# Study of Dose-Weight Proportionality in Extended Release Multiparticulate Systems

**Manish Rane*, Raxit Mehta and Ali Rajabi-Siahboomi**
**Colorcon, Inc., Harleysville, PA USA**

CRS
Poster Reprint 2016

## Summary

Acetaminophen (APAP) layered sugar spheres were coated with an ethylcellulose barrier membrane using fluid bed coater. Different doses of the coated APAP multiparticulates were tested for dose-weight proportionality; drug release profiles were compared. The concept of dose-weight proportionality in extended release multiparticulate systems was demonstrated. This work was a continuation of the evaluation of different sustained release formulation strategies to achieve dose-weight proportionality. [1-2]

## Purpose

Multiparticulate dosage forms offer unique advantages and flexibility to formulators as well as patients and care providers: (a) choice of the finished dosage form such as capsules, sachets or compressed into tablets, (b) modulation of drug release by mixing beads with different coatings to achieve range of drug release profiles, (c) fixed dose combination formulation, (d) reduction in intra or inter-subject variability due to reduced gastric emptying rates and overall gastro-intestinal transit time, (e) flexibility in dose titration without compromising drug release, which is often an issue for extended release monolithic tablets, (f) ability to mix with food for ease of swallowability, in the case of pediatric and geriatric population.[3]

Developing multiple strengths of a modified release formulation is a challenge, and this is when the concept of dose-weight proportionality becomes important. Dose-weight proportional formulation design means developing one formulation, which is weighed per unit dosage form in a proportional manner for different doses. This approach saves time for formulation design, Quality by Design (QbD) study, stability, validation study and potentially bio-equivalence in vivo studies. The purpose of this work was to formulate dose-weight proportional extended release (ER) multiparticulate formulations of a model drug, APAP, at 30, 60 and 120 mg doses, using drug layered and barrier membrane coated sugar spheres.

## Methods

### Preparation and Evaluation of ER Multiparticulate Containing APAP

**(A) 18/20# Sugar Spheres**

Uncoated sugar spheres mesh 18/20 # (Suglets® PF011, 850-1000 µm Colorcon, USA) were layered with APAP using an HPMC-based Opadry® film coating system as a binder, in an Oyster Huttlin Unilab fluid bed coater. The drug layered beads were screened, then barrier membrane coated using ethylcellulose 10 cP viscosity grade (ETHOCEL™ 10 Standard Premium, Dow Chemical Company, USA) at 7.5% weight gain using dibutyl sebacate as a plasticizer[4]. Isopropyl alcohol and water in 90:10 ratio was used as the solvent. Organic coating trials were carried out using Glatt GPCG-2 coater (Glatt Air Techniques Inc., USA). Table 1 shows the composition of the APAP ER multiparticulate formulations. Table 2 shows the process parameters used for drug layering and barrier membrane coating applications. The dissolution study was performed in USP Apparatus I (basket) at 100 rpm speed using 1000 mL of deionized water at 37 ± 0.5ºC. Drug release was determined spectrophotometrically at a wavelength of 243 nm. Particle size of the multiparticulates was determined at different stages using a Camsizer Dynamic Image Analyzer (Horiba Inc., USA).

**Table 1: Composition of APAP Barrier Membrane ER Multiparticulate (Sugar Spheres Mesh 18/20#)**

| Drug layer | mg/ g | % w/w |
|---|---|---|
| Acetaminophen (APAP) | 70.00 | 7.00 |
| Opadry (HPMC based) | 70.00 | 7.00 |
| Suglets PF011 | 860.00 | 86.00 |
| Water | q.s. | q.s. |
| ***Total*** | ***1000*** | ***100*** |
| **Barrier membrane** | **mg/ g** | **% w/w** |
| ETHOCEL 10 cP | 67.50 | 6.75 |
| Dibutyl sebacate | 7.50 | 0.75 |
| Isopropyl alcohol | q.s. | q.s. |
| Water | q.s. | q.s. |
| ***Total*** | ***75.00*** | ***7.50*** |

