Study of Dose-Proportionality in Hydrophilic Matrix Tablets Using Propranolol HCl as a Model Drug

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Purpose

The purpose of this work was to formulate dose-proportional formulation of a model drug, propranolol hydrochloride (HCl), at 40, 80, 120 and 160 mg doses using standard round concave tooling of proportional or similar dimensions and achieving similar drug release profiles. It is generally recommended to apply a suitable film coat to impart mechanical strength, assist packaging, enhance appearance, and support product stability, while improving patient compliance. In this study the surface area to volume ratio (SA/V) of uncoated matrices was analyzed to explore feasibility of getting similar release profile at proportional weights of tablets.

Methods

Preparation of Hydrophilic Matrix Tablets of Propranolol HCl

Extended release (ER) matrix tablets of propranolol HCl (40, 80, 120 and 160 mg strength) were prepared by direct compression using 30% w/w METHOCEL™ K4M Premium CR (Dow). Dose-weight proportional formulations were prepared at 15%, 25% and 35% w/w drug loading (Table 1). Direct compression blends were prepared using Turbula Mixer and compressed (GlobePharma Manual Press) using standard concave round tooling, at a compression force of 4000 lb (17.8 kN) and a dwell time of 2 seconds. Tablet tooling was selected to accommodate the drug loadings and on the basis of linearity of total tablet weight as shown in Figure 1. Tablets of different drug loading had SA/V proportional to different doses. Photograph of these tablets (containing 25% drug loading) is shown in Figure 2A. Based on the results of drug loading study, additional experiments were conducted as follows:

(1) The lower strength of 40 mg was compressed at a weight and SA / V ratio similar to that of 80 mg strength containing 25% drug loading using 9.5 mm round tooling. All other strengths were kept as dose-weight proportional containing 25% drug loading (Table 1). Photograph of these tablets is shown in Figure 2B.

(2) All the strengths were compressed at same weight and SA / V ratio using 11.00 mm round tooling (Table 2). Photograph of these tablets is shown in Figure 2C.

Table 1: Composition of ER Propranolol HCl Hydrophilic Matrix Tablets at Different Drug Loading (Dose-Weight Proportional)

	15% Drug Loading				25% Drug Loading #				35% Drug Loading			
Ingredients	mg / tablet											
Propranolol HCl	40.0	80.0	120.0	160.0	40.0	80.0	120.0	160.0	40.0	80.0	120.0	160.0
METHOCEL K4M Premium CR	80.0	160.0	240.0	320.0	48.0	96.0	144.0	192.0	34.3	68.6	102.9	137.1
Starch 1500	145.3	290.7	436.0	581.3	71.2	142.4	213.6	284.8	39.4	78.9	118.3	157.7
Magnesium Stearate	1.3	2.7	4.0	5.3	0.8	1.6	2.4	3.2	0.6	1.1	1.7	2.3
Total Tablet Weight (mg)	266.7	533.3	800.0	1066.7	160.0	320.0	480.0	640.0	114.3	228.6	342.9	457.1
Tooling size (mm)	9.5	11.0	11.9	12.7	7.9	9.5	10.3	11.9	7.9	9.5	9.9	11.0

Dissolution Testing

Drug release testing was conducted using USP Apparatus II (100 rpm) with sinkers in 900 mL of deionized water for 12 hours. The amount of propranolol released was determined spectrophotometrically at 289 nm, using in-line detection system. Drug release profiles were compared for similarity factor (f_2).

Figure 1: Selection of Round Tooling for Dose-Weight Proportional Formulations of Propranolol HCl Matrix ER Tablets at (A) 15%, (B) 25% and (C) 35% Drug Loading

