity of 25 °C/60% relative

Figure 2a. Qualitative physical attributes testing (QPAT) performed on artesunate soft gelatin capsules in pH 7.2+1.5% CTAB/10 mL.

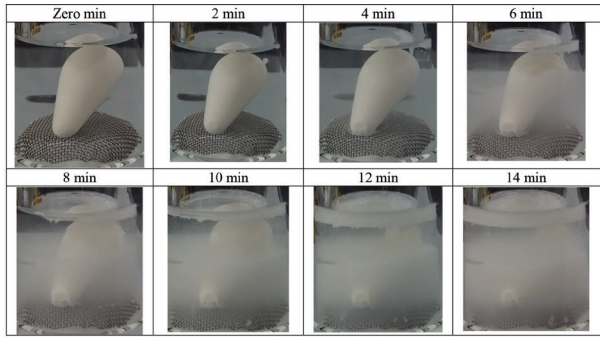


Figure 2b. Qualitative physical attributes testing (QPAT) performed on artesunate soft gelatin capsules in water/10 mL.

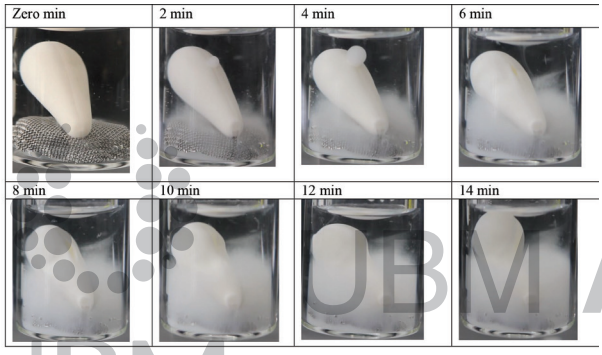
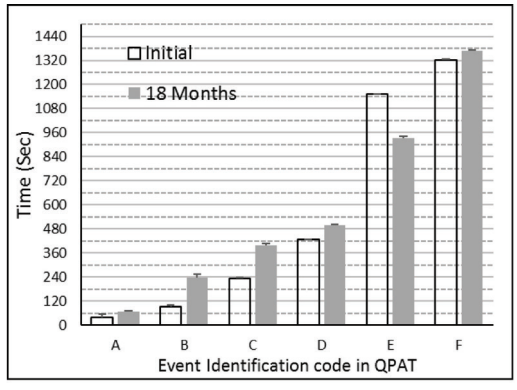


Figure 3. Qualitative physical attributes testing (QPAT) events compared as a function of time between initial and stability samples in phosphate buffer (pH 7.2, 1.5% CTAB/10mL). Data given in mean±standard deviation (N=3). Event identification codes given in X-axis are described as follows: A–first sign of physical breakdown of the surface, thereby effecting release of the blend of drug product contained within; B–progressive disintegration of the dosage unit; C–substantial deformation of the shape of the dosage unit; D–substantial decrease/change in the size of the dosage unit; E–near-to-complete disintegration of the dosage unit; F–physical disintegration of the soft rectal capsule.



humidity (RH) for 18 months. Similarly, substantial deformation of the shape of SGC (event C) occurred in less than 10 min. However, the third critical event of near-to-complete disintegration (event E) occurred not longer than 20 min., which was higher than the pre-set acceptance criteria of not longer than 15 min. Thus, the acceptance criteria was reset to not longer than 20 min. for the third event (event E) in the final quality specifications.

Discussion

Acceptable disintegration and dissolution in relevant biological fluids is essential for the required performance of the SGC *in vivo*. With respect to the disintegration test of SGC, various pharmacopeia offer standardized procedures to evaluate the disintegration or rupture of SGC. The *United States Pharmacopeia* (*USP*) describes a rupture test for quality control of SGC containing dietary supplements, performed in dissolution apparatus two (paddle) at a rotational speed of 50 rpm with 500 mL of immersion medium (4). *British Pharmacopoeia* (*BP*) prescribes a standard disintegration apparatus for SGC not administered by rectal or vaginal route using water as the immersion medium, or 0.1M hydrochloric acid/ artificial gastric juice can be used when justified and authorized. In the case of rectally/vaginally administered SGC, BP uses a different apparatus to contain four to 12 L of immersion medium and a specially designed holder to place the dosage forms. Apparently, these methods do not mimic the biorelevant conditions prevalent in the rectal region, where the volume of liquid is reportedly relatively low (1–3 mL) and the pH neutral at pH 7–8 with low buffer capacity (9). Further, the rectal region is significantly static compared to the other regions of the gastrointestinal tract (10). Hence, development of suitable methods for evaluating the physical attributes of the disintegration of rectally administered SGC in biologically relevant conditions is useful for efficient quality control.

SGCs fail to disintegrate *in vitro* primarily due to gelatin cross-linking upon aging, when exposed to physical conditions such as high temperature and humidity, ultraviolet radiation, gamma-radiation, rapid drying, and chemical substances such as aldehydes, ketones, imines, and carbodiimides (1). However, gelatin cross-linking does not impact the *in-vivo* performance of orally administered SGC, because the digestive enzymes (i.e., pepsin or pancreatin) present in the gastrointestinal tract digest the gelatin cross-linking, enabling the disintegration or dissolution of the gelatin shell *in vivo*. In contrast, the rectal region does not contain digestive enzymes to dissolve cross-linked gelatin, which could lead to product failure. Hence, a biomimetic method to evaluate the disintegration/rupture of rectally administered SGC is even more important to ensure product quality throughout its shelf-life.