**Table 2: Coating Process Parameters for APAP Barrier Membrane ER Multiparticulate (Sugar Spheres Mesh 18/20#)**

| Process Parameter | Drug Layering | Barrier Membrane Coating |
|---|---|---|
| Equipment | Oyster Huttlin Unilab | Glatt GPCG-2 |
| Process | Tangential coating | Bottom spray (Wurster) coating |
| Batch size (g) | 5500 | 750 |
| Inlet temperature (°C) | 56 – 57 | 38 – 42 |
| Product temperature (°C) | 47 - 50 | 30 – 32 |
| Outlet temperature (°C) | 44 - 48 | 29 – 31 |
| Atomizing air (bar) | 1.4 | 1.3 |
| Air volume ($m^3$/ hr) | 334 - 335 | 45 - 50 |
| Fluid delivery rate (g/ min) | 23 - 26 | 5 – 7 |
| Wurster insert | NA | 4" |
| Wurster base plate | NA | "C" |

**(B) 30/35# Sugar Spheres**

Uncoated sugar spheres mesh 30/35# (Suglets® PF006, 500-600 µm Colorcon, USA) were drug layered with APAP as described above, then barrier membrane coated using ETHOCEL™ 10 Standard Premium at 13.5% weight gain, using dibutyl sebacate as a plasticizer, under similar conditions as above using VFC Lab-3 Flo Coater (Freund-Vector Corp., USA). Table 4 shows the composition of the APAP extended release multiparticulates. Table 5 shows the process parameters for drug layering and extended release film coating application. Particle size analysis and drug release profiles of the multiparticulate systems were measured as described above.

**Table 3: Composition of APAP Barrier Membrane ER Multiparticulate (Sugar Spheres Mesh 30/35#)**

| Drug layer | mg/ g | % w/w |
|---|---|---|
| Acetaminophen (APAP) | 70.00 | 7.00 |
| Opadry (HPMC based) | 70.00 | 7.00 |
| Suglets PF006 | 860.00 | 86.00 |
| Water | q.s. | q.s. |
| ***Total*** | ***1000*** | ***100*** |
| **Barrier Membrane** | **mg/ g** | **% w/w** |
| ETHOCEL 10 cP | 121.50 | 12.15 |
| Dibutyl sebacate | 13.50 | 1.35 |
| Isopropyl alcohol | q.s. | q.s. |
| Water | q.s. | q.s. |
| ***Total*** | ***135.00*** | ***13.50*** |

**Table 4: Coating Process Parameters for APAP Barrier Membrane ER Multiparticulate (Sugar Spheres Mesh 30/35#)**

| Process Parameter | Drug Layering | Barrier Membrane Coating |
|---|---|---|
| Equipment | Oyster Huttlin Unilab | VFC Lab-3 Flo Coater |
| Process | Tangential coating | Bottom spray (Wurster) coating |
| Batch size (g) | 5500 | 1000 |
| Inlet temperature (°C) | 57 – 75 | 44 – 47 |
| Product temperature (°C) | 45 – 48 | 32 – 34 |
| Outlet temperature (°C) | 47 - 54 | 32 – 34 |
| Atomizing air (bar) | 1.4 | 1.3 |
| Air volume ($m^3$/ hr) | 300 - 350 | 94 |
| Fluid delivery rate (g/ min) | 13 - 30 | 3 – 10 |
| Wurster insert | NA | 6" |
| Wurster base plate | NA | "FP-2" |

## Results

The final APAP assay of barrier membrane coated beads with mesh 18/20# was 92.14%. The dissolution study was performed on different doses of APAP chosen from the same lot of drug loaded; barrier membrane coated extended release beads. Increasing APAP doses of 30, 60 and 120 mg were achieved by weighing 500, 1000 and 2000 mg of multiparticulates based on assay. The drug dissolution profiles were similar as showed in Figure 1.

A similar study was performed by layering APAP on smaller size sugar spheres (mesh 30/35#), also barrier membrane coated with ETHOCEL™ 10 cP at 13.5% WG. The dissolution study was performed on different doses of APAP chosen from the same lot of drug loaded, and barrier membrane coated ER beads. Doses of 30, 60 and 120 mg were achieved by weighing 500, 1000 and 2000 mg of multiparticulates based on assay. The drug dissolution study gave similar % cumulative release of APAP, as showed in Figure 2.

