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Investigation of a Small Volume Dissolution Method to Simulate Mouth Cavity Condition for Taste-masking Evaluation of Dextromethorphan – Resin Complex

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Purpose

Saliva volume is small in the oral cavity and residence time of the dosage form is short; however, the perception of bitter taste occurs within seconds. Compendial dissolution testing with large media volume and long exposure may not be a sufficient or appropriate method for evaluating the taste-mask effectiveness of a drug formulation. Further, the use of large volume dissolution media may inadvertently increase the drug release from taste-masked drug-resin complex due to the increased presence of counterions. The objective of this investigation was to develop a small volume dissolution apparatus to simulate oral cavity conditions, with a rapid drug release measurement capability in simulated saliva. Unmodified drug or drug-resins complex were characterized by drug release properties in the novel small volume dissolution method, and compendial dissolution method.

Methods

Small Volume Method

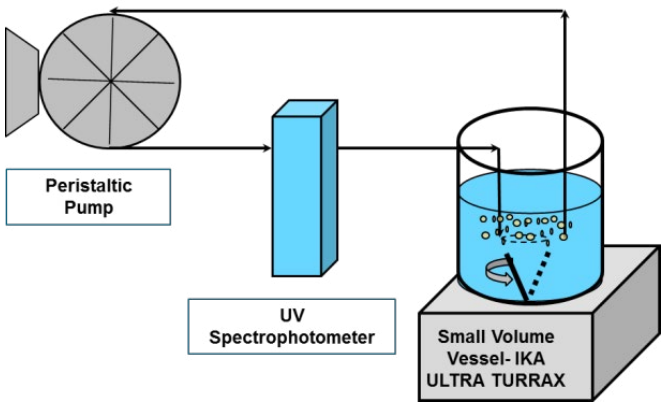
To simulate the oral cavity, a small volume dissolution method was used, with an IKA ULTRA-TURRAX Tube Drive (IKA Works Inc., USA) equipped with 20 mL mixing vessel (Figure 1). As displayed in Figure 2, dextromethorphan (DXM) release was measured using 10 mL of simulated saliva (pH 6.2) with periodic sampling through a cannula connected to a UV cell, which then returned to the mixing vessel. Unmodified drug and drug-resin complexes of strong cationic resin (AMBERLITE™ IRP69, The Dow Chemical Company) and weak cationic resin (AMBERLITE™ IRP88) at 1:1, 1:2 and 1:3 w/w drug to resin ratios, were individually added to the mixing vessel for drug release evaluation. Samples were mixed at 750 rpm and drug release was characterized using online UV-Vis spectrophotometer at 278 nm wavelength at 20, 30 and 60 seconds intervals for 10 minutes.

Compendial Method

To evaluate the effect of excessive media volume, the drug release from unmodified drug and drug-resin complexes of strong cationic resin (AMBERLITE™ IRP69) and weak cationic resin (AMBERLITE™ IRP88), at 1:1, 1:2 and 1:3 w/w drug to resin ratios, was also characterized using compendial methods. The compendial method utilizes 500mL of 0.1N HCl and apparatus II (paddles) (Agilent Technologies, USA) at 50 rpm. The drug release was characterized at 37°C for 3 hrs.

Figure 1: IKA Ultra Turrax Tube Drive Control Equipped with 20 mL Mixing Vessel

Figure 2: Schematic of Small Volume Dissolution Set Up

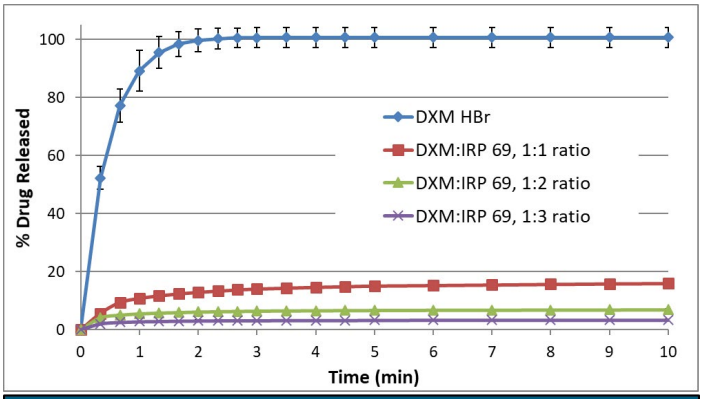


Results

Drug Release Characterization using Small Volume Method

DXM-resin complexation resulted in a small amount of drug release (< 20% w/w) in the simulated saliva, compared to the unmodified drug released (100% w/w), which is highly desirable for tastemasking purposes. The amount of drug released from the strong cationic resin complex was significantly lower (Figure 3) as compared to the weak cationic resin complex (Figure 4).

