Study of Dose-Weight Proportionality in Osmotic Push-Pull Technology using Theophylline as a Model Drug

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Purpose

The purpose of this work was to formulate dose-weight proportional formulation of model drug (theophylline) at 10, 15 and 20 mg doses using standard round concave (SRC) tooling of proportional dimensions to achieve similar drug release profiles. Surface area, volume and shape of the osmotic tablets were analyzed to further explore mechanism of drug release.

Experimental Methods

Preparation of Core Bilayer Tablets

The composition of theophylline push-pull osmotic pump (PPOP) core tablets is given in Table 1. The pull (drug) layer containing theophylline, POLYOX™ WSR N-80 NF LEO and METHOCEL™ E6 Premium LV was prepared by high shear wet granulation (Diosna P/VAC-10) using an ethanol : water mixture (85:15 ratio). Push layer containing POLYOX WSR Coagulant NF LEO, milled sodium chloride and iron oxide red pigment was prepared by dry blending. The bilayer tablets, using pull to push layer ratio of 2 : 1, and dose-weight proportional, were compressed (GlobePharma Manual Press) to 10 mg, 15 mg and 20 mg strength of theophylline using 9.5 mm, 10.3 mm and 11.9 mm standard concave round tooling, at a compression force of 4000 lb (dwell time of 2 sec). Round tooling of different diameters were selected on the basis of linearity to total tablet weight (Figure 1). 10 mg dose tablets were further compressed using pentagon and caplet shapes, with similar surface area to 9.5 mm round tablets. Physical properties of the different size and shape of core tablets are shown in Table 2.

Table 1. Composition of Extended Release Theophylline PPOP Tablets

Ingredient	% Layer	Low dose (10 mg)	Medium dose (15 mg)	High dose (20 mg)
Drug Layer		**mg / tablet**	**mg / tablet**	**mg / tablet**
Theophylline anhydrous	5.00	10.00	15.00	20.00
POLYOX WSR N-80 NF LEO	92.75	185.50	278.25	371.00
METHOCEL E6 LV	2.00	4.00	6.00	8.00
Magnesium stearate	0.25	0.50	0.75	1.00
Sub total	*100.00*	*200.00*	*300.00*	*400.00*
Push Layer				
POLYOX™ WSR Coagulant NF LEO	64.25	64.25	96.37	128.50
Sodium chloride	35.00	35.00	52.50	70.00
Iron oxide red	0.50	0.05	0.075	0.10
Magnesium stearate	0.25	0.25	0.38	0.50
Sub total	*100.0*	*100.0*	*150.0*	*200.0*
Total Tablet	--	**300.0**	**450.0**	**600.0**
Tooling shape/Size		Round (9.5 mm) Pentagon (8.1 x 7.9 mm) Caplet (9.5 x 6.6 mm)	Round 10.3 mm	Round 11.9 mm

Figure 1. Selection of Round Tooling for Dose-Weight Proportional Formulations

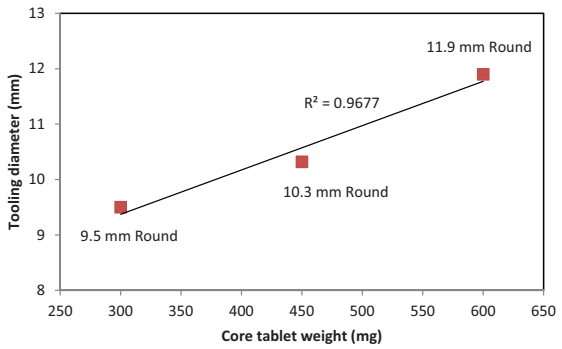
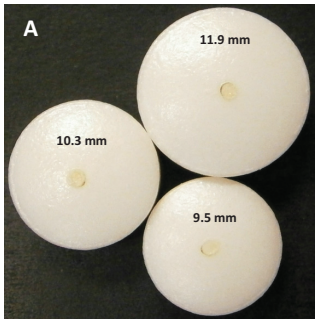
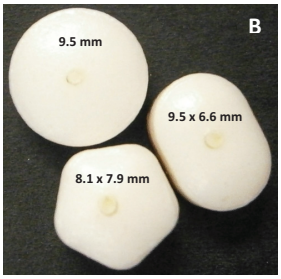


