Study of Dose-Weight Proportionality of IR/SR Fixed Dose Combination (FDC)

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Purpose

Fixed dose combinations (FDC) offer unique benefits to patients by reducing dosing regimens and value to the pharmaceutical industry through intellectual property and market exclusivity creation.[1-2] FDC of two different drugs may be developed with multiple doses and release profiles; however, developing multiple dose strength FDC with different release profiles may be challenging, so the concept of dose-weight proportionality could help in reducing pre-formulation and formulation development timelines. The purpose of this work is to evaluate dose-weight proportionality in FDC for two model drugs (water soluble) with a constant immediate release (IR) dose and variable sustained release (SR) dose, and vice-versa; while maintaining similar drug release profiles and understanding the impact of change for tablet diameter of a bilayer FDC to provide optimal tablet thickness.

Experimental Methods

Bilayer tablets containing an IR layer of highly soluble model drug metformin HCl (MF) and SR layer of soluble model drug propranolol HCl (PPL) were prepared using direct compression on a manual tablet press (MTCM-1, Globe Pharma, USA) at 3000 psi and dwell time of 2 seconds. FDC of these two model drugs is not available in the market. The doses studied were: (A) constant metformin IR dose, different propranolol SR doses (40/80 mg, 40/120 mg, 40/160 mg strengths); (B) different metformin IR doses, constant propranolol SR dose (20/160 mg, 30/160 mg, 40/160 mg). Tables 1 and 2 show the composition for the various FDC formulations. The IR layer was pigmented with red iron oxide for easy visual identification. Based on previous work, tablet tooling was selected for propranolol SR layer.[3] Larger tablet tooling (revised tooling) was also studied to achieve optimal tablet thickness. The dissolution study was performed in a USP Apparatus II (paddle) using sinkers at 100 rpm in 1000 mL of deionized water at 37°C. Metformin and propranolol were analyzed spectrophotometrically at 233 and 289 nm each and release profiles quantitated by applying simultaneous equations (Vierordt's method).[4] The dissolution profiles for propranolol were compared for similarity factor (f_2).

Table 1: Composition of FDC Tablets with Constant Metformin (MF) IR Dose with Different Propranolol (PPL) SR Doses (Dose-Weight Proportional)

Ingredients		MF40/PPL80	MF40/PPL120	MF40/PPL160
IR Layer	% w/w	Constant IR Dose (mg/tablet)		
Metformin HCl (MF)	20.0	40.0	40.0	40.0
Pregelatinized starch (Starch 1500®)	30.0	60.0	60.0	60.0
MCC (50 micron)	44.0	88.0	88.0	88.0
Magnesium stearate	0.5	1.0	1.0	1.0
Iron oxide red	0.5	1.0	1.0	1.0
Weight of IR Layer	**100.0**	**200.0**	**200.0**	**200.0**
SR Layer	% w/w	Different SR Doses (mg/tablet)		
Propranolol HCl (PPL)	25.0	80.0	120.0	160.0
METHOCEL™ K4M Premium CR	30.0	96.0	144.0	192.0
Pregelatinized starch (Starch 1500®)	44.5	142.4	213.6	284.8
Magnesium stearate	0.5	1.6	2.4	3.2
Weight of SR Layer	**100.0**	**320.0**	**480.0**	**640.0**
Total Tablet Weight		**520.0**	**680.0**	**840.0**

Table 2: Composition of FDC Tablets Having Different Metformin (MF) IR Doses with Constant Propranolol (PPL) SR Dose (Dose-Weight Proportional)