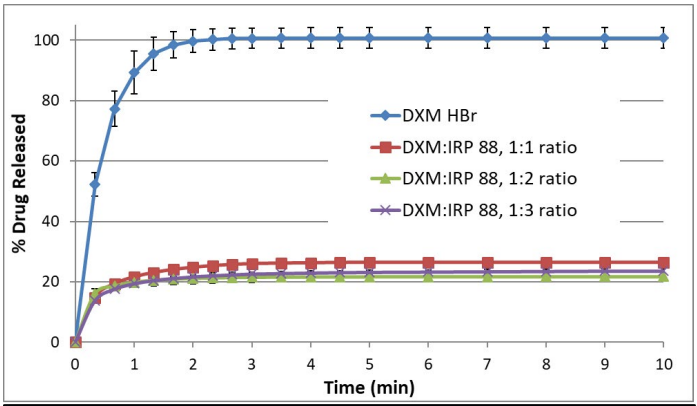
Figure 3: DXM Release from Drug-AMBERLITE™ IRP69 Complex using Small Volume Dissolution Method



Small amount of drug release (< 20%w/w) from DXM- strong cationic resin complexes compared to unmodified drug in 10 min.

In addition, use of higher resin concentrations resulted in a slightly lower amount of drug release into the media. Drug release reached an equilibrium concentration since the use of small media volume provides a limited quantity of counterions for uncoupling of the drug from the drug-resin complex.

Figure 4: DXM Release from Drug-AMBERLITE™ IRP88 Complex using Small Volume Dissolution Methodd

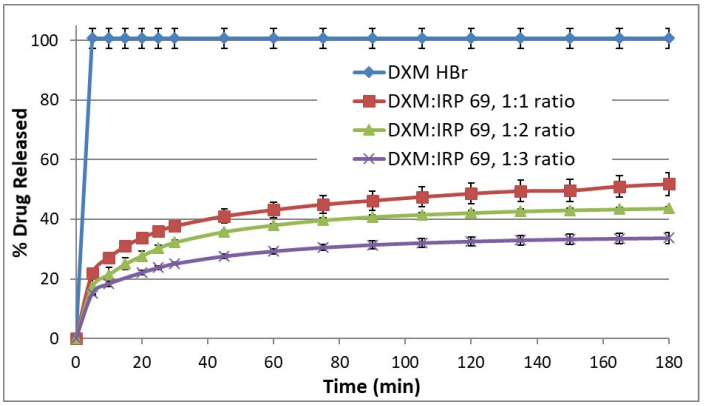


Small amount of drug release (< 30%w/w) from DXM-weak cationic resin complexes compared to unmodified drug in 10 min.

Drug Release Characterization using Compendial Method

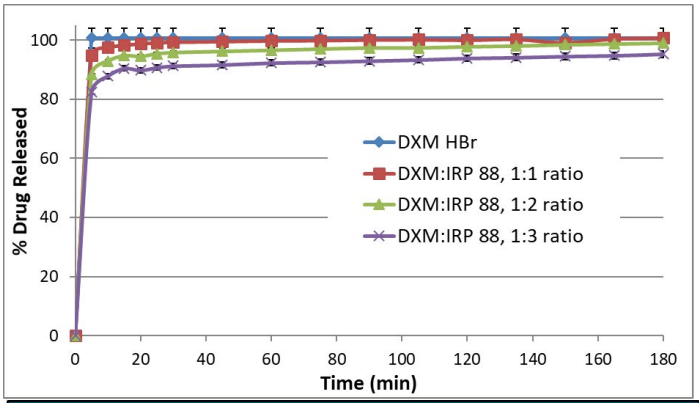
DXM-weak cationic resin complexes provided more than 80% of drug release (Figure 5), whereas DXM-strong cationic resin complexes exhibited controlled drug release behavior and provided <50% of drug release under compendial dissolution method (Figure 6).