Table 2. Physical Properties of Bilayer Core Tablets of Theophylline

Bilayer Core Tablets (uncoated)	Low dose (10 mg)	Medium dose (15 mg)	High dose (20 mg)	Low dose (10 mg)	Low dose (10 mg)
Tablet Shape/Size	*9.5 mm Round*	*10.3 mm Round*	*11.9 mm Round*	Pentagon	Caplet
Weight (mg)	301.50 ± 2.20	453.24 ± 1.11	602.08 ±1.17	303.00 ± 2.59	300.00 ± 1.83
Diameter (mm)	9.48 ± 0.01	10.27 ± 0.00	11.86 ± 0.01	7.90 ± 0.01	*(L) 9.48 ± 0.00 (B) 6.57 ± 0.00
Thickness (mm)	4.37 ± 0.03	5.43 ± 0.01	5.51 ± 0.01	6.01 ± 0.05	5.51 ± 0.03
Surface area, SA (cm^2)	2.24	2.87	3.58	2.06	2.03
Volume, V (cm^3)	0.25	0.37	0.50	0.24	0.25
Surface area / volume, SA/V (cm^{-1})	9.06	7.66	7.17	8.45	8.26

Figure 2. Theophylline PPOP Tablets (a) Dose-Proportional Formulations (Different Size) and (b) Same Dose Formulations (Different Shape)





Application of Opadry CA® Coating and Orifice Drilling

The bilayer tablets were coated using Opadry CA clear, a fully formulated semipermeable film coating system using acetone:water solvent system at different weight gains (Vector LDCS coating machine)[1]. Drug delivery orifice was drilled (1mm in diameter) on the drug layer side of coated tablets using laser drill (Cobalt 420, InkCupsNow). The resulting images of different size and shape theophylline PPOP tablets are shown in Figure 2.

Dissolution Studies

In vitro dissolution studies were conducted using Apparatus II (100 rpm) with sinkers in 900 mL of deionized water for 22 hours. Theophylline release was determined spectrophotometrically at 272 nm, using in-line detection system. Drug release profiles were compared for release rate, lag time and also similarity factor (f_2).

Results

A) Dose-Weight Proportional Formulations – Effect of Different Tablet Size and Different SA/V Ratio

Table 3 shows physical properties of tablets coated at similar weight gain. Dose-weight proportional tablets coated at similar weight gain showed different release profiles (Figure 3). However, when dose-weight proportional tablet formulations were coated at a weight gain to represent similar film coating thickness and amount of coating per square mm area (Table 4), the drug release was similar (Figure 4). Weight gain followed rank order of a low dose (10 mg, 9.5 mm round) > medium dose (20 mg, 10.3 mm round) > high dose (20 mg, 11.9 mm round). As shown in Table 5 the f_2 values indicated similar release profiles. The lag time and the release rate constants were also similar. The drug release in the ascending part of profiles followed zero order.

Table 3. Physical Properties of Dose-Weight Proportional Theophylline PPOP Tablets Coated at Similar Weight Gain and Different Film Thickness

Coated tablets	Low dose (10mg)	Medium dose (15mg)	High dose (20mg)
Tablet Shape, size	*Round, 9.5 mm*	*Round, 10.3 mm*	*Round, 11.9 mm*
Actual WG %	9.7	10.0	9.3
Average film thickness - face of tablet (µm)	150 ± 4.0	166 ± 11.1	167 ± 2.9
Average film thickness – side of tablet (µm)	66 ± 6.5	88 ± 2.5	81 ± 2.5
Coating per mm² (mg/mm²)	0.13	0.15	0.15

Table 4. Physical Properties of Dose-Weight Proportional PPOP Tablets of Theophylline, Coated at Different Weight Gain and Similar Film Thickness

Coated tablets	Low dose (10 mg)	Medium dose (15 mg)	High dose (20 mg)
Tablet Shape, size	*Round, 9.5 mm*	*Round, 10.3 mm*	*Round, 11.9 mm*
Actual weight gain %	9.7	7.8	6.6
Average film thickness - face of tablet (µm)	150 ± 4.0	150 ± 4.0	150 ± 6.0
Average film thickness – side of tablet (µm)	66 ± 6.5	66 ± 0.0	66 ± 3.0
Coating per mm² (mg/mm²)	0.13	0.12	0.12

Figure 3. Dissolution Profiles of Theophylline PPOP Tablets Coated at Similar Weight Gain and Different Film Thickness