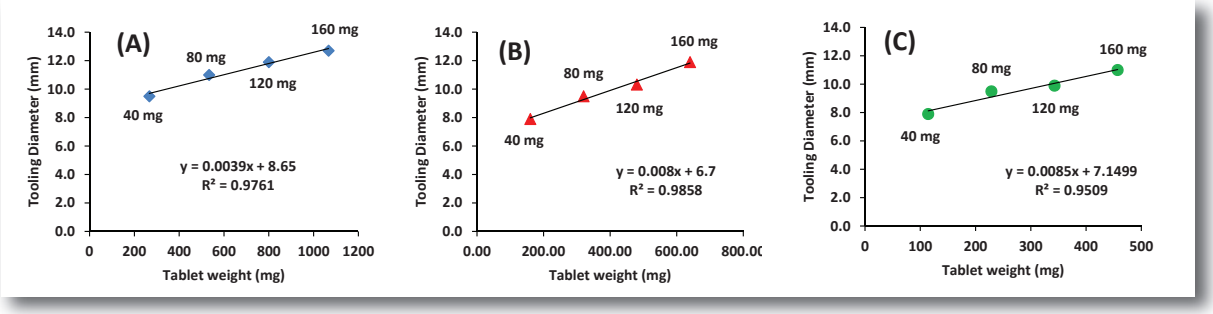


Figure 2: Photograph of Propranolol HCl Matrix ER Tablets (A) Dose-Weight Proportional Formulations at 25% Drug Loading (Different Size Tablets); (B) Dose-Weight Proportional Formulations (All, Except 40 mg Strength Formulation) and (C) Dose-Proportional, Weight Similar Formulations (Same Size Tablets)

Photographs were not taken at same scale/zoom

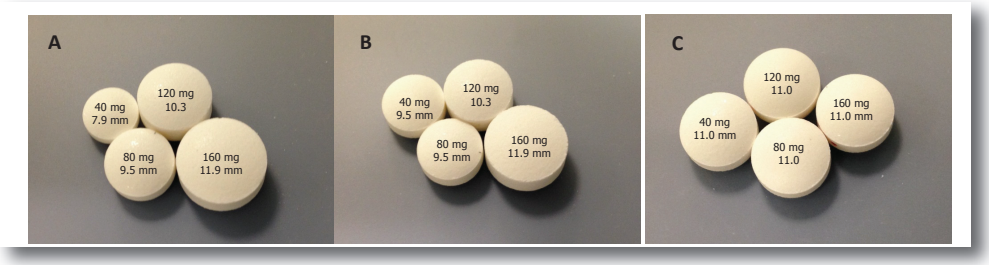


Table 2: Composition of ER Propranolol HCl Hydrophilic Matrix Tablets (Dose-Linear, Weight Similar)

Ingredients	mg / tablet			
Propranolol HCl	40.0	80.0	120.0	160.0
METHOCEL K4M Premium CR	137.1	137.1	137.1	137.1
Starch 1500	277.7	237.7	197.7	157.7
Magnesium Stearate	2.3	2.3	2.3	2.3
Total Tablet Weight	457.1	457.1	457.1	457.1
Tooling size (mm)	11.0	11.0	11.0	11.0

Results and Discussion

Dose-Weight Proportional Formulations (at Different Drug Loadings)

Formulation of dose-weight proportional hydrophilic matrix tablets of propranolol HCl was a challenge, due to different SA/V, and highly dependent on the drug loading. Various physical properties of the tablets are shown in Table 3. Drug release profiles of propanolol HCl from tablets containing 15%, 25% and 35% w/w drug loading are shown in Figure 3, 4 and 5 respectively. Formulations containing 15% and 35% drug loading presented challenge in accommodating weight of tablets for higher strength of 160 mg and lower strength of 40 mg respectively. At 15% drug loading, drug release from 120 mg and 160 mg was slow (Figure 3) whereas at 35% drug loading, drug release from 40 mg and 80 mg was fast (Figure 5). At 25% drug loading, the release profile from 80 mg, 120 mg and 160 mg strength formulations, were similar with $f_2 > 50$; however, 40 mg strength gave faster dissolution due to high SA / V ratio (Figure 4).

Table 3: Physical Properties of Propranolol HCl Hydrophilic Matrix Tablets containing Different Drug Loading (Dose-Weight Proportional Formulations)

	15% Drug Loading				25% Drug Loading				35% Drug Loading			
Dose (mg)	40 mg	80 mg	120 mg	160 mg	40 mg	80 mg	120 mg	160 mg	40 mg	80 mg	120 mg	160 mg
Diameter (mm)	9.50	11.00	11.90	12.70	7.90	9.50	10.30	11.90	7.90	9.50	9.90	11.00
Thickness (mm)	4.1	6.07	7.06	8.71	3.70	4.80	5.82	5.93	2.92	3.74	4.75	5.52
Surface area, SA (cm^2)	2.16	3.36	4.16	5.21	1.53	2.37	2.99	3.73	1.33	2.05	2.53	3.17
Volume, V (cm^3)	0.23	0.48	0.67	0.97	0.14	0.28	0.41	0.55	0.10	0.20	0.30	0.43
Surface area / volume, SA / V (cm^{-1})	9.43	6.98	6.19	5.39	10.83	8.52	7.35	6.84	13.02	10.14	8.42	7.39

Figure 3: Dissolution Profiles of Propranolol HCl from Dose-Weight Proportional Tablet Formulations with 15% Drug Loading