The QPAT method developed in this experiment offers a simple, flexible, robust and reproducible way of quality control of rectal SGC. The proposed method can be adopted

even in a setup with limited resources. It also provides opportunity to handle less volume of fluid (<10mL) while maintaining desirable hydrodynamics and visualization of disintegration events. These events can also be video recorded or photographed for robust data maintenance. The opportunity to compare the change in various events during disintegration as a function of time (i.e., during shelf life) in QPAT setup is unique. Though the current scope of QPAT is only for rectal SGC, it can be conveniently applied to other types of SGC, such as vaginal SGC.

The International Council for Harmonization (ICH) guideline Q6A, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, provides guidance on the setting and justification of acceptance criteria and the selection of test procedures (11). Accordingly, the decision tree #7.1 in the guidance document allows disintegration testing, instead of dissolution testing, to be used as a performance/quality control test for rapidly dissolving dosage forms (Q>80% in 15 minutes) containing highly soluble drugs (Biopharmaceutic Classification System class I/III), if a relationship between dissolution and disintegration has been established. Similarly, the QPAT method could potentially replace the dissolution testing of rectal SGC containing liquids.

A major shortcoming of the developed method is the difficulty in observing the physical events when the SGC or its contents have intense color. However, this could be overcome by adopting a continuous replacement system using a reciprocating pump or intermittent replacement of whole fluid.

Conclusion

For rectal suppositories, a bio-mimetic disintegration test enables efficient quality control of SGC to assure product quality throughout the shelf-life. In order to simulate conditions within the human body, this method should not replicate requirements for oral gelatin capsules, but must show acceptable disintegration in lower volumes of a medium that is free of digestive enzymes at milder hydrodynamics. QPAT offers a methodology that can be readily adopted for routine quality control. This method offers the advantage of easy setup, even with limited resources. The World Health Organization has already accepted the method for quality control of artesunate SGC for disintegration events (12).

Acknowledgements

The authors would like to thank Preeti Raut and Anita Desai for their critical inputs during the study. Special thanks to Geena Malhotra, head of R&D, for her continuous encouragement. The authors also wish to thank Prof. Umesh Banakar, Banakar Consulting Services, for his critical inputs in developing QPAT as a quality control tool.

References

1. R.P. Gullapalli. *J Pharm Sci.* 99 (10) 4107–4148 (2010).
2. R.I. Mahato and A.S. Narang, "Capsules," in *Pharmaceutical Dosage Forms and Drug Delivery: Third edition Revised and Expanded*, pp.509-531 (CRC press, Taylor & Francis Group, 2018).
3. M.S.Uddin, et al., *Br J Pharm Res.* 9 (2) 1–9, 2016.
4. USP, *USP 39-NF 34* General Chapter <2040>, "Disintegration and Dissolution of Dietary Supplements" (US Pharmacopeial Convention, Rockville, MD, 2015).
5. BP, *British Pharmacopoeia* Appendix XII A, "Disintegration of Tablets and Capsules" (BP, 2017).
6. BP, *British Pharmacopoeia* Appendix XII A, "Disintegration Test for Suppositories and Pessaries" (BP, 2017).
7. R.A. Speerhas, A. Bragalone, and S. Wagner, "Medication Delivery in Intestinal Failure," in *Intestinal Failure and Rehabilitation: A Clinical Guide*, L.E. Matarese, E. Steiger, and D.L. Seidner. Eds., pp.313-343 (CRC press, Taylor & Francis Group, 2005).
8. World Health Organization, "Rectal Artesunate for Pre-Referral Treatment of Severe Malaria," October 2017, http://apps.who.int/iris/bitstream/handle/10665/259356/WHO-HTM-GMP-2017.19-eng.pdf?sequence=1
9. V. Jannin, et al., *Adv Drug Deliv Rev.* 73, 34–49 (2014).
10. J.H. Rytting and J.A. Fix. "Drug Delivery—Rectal Route," in *Encyclopedia of Pharmaceutical Technology*, J. Swarbrick, J.C. Boylan. Eds., pp. 1298-1310 (Informa Healthcare USA, Inc., New York, 3rd ed., 2007).
11. ICH, *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, 2000.
12. World Health Organization, "Artesunate 100 mg Suppositories," April 2018, https://protect-eu.mimecast.com/s/DRZGC91EEsxA9qZFo8OCz?domain=extranet.who.int. **PT**

Yasvanth Ashokraj*, yasvanth.ashokraj@cipla.com, **Swati Laud**, **Kalpesh Sawant**, **Prashant Modak**, and **Praveen Date** all work in Integrated Product Development at CIPLA.

*To whom all correspondence should be addressed.

Read more about quality control testing

For more about quality control testing, read these articles at PharmTech.com:

- **Improving Production: How IT, OT, and Quality Can Collaborate**
  www.pharmtech.com/improving-production-how-it-ot-and-quality-can-collaborate
- **Sartan Recalls Beg the Question: Is Compendial Impurity Testing Enough?**
  www.pharmtech.com/sartan-recalls-beg-question-compendial-impurity-testing-enough
- **Pharma Collaboration Proposes Retirement of Obsolete Heavy Metals Tests**
  www.pharmtech.com/pharma-collaboration-proposes-retirement-obsolete-heavy-metals-tests