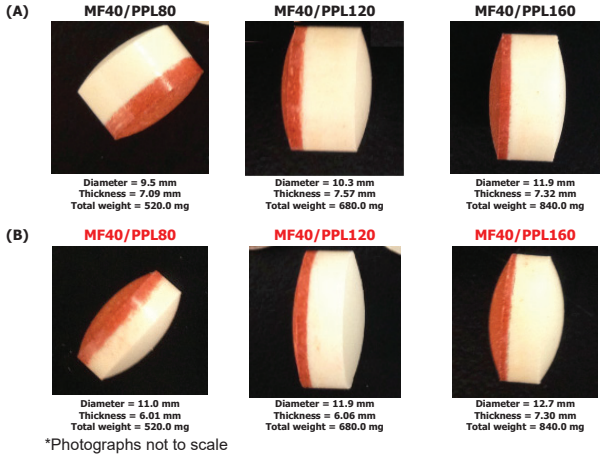
Ingredients		MF20/PPL160	MF30/PPL160	MT40/PPL160
IR Layer	% w/w	Different IR Doses (mg/tablet)		
Metformin HCl (MF)	20.0	20.0	30.0	40.0
Pregelatinized starch (Starch 1500®)	30.0	30.0	45.0	60.0
MCC 50 micron	44.0	44.0	66.0	88.0
Magnesium stearate	0.5	0.5	0.75	1.0
Iron oxide red	0.5	0.5	0.75	1.0
Weight of IR Layer	**100.0**	**100.0**	**150.0**	**200.0**
SR Layer	% w/w	Constant SR Dose (mg/tablet)		
Propranolol HCl (PPL)	25.0	160.0	160.0	160.0
METHOCEL™ K4M Premium CR	30.0	192.0	192.0	192.0
Pregelatinized starch (Starch 1500®)	44.5	284.8	284.8	284.8
Magnesium stearate	0.5	3.2	3.2	3.2
Weight of SR Layer	**100.0**	**640.0**	**640.0**	**640.0**
Total Tablet Weight		**740.0**	**790.0**	**840.0**

Results

(A) Constant IR Dose with Different SR Doses

Based on our previous study, dose-weight proportional propranolol SR hydrophilic matrices were possible with a drug loading of 25% w/w in the tablets.[3] Constant IR metformin dose (40 mg) and different SR propranolol dose (80, 120, 160 mg) were compressed into FDC bilayer tablets (Figure 1A). Incorporation of IR metformin layer to SR propranolol layer did not impact the release profile of metformin (Figure 2A), as indicated by IR of >90% metformin within 15 minutes. Similarly, release profile of propranolol (Figure 2B) was not significantly impacted due to presence of IR metformin layer. This may be due to fast dissolution and release of the IR layer, which did not restrict hydration of polymer in the SR layer. Dose weight proportionality was achieved for all formulations containing constant IR dose and varying SR doses (f_2 value between 55.2 to 84.3). It was seen that incorporation of IR layer to SR layer increased the tablet thickness. Further study was conducted to increase the tablet diameter to achieve lower tablet thickness, while maintaining the same weight of each layer and total weight of bilayer tablet (Figure 1B). It was found that release from the IR metformin was similar (Figure 3A); however, with increasing tablet diameter, the drug release from 80 and 120 mg SR propranolol layer slowed (Figure 3B) compared to drug release from initial tablet diameter (Figure 2B). This could be due to the change in surface area to volume ratio for lower or medium strength. However, drug release from 160 mg strength propranolol with revised tooling, was unaffected.

Figure 1: FDC Tablets of Constant Metformin IR Dose, Different Propranolol SR Doses Using (A) Initial Tablet Tooling[3] and (B) Revised Tablet Tooling



*Photographs not to scale

Figure 2: Dissolution Profiles of (A) Metformin IR and (B) Propranolol SR from FDC Tablets (Constant IR Dose, Different SR Doses) Compressed Using Initial Tooling