**Figure 1: Dissolution Profiles of APAP Dose-Weight Proportional ER Pellets (Drug Layered on Sugar Sphere 18/20#) at 7.5% Theoretical WG of Ethylcellulose Coating System**

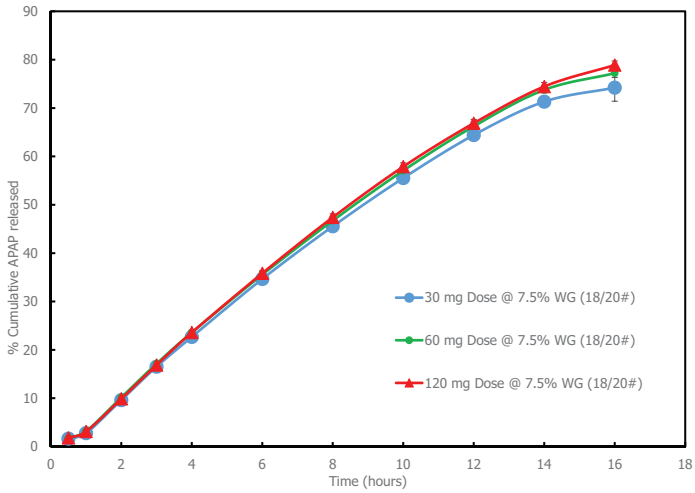
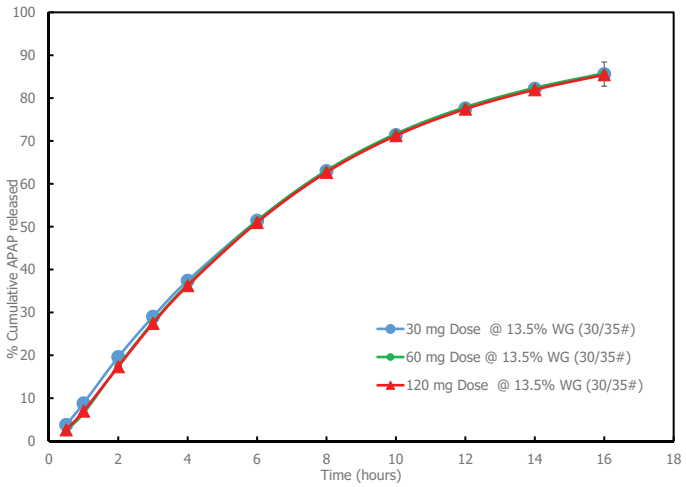



**Figure 2: Dissolution Profiles of APAP Dose-Weight Proportional ER Pellets (Drug Layered On Sugar Sphere 30/35#) at 13.5% Theoretical WG of Ethylcellulose Coating System**




Irrespective of the starting size of sugar spheres used for drug layering, the multiparticulate ER formulation of APAP was found to be dose-weight proportional. Figure 3 shows the particle size distribution of the different sized multiparticulates, before and after the drug layer and barrier membrane coating are applied. Table 5 gives values of average particle size during different stages of drug layering and barrier membrane coating determined by Camsizer.

**Figure 3: Particle Size Distribution of Different Size of Sugar Spheres Drug Loaded with APAP and Barrier Membrane Coated with ETHOCEL™**

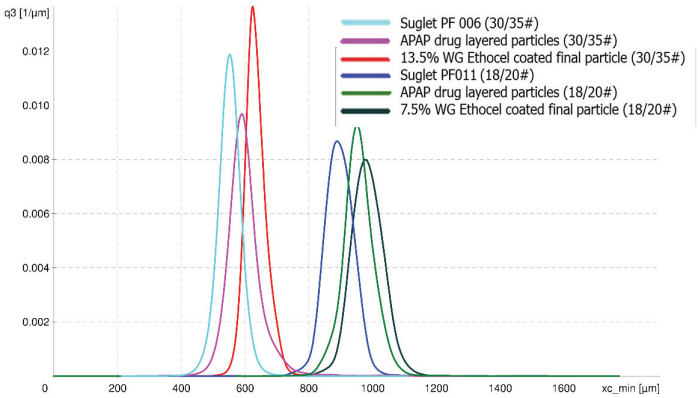



**Table 5: Average Particle Size of Drug Layered and Extended Release Coated APAP Multiparticulate Systems**

| Size / Thickness | 18/20# | 30/35# |
|---|---|---|
| Sugar sphere particle size (d50, µm) | 895 | 551 |
| APAP drug layered final particle size (d50, µm) | 954 | 593 |
| ETHOCEL coated final particle size (d50, µm) | 982 | 630 |
| ETHOCEL coating membrane thickness (µm) | 28 | 37 |