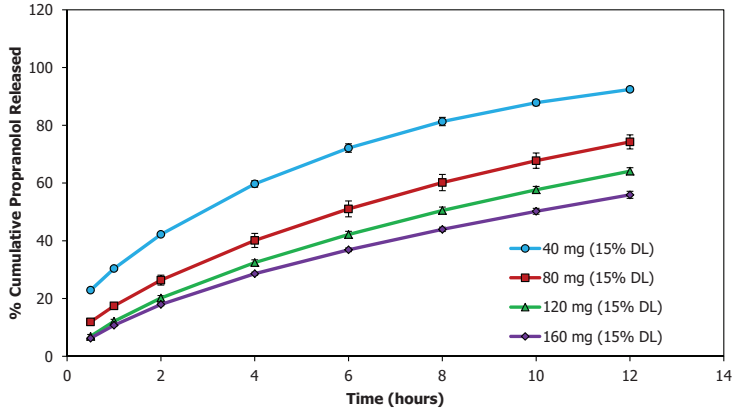


Figure 4: Dissolution Profiles of Propranolol HCl from Dose-Weight Proportional Tablet Formulations with 25% Drug Loading

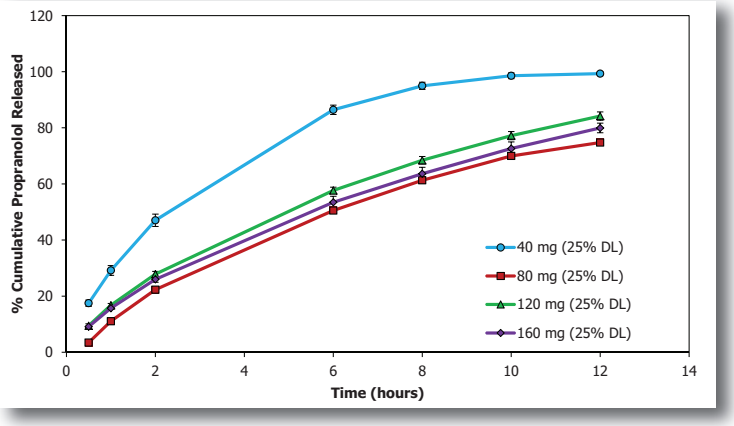
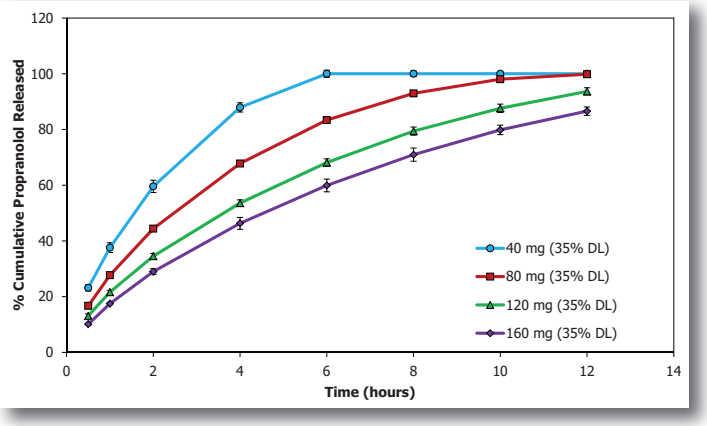


Figure 5: Dissolution Profiles of Propranolol HCl from Dose-Weight Proportional Tablet Formulations with 35% Drug Loading



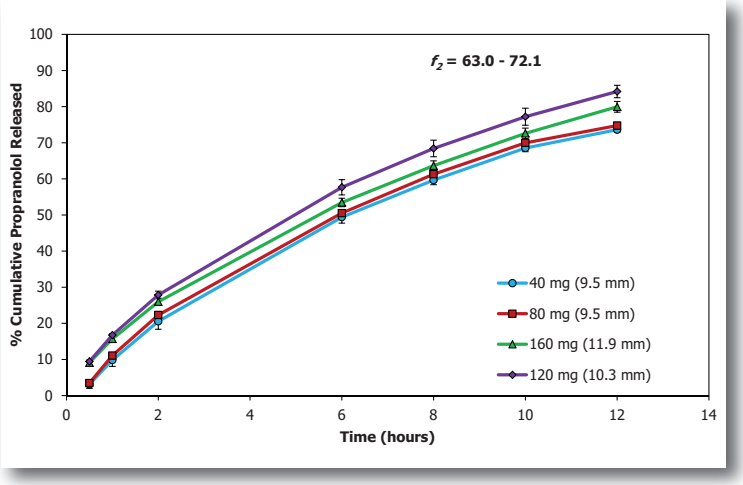
Dose-Weight Proportional Formulations, (Except 40 mg Strength)

At 25% drug loading, 80 mg, 120 mg and 160 mg at proportional weights gave similar release profile with the exception of 40 mg strength (Figure 4). Hence, in this experiment, 40 mg strength formulation was compressed at SA / V ratio similar to that of the 80 mg strength, while maintaining the polymer content at 30% w/w. The physical properties of tablets are shown in Table 4. The drug release profiles of all the strengths were found to be similar (Figure 6) with f_2 value within 63.0 – 72.1.

