A Flow-through Dissolution Method for Evaluation of Drug Release from Manipulated Abuse Deterrent Formulations

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PURPOSE

Development and assessment of opioid drug products with abuse deterrent properties, also called abuse deterrent formulations (ADFs), are important steps towards safer opioid analgesics. Conventional dissolution methods, such those which use United States Pharmacopeia (USP) apparatus 1 or 2, are designed for testing of finished drug products, where the process of sample dispersion/addition is generally considered to be reproducible and robust. However, for ADFs, particularly after manipulation, polymeric excipients within the sample matrix can greatly influence the dispersion process, and may lead to problematic dissolution behavior such as incomplete release or high variability. USP apparatus 4 could potentially offer better repeatability with a fixed powder dispersion pattern. The objective of the current study was to develop an in vitro dissolution method based on flow-through USP apparatus 4 for evaluating drug release from manipulated ADFs. Moreover, dissolution of manipulated ADF powder was also investigated using USP apparatus 1 and 2 for comparison purposes.

METHODS

Metoprolol succinate tablets with ADF-like properties were prepared by direct compression followed by curing at 80°C for 30 min. Metoprolol succinate is intended to act as a surrogate for oxycodone HCl because it has similar physicochemical properties and the analytical method has been previously established. The tablets were comminuted using a mechanical grinder to reduce the size of the tablet. The particles from the comminuted tablet were sieved to a coarse (500-1000 µm) and fine (106-500 µm) range. USP apparatus 4 was employed in a closed loop configuration through coupling with a USP apparatus 2 which was used as a controlled mixer and reservoir for auto sampling (Figure 1). Flow-through cells of 12 mm diameter were loaded with 82 mg of sample material and 9 g of glass beads of 1 mm diameter as packing material (Figure 2). The dissolution condition was screened in terms of sample packaging configuration (1, 3, 8 separated layers and uniform blend within the glass beads), flow rate (4, 8, 16 mL/min) and dissolution medium ionic strength (0.017, 0.077 and 0.154 M). Dissolution characteristics of surrogate ADF using USP 4 apparatus was compared with those when using USP apparatus 1 and 2.

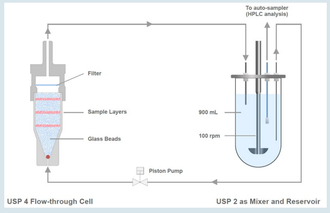

Figure 1. Schematic diagram of the modified USP apparatus 4 flow-through dissolution set up.

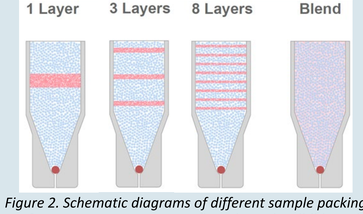

Figure 2. Schematic diagrams of different sample packing configurations using a 12-mm flow-through cell (blue: glass beads; red: sample powders).

RESULTS

- USP 4 apparatus showed a complete drug release and good repeatability under all experimental conditions. Packing loaded sample as one layer in the flow cells resulted in a discrimination between the fine and coarse powders only during initial phase of dissolution (0 – 4 hrs). However, dividing the loaded sample into more separated layers within glass beads lead to faster dissolution, as well as improved discrimination and repeatability with RSD less than 5% (Figure 3).
- Increasing flow rate from 4 to 16 mL/min resulted in faster onset of dissolution from fine powder within 1 hour of dissolution (Figure 4).
- Changing media ionic strength from 0. 017 to 0. 154 M did not impact the dissolution profiles (Figure 5).
- In contrast, large variations were observed with USP apparatus 1 method (Figure 6). Using USP apparatus 2 with powder, faster dissolution was obtained, but the powders were found to be floating and sticking to the wall which frequently clogged sampling cannula and prevented sampling. The use of powder filled capsules with sinkers overcame the floating and sticking issues; however, slower release rate was observed due to the rapid gelation of the polymeric matrix.