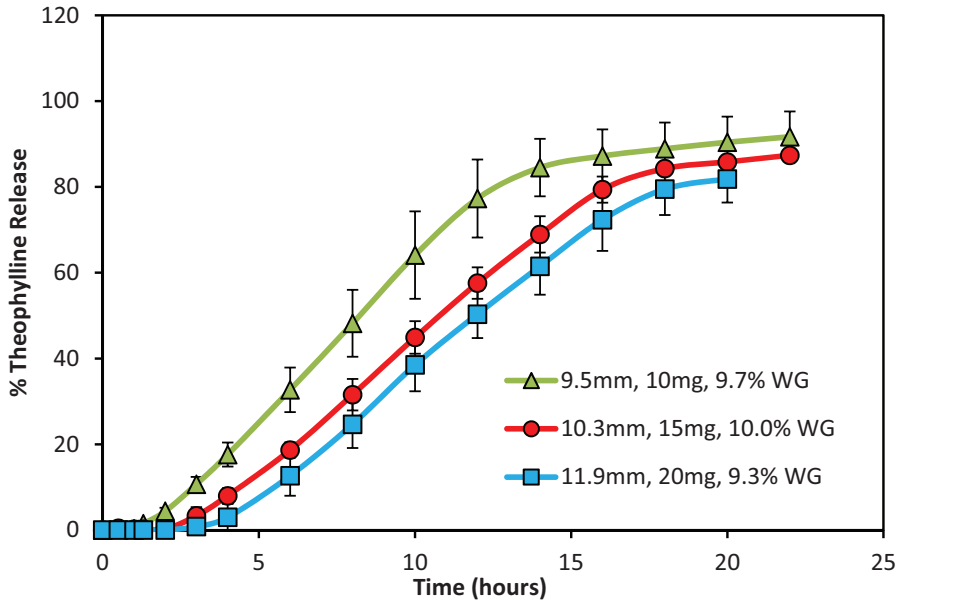


Figure 4. Dissolution Profiles of Theophylline Dose-Weight Proportional Osmotic Tablets Coated at Different Weight Gain and Similar Film Thickness

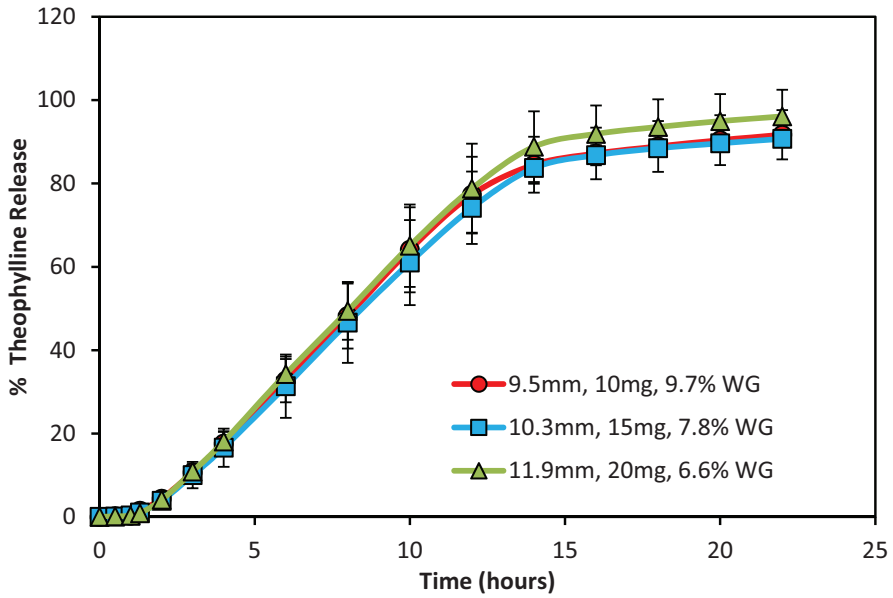


Table 5. Drug Release Profile Evaluation of Dose-Weight Proportional Theophylline PPOP Tablets

Dose-weight (linear) proportional	Low dose (10 mg)	Medium dose (15 mg)	High dose (20 mg)
Tablet Shape	***9.5 mm Round***	***10.3 mm Round***	***11.9 mm Round***
Lag time (h)	1.50	1.50	1.50
Release rate from 2 to 14h (mg/h)	0.70	1.03	1.45
Release rate from 2 to 14h (%/hr)	7.02	6.89	7.29
Zero order regression (r^2)	0.99	0.99	0.99
f_2 (similarity factor)	reference	84.40	78.90