Figure 5: DXM Release from Drug-AMBERLITE™ IRP69 Complex using Compendial Dissolution Method



Use of large media volume resulted in < 50% drug release from DXM-strong cationic resin complexes in 3hrs.

Figure 6: DXM Release from Drug-AMBERLITE™ IRP88 Complex using Compendial Dissolution Method



Use of large media volume resulted in > 80% drug release from DXM-weak cationic resin complexes in 3hrs.

Drug Release Comparison

Five (5) minutes was selected as a suitable residence time of the dosage form in the mouth cavity. Figure 7 & 8 show drug release comparison at 5 min. intervals between the compendial and small volume dissolution method. Use of compendial dissolution method provided noticeable higher drug release, which can be attributed to large media volume and availability of more counterion for drug release.

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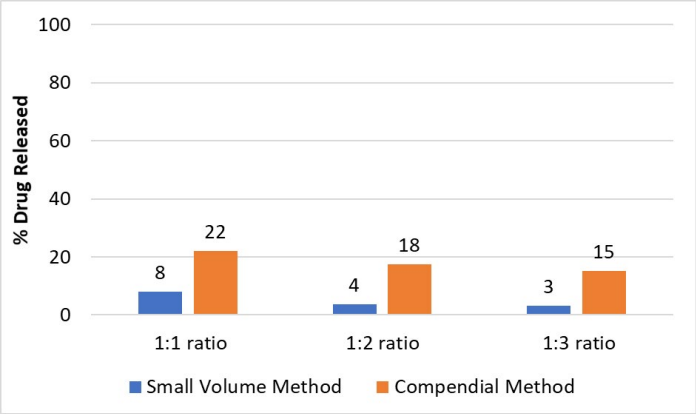
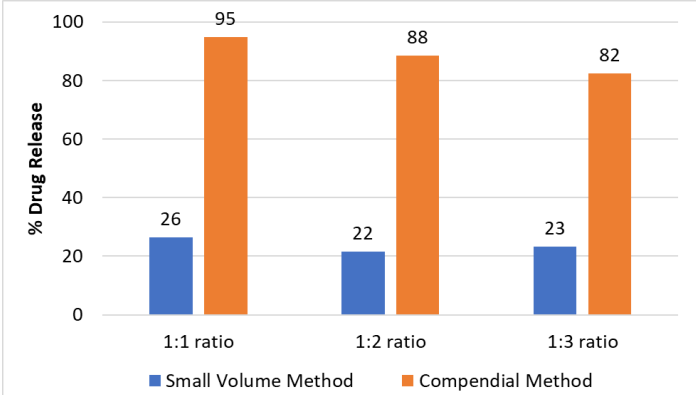
Figure 7: Comparison of DXM Release from Drug-AMBERLITE™ IRP69 Complex at 5 Minutes



Comparing drug release at 5 min. interval, use of compendial method resulted in higher drug release

Figure 8: Comparison of DXM Release from Drug-AMBERLITE™ IRP88 Complex at 5 mins



Comparing drug release at 5 min. interval, use of compendial method resulted in higher drug release

Further, the drug-resin complexes of weak cationic resin resulted in more than 80% of drug release in 5 min. (Figure 8), suggesting poor taste-masking using the compendial dissolution method. However, use of the small volume method, and simulation of the mouth cavity environment resulted in <30% of drug release to indicate appropriate drug taste-masking.

Conclusions

A small volume method for the characterization of taste-masking for the drug-resin complex was developed. This method utilizes 10 mL of simulated saliva, as dissolution media, and analyzes drug release at 20 seconds intervals. Small volume dissolution method may be an appropriate, and complementary to compendial method, during formulation screening and development of taste-masked dosage forms using ion-exchange resin complexes. Use of resin complexation reduced the availability of free drug, which enables taste-masking of the bitter drug. Drug and strong cationic resin (DXM- AMBERLITE™ IRP69) complex resulted in a lower level of drug release, as compared to the weak cationic (DXM- AMBERLITE™ IRP88) drug complex.