Table 4: Physical Properties of Propranolol HCl Hydrophilic Matrix Tablets Containing Different Drug Loading (Dose-Weight Proportional Formulations, Except 40 mg Strength)

Dose (mg)	40 mg	80 mg	120 mg	160 mg
Diameter (mm)	9.50	9.50	10.30	11.90
Thickness (mm)	4.80	4.80	5.82	5.93
Surface area, SA (cm^2)	2.37	2.37	2.99	3.73
Volume, V (cm^3)	0.28	0.28	0.41	0.55
Surface area / volume, SA / V (cm^{-1})	**8.52**	**8.52**	**7.35**	**6.84**

Figure 6: Dissolution Profiles of Propranolol HCl from Dose-Weight Proportional Tablet Formulations, Except 40 mg Strength



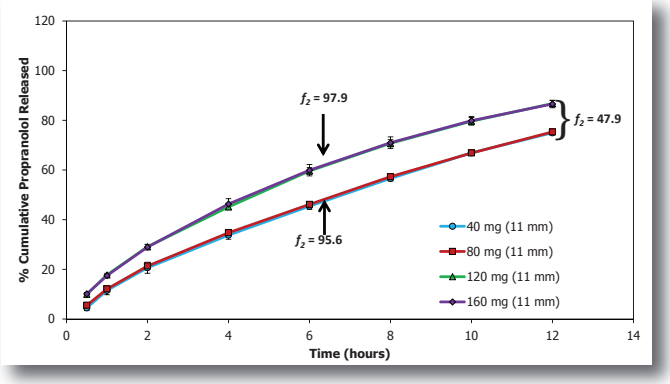
Dose-Proportional, Weight-Similar (All Strengths having Similar SA / V ratio)

The physical properties of tablets are shown in Table 5. As shown in Figure 7, the release profiles from 40 mg and 80 mg were not similar to the release profiles from 120 mg and 160 mg strength formulations (f_2 = 47.9). However, the release profile from 120 mg and 160 mg strength formulations were similar (f_2 value = 97.9), and drug release profile from 40 mg and 80 mg strength formulation were similar (f_2 value = 95.6). In work presented earlier by Palmer et al[1], insoluble drug formulation compressed at different drug loading showed differences due to substitution of drug with insoluble excipient. This could impact the formulation balance between soluble and insoluble components affecting the swelling and erosion characteristics. Further exploration on this topic is needed to understand this fully.

Table 5: Physical Properties of Propranolol HCl Hydrophilic Matrix Tablets containing Different Drug Loading (Dose-Weight Proportional Formulations, Except 40 mg Strength)

Dose (mg)	40 mg	80 mg	120 mg	160 mg
Diameter (mm)	11.00	11.00	11.00	11.00
Thickness (mm)	5.52	5.52	5.52	5.52
Surface area, SA (cm^2)	3.17	3.17	3.17	3.17
Volume, V (cm^3)	0.43	0.43	0.43	0.43
Surface area / volume, SA / V (cm^{-1})	**7.39**	**7.39**	**7.39**	**7.39**

Figure 7: Dissolution Profiles of Propranolol HCl from Dose-Proportional, Weight-Similar Tablet Formulations



Conclusions

Formulation of dose-proportional hydrophilic matrix tablets is achievable by keeping tight control of SA/V. Lower dose of 40 mg was difficult to formulate in a dose-weight proportional formulation. At 25% drug loading, dose-weight proportional formulations of 80 mg, 120 mg and 160 mg strengths, gave similar release profile. It was possible to achieve similar release profile from lower strength of 40 mg, when SA / V was kept similar to that of 80 mg strength (at 25% drug loading). The drug loading levels were selected to keep optimal tablet dimension for ease of handling and swallowability. Film coating of multiple doses would enhance patient compliance by helping in easy identification and swallowability of the tablets[2], without affecting the drug release profile[3].

References

1. Palmer F, Jordan M and Rajabi-Siahboomi R, Maintaining similar drug release profiles from hydrophilic matrices having identical dimensions but different dose strengths, Controlled Release Society Annual Meeting, July 2004.
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