To put a theoretical perspective for why cumulative % release of drug from dose-weight proportional APAP ER multiparticulate systems was similar, surface area to volume ratio and surface area to film thickness ratio were calculated (Tables 6 & 7). It was seen that irrespective of different doses corresponding to different fill weight (for a capsule or sachet dosage form), each pellet acts as an individual dosage form. The surface area to volume ratio, as well as surface area to film thickness ratio, remained constant for different dose-weight proportional multiparticulate system batch for each size of the sugar sphere used. This explains similar drug release profiles resulting from dose-weight proportional formulation for a multiparticulate system.

**Table 6: Calculated Parameters for Dose-Weight Proportional APAP ER Pellets (Drug Layered on Mesh 18/20# Sugar Spheres)**

| Calculated Parameters* | APAP Dose 30 mg | APAP Dose 60 mg | APAP Dose 120 mg |
|---|---|---|---|
| Fill Weight | 500 mg | 1000 mg | 2000 mg |
| Total Number of Pellets | 747 | 1494 | 2989 |
| Total Surface Area (SA) ($cm^2$) | 21.62 | 43.24 | 129.72 |
| Total Volume (V) ($cm^3$) | 0.37 | 0.74 | 1.48 |
| SA / V Ratio ($cm^{-1}$) | 58.43 | 58.43 | 58.43 |
| Film Thickness per Pellet (µm) | 28 | 28 | 28 |
| SA / Film Thickness Ratio (µm) | 10 | 10 | 10 |

** Particle size considered for calculation is 982 µm*

**Table 7: Calculated Parameters for Dose-Weight Proportional APAP ER Pellets (Drug Layered on Mesh 30/35# Sugar Spheres)**

| Calculated Parameters** | APAP Dose 30 mg | APAP Dose 60 mg | APAP Dose 120 mg |
|---|---|---|---|
| Fill Weight | 500 mg | 1000 mg | 2000 mg |
| Total Number of Pellets | 2830 | 5660 | 11320 |
| Total Surface Area (SA) ($cm^2$) | 35.27 | 70.54 | 141.08 |
| Total Volume (V) ($cm^3$) | 0.37 | 0.74 | 1.48 |
| SA / V Ratio ($cm^{-1}$) | 95.32 | 95.32 | 95.32 |
| Film Thickness per Pellet (µm) | 37 | 37 | 37 |
| SA / Film Thickness Ratio (µm) | 3.37 | 3.37 | 3.37 |

*** Particle size considered for calculation is 630 µm*

## Conclusions

Unlike single unit monolithic ER dosage forms, development of dose-weight proportional formulations using multiparticulate dose system is feasible; this offers time saving benefits to formulators during development of validation batches. When working on multiple formulations. Using similar beads (from the same batch), surface area to volume ratio and surface area to film thickness ratio remain constant for different multiple strength, dose-weight proportional formulations.

## References


1. M. Rane, A. Rajabi-Siahboomi, Study of dose-weight proportionality in osmotic push-pull technology using theophylline as a model drug, AAPS Annual Meeting and Exposition, 2013.
2. M. Rane, A. Rajabi-Siahboomi, Study of dose-proportionality in hydrophilic matrix tablets using propranolol HCl as a model drug, AAPS Annual Meeting and Exposition, 2014.
3. J. Parmar, M. Rane, et al., Formulation of extended release multiparticulate systems using ethylcellulose, *Pharma Times*, 42(4), 2010, 34-39.
4. R. Mehta, J. Teckoe, et al., Investigation of the effect of ethylcellullose viscosity variation using QbD samples on drug release from extended release multiparticulate, CRS Annual Meeting, 2014.





For more information, contact your Colorcon representative or call:

| North America | Europe/Middle East/Africa | Latin America | India | China |
|---|---|---|---|---|
| +1-215-699-7733 | +44-(0)-1322-293000 | +54-1-5556-7700 | +91-832-672373 | +86-21-61982300 |