B) Same Dose Formulations – Effect of Different Tablet Shape and Similar SA/V ratio

Same dose theophylline PPOP tablets (10mg) with different shapes but similar SA/V ratio were prepared and coated at similar weight gain had similar film thickness and the amount of coating per square mm area (Table 6). These tablets had similar drug release profile (Figure 5). As shown in Table 7 the f_2 values indicated similar release profiles. The lag time and the release rate constants were also similar. The drug release in the ascending part of profiles followed zero order

Table 6. Properties of Coated Same Dose Theophylline Osmotic Tablets Having Different Shape

Coated tablets	9.5 mm Round (10 mg)	Pentagon (10 mg)	Caplet (10 mg)
Actual weight gain %	9.7	9.0	8.8
Average film thickness - face (µm)	150 ± 4.0	150 ± 1.5	144 ± 4.5
Average film thickness – side (µm)	66 ± 6.5	95 ± 2.0	(L) 101 ± 4.5; (B) 69 ± 6.5
Coating per mm^2 (mg/mm^2)	0.13	0.14	0.13

Figure 5. : Dissolution Profiles of Theophylline 10 mg PPOP Tablets with Different Shape, Similar Surface Area

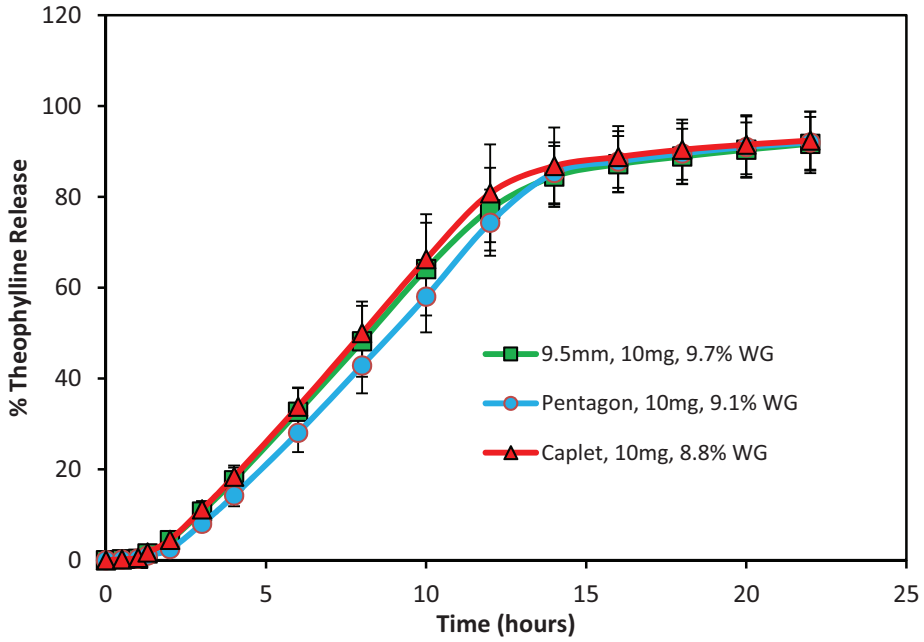


Table 7. Drug Release Profile Evaluation of Same Dose Theophylline PPOP Tablets

Shape of tablet (Dose)	Round, 9.5 mm (10 mg)	Pentagon (10 mg)	Caplet (10 mg)
Lag time (hr)	1.50	1.50	1.50
Release rate from 2 to14 hr (mg/hr)	0.70	0.71	0.72
Zero order regression (r^2)	0.99	0.99	0.99
f_2 (similarity factor)	reference	70.30	83.00

Conclusions

Dose-weight proportional PPOP tablets of differing size and SA or SA/V ratio can be tailored to give similar drug release profiles by keeping coating film thickness similar. PPOP tablets compressed in different shapes having similar SA or SA/V ratio can be tailored to give similar drug release profiles by keeping both weight gain and film thickness similar. This concept can be used for rapid screening of formulations.

References

1. Opadry CA coating process parameters (http://www.colorcon.com/literature/marketing/fc/Opadry%20CA/pi_opadry_CA_coat_param_v2.pdf)