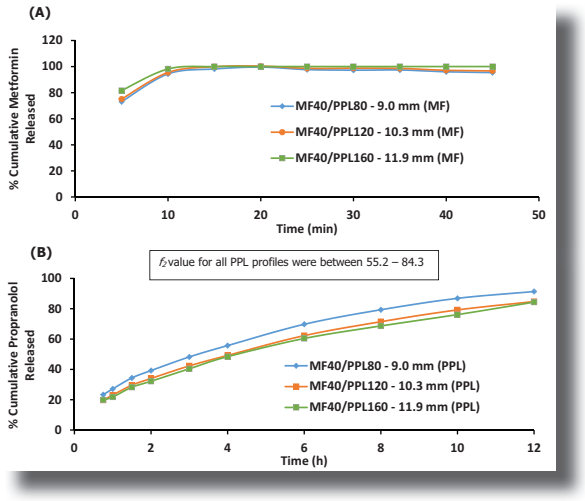
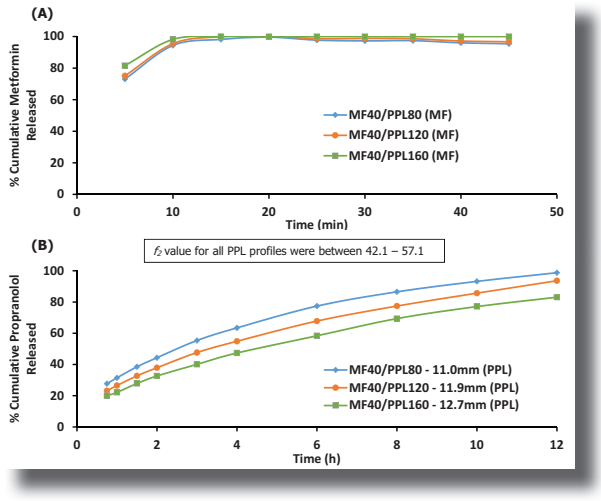


Figure 3: Dissolution Profiles of (A) Metformin IR and (B) Propranolol SR from FDC Tablets (Constant IR Dose, Different SR Doses) Compressed Using Revised Tooling



(B) Different IR Doses and Constant SR Dose

Different metformin IR doses (20, 30, 40 mg) and constant propranolol SR dose (160 mg) using 11.9 mm diameter tooling resulted in different sized tablets (Figure 4A). Incorporation of metformin IR layer to SR propranolol layer did not impact the release profile for metformin (Figure 5A). Similarly, the release profile of propranolol (Figure 5B) was not affected by presence of IR metformin layer. Dose weight proportionality was achieved for all formulations containing different IR doses and constant SR dose. It was seen that incorporation of IR layer to SR layer increased the tablet thickness. Further study was conducted to increase the tablet diameter from 11.9 mm to 12.7 mm to lower tablet thickness, while maintaining the weight of each layer and total weight of bilayer tablet (Figure 4B). It was found that the IR metformin release was similar (Figure 6A), as was propranolol release (Figure 6B). Change of tablet tooling diameter had no major impact on release profile of propranolol.

Figure 4: Photograph of FDC Tablets of Different Metformin (MF) IR Doses, Constant Propranolol SR Dose Using (A) Initial Tablet Tooling[3] and (B) Revised Tablet Tooling

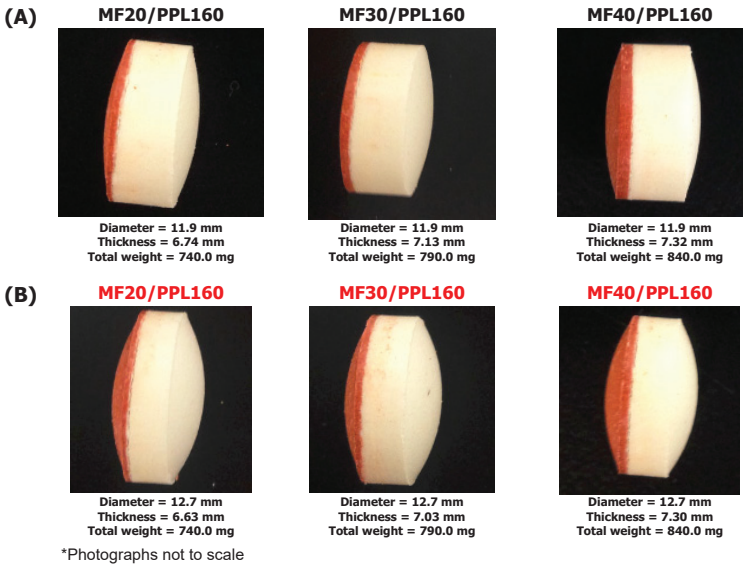


Figure 5: Dissolution Profiles of (A) Metformin IR and (B) Propranolol SR from FDC Tablets (Different IR Doses, Constant SR Dose) Compressed Using Initial Tooling