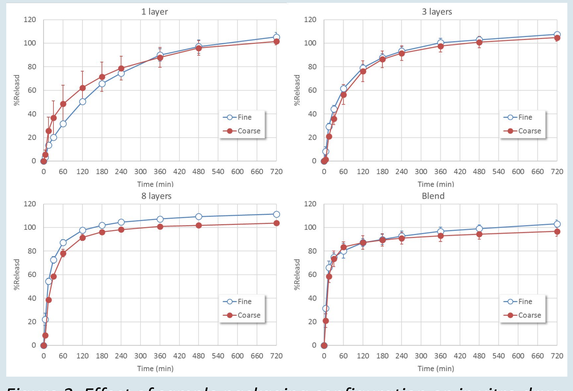

Figure 3. Effect of sample packaging configuration on in vitro drug release from comminuted tablet using USP apparatus 4 (mean ± SD, n=3). The flow rate used was 8 ml/min. Dissolution media were phosphate buffer solution (0.05 M, pH 6.4).

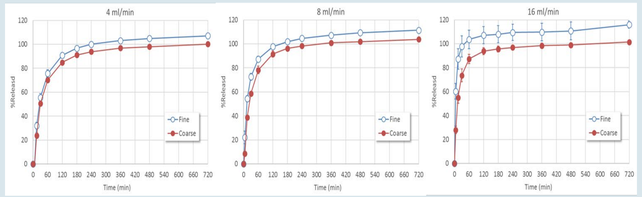

Figure 4. Effect of flow rate on in vitro drug release from comminuted tablet using USP apparatus 4 (mean ± SD, n=3). The sample packaging configuration used was 8 layers. Dissolution media were phosphate buffer solution (0.05 M, pH 6.4).

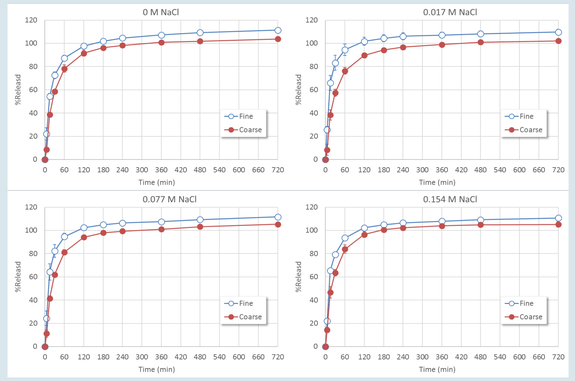

Figure 5. Effect of dissolution media ionic strength on in vitro drug release from comminuted tablet using USP apparatus 4 (mean ± SD, n=3). The flow rate used was 8 ml/min and The sample packaging configuration used was 8 layers.

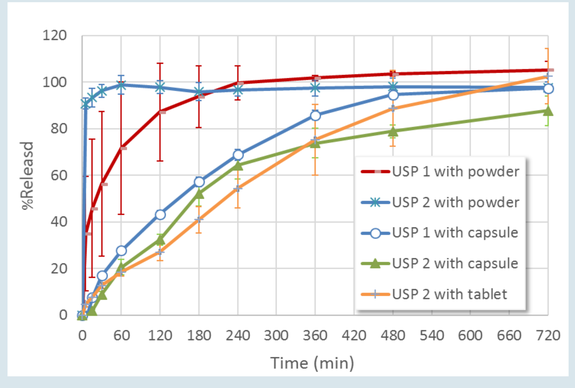

Figure 6. Effect of sample preparation on in vitro drug release from fine powder samples using USP apparatus 1 and 2 (mean ± SD, n=3).

CONCLUSIONS

- A USP apparatus 4 method was developed to discriminate release from metoprolol succinate tablets with ADF-like properties that were comminuted to fine (106-500 µm) and coarse (500-1000 µm) discrete particle size ranges.
- Procedures to improve dispersion of samples significantly altered the dissolution characteristics of powdered samples for both USP 1 and USP 2 methods.
- The USP 4 dissolution method for the study drug was optimized by using a packing configuration of 8 layers, which exhibited better repeatability and discrimination between coarse and fine particles compared to 0 ,1, or 3 layers.
- Altering the flow rate or ionic strength did not alter the discriminatory power of the USP 4 method between coarse and fine particles.

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