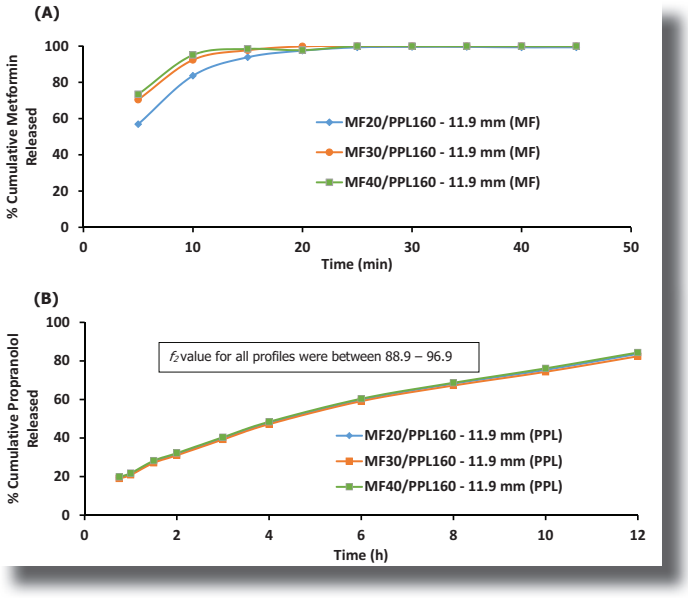
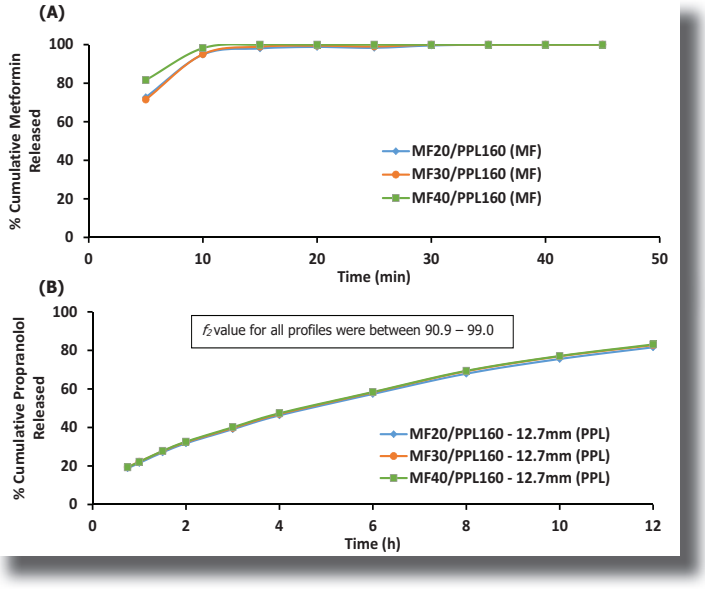


Figure 6: Dissolution Profiles of (A) Metformin IR and (B) Propranolol SR from FDC Tablets (Different IR Doses, Constant SR Dose) Compressed Using Revised Tooling



Conclusions

Using two different model actives, dose-weight proportionality was achieved in FDC bilayer tablets with constant IR dose, different SR doses and vice-versa. Immediate release of the highly soluble model drug metformin (MF) was easily achieved from all formulations irrespective of changes in tablet thickness, tablet diameter or presence of SR layer. Sustained release of the soluble model drug propranolol (PPL) was only sensitive to changes in tablet thickness and diameter, when using revised tooling for lower strengths; however, its high dose-strength was unaffected by changes in tablet thickness and diameter. It is recommended to film coat the fixed dose combinations to increase mechanical strength, ease packaging, improve swallowability and reduce the risk of capping or layer-separation of the tablets. A clear film coat can also help to show the different bilayers.

References

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