EXCIPIENTS

Poster Reprint
American Association
Of Pharmaceutical Scientists
(AAPS) Annual Meeting

November 2008

Development of Common Formulations for Both Encapsulation and Tableting – Narrowing the Gap Between Clinical and Commercial Formulations

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PURPOSE

Based on formulation simplicity and blinding capability, hard gelatin capsules are preferred over other oral solid dosage forms including tablets in the early clinical phases of drug development. However, due to economic and other marketing considerations, most oral solid dosage forms on the market today are tablets.[1] The authors suggest that there may be some opportunity for time savings in formulation development if relatively simple, common formulations, suitable for use in both capsule and tablet dosage forms, can be developed in the pre-clinical phase. Therefore, the purpose of this work was to demonstrate the feasibility of developing a single formula that can be encapsulated into hard gelatin capsules for clinical studies and compressed into tablets for commercialization.

METHODS

Eight formulations containing active pharmaceutical ingredients (API's) of varying dose and solubility were studied; however, for the sake of brevity, details on four model drugs with different doses, concentrations, and water solubilities were selected for inclusion in this poster (Tables 1 & 2).

Table 1. Study Design with Model Drugs

Drug Name	Dose (mg)	Concentration (%)	Water Solubility (mg/mL)
Amlodipine Besylate	5	3.47	1
Theophylline	100	40.00	1
Gabapentin	100	40.00	100
Caffeine	200	34.72	22

Table 2. Compositions of Capsule-to-Tablet™ Formulae

Drug Name	Ingredient Percentage				
	Active	Starch-based Excipient	Microcrystalline Cellulose	Colloidal Silicon Dioxide	Magnesium Stearate
Amlodipine Besylate	3.47	48.04*	48.04	0.25	0.20
Theophylline	40.00	29.75*	29.75	0.25	0.25
Gabapentin	40.00	17.93**	41.83	------	0.25
Caffeine	34.72	21.68*	43.35	------	0.25

Notes: * Starch 1500® Partially pregelatinized maize starch
** StarCap 1500® Co-processed starch excipient

The tablets were film coated with Opadry® II 85 Series™ PVA-based, high productivity film coating, 85F18422, white.

Manufacturing Process

With the exception of caffeine tablets that were manufactured by roller compaction method, other formulae were processed by direct compression. The common granulation was encapsulated into hard gelatin capsules. The caffeine formula was compacted on an Alexanderwerk WP120 roller compactor set at 5 rpm roll speed, 30 bar roll pressure, 36 rpm feed screw speed and 2 mm roll gap. The tableting operation was conducted on a 10-station instrumented Piccola tablet press at 30 rpm, and the encapsulation on a on a tamp-filling machine, In-Cap (Dott. & Bonapace C.) with a throughput of 1,500 capsules/hour.

Film Coating Process

All tablets were coated to a 3% weight gain (WG) in a Thomas 15" side-vented, fully-perforated coating pan with Opadry II 85F18422 white at 20% solids concentration (Table 3).

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Table 3. Film Coating Parameters

Process Parameter	Target Value
Inlet air temperature	60°C
Exhaust air temperature	45°C
Tablet bed temperature	48°C
Air flow	306 m^3/hr (180 ft^3/min)
Spray rate	8.0 g/min
Spray nozzle size	1 mm
Number of guns	1
Atomization air pressure	1.7 bar (25 psi)
Pattern air pressure	1.7 bar (25 psi)
Pan speed	15 rpm
Pan load	1 kg

The content uniformity test was conducted only with capsules and coated tablets. Ten capsules or tablets were collected from the bulk and assayed individually. The assay method described in the USP XXXI was used for the testing of theophylline, gabapentin and caffeine products. The potency assay of amlodipine besylate products was performed using Colorcon's in-house test method based on the technical aspects of the proposed amlodipine besylate monograph (USPPF 32(3)) (Table 4).

Table 4. Dissolution and Content Uniformity Methods

Drug Name	USP Apparatus	Speed (rpm)	Medium	Vol. (ml)
Amlodipine Besylate	II (paddle)	75	0.01N HCl	500
Theophylline	II (paddle)	50	water	900
Gabapentin	II (paddle)	50	0.06N HCl	900
Caffeine	II (paddle)	100	water	900

RESULTS

Comparative dissolution profiles were generated with capsules, uncoated and coated tablets for the *in-vitro* performance similarity. In all cases, tablets and capsules manufactured from a common granulation had similar dissolution profiles, with complete drug release within the first 15 minutes (Figures 1 - 4).

Figure 1. Comparative Dissolution Profiles of Amlodipine Besylate Capsules, Uncoated Tablets, and Film Coated Tablets (0.01 N HCl)

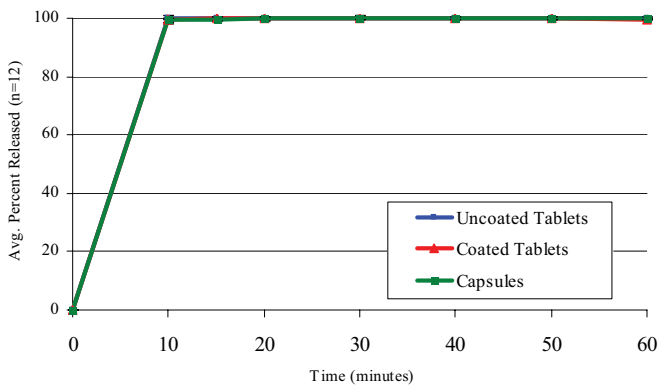


Figure 2. Comparative Dissolution Profiles of Theophylline Capsules, Uncoated Tablets, and Film Coated Tablets (deionized water)

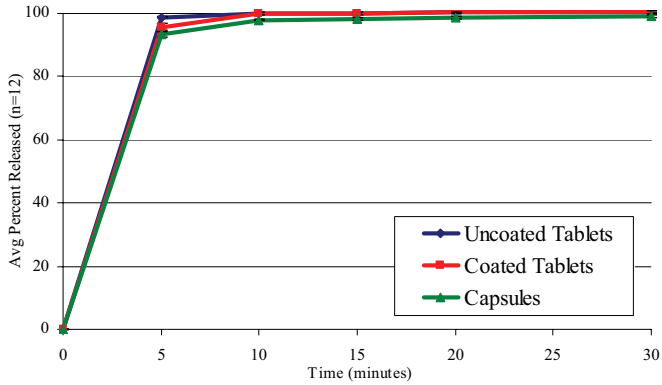


Figure 3. Comparative Dissolution Profiles of Gabapentin Capsules, Uncoated Tablets, and Film Coated Tablets (0.06 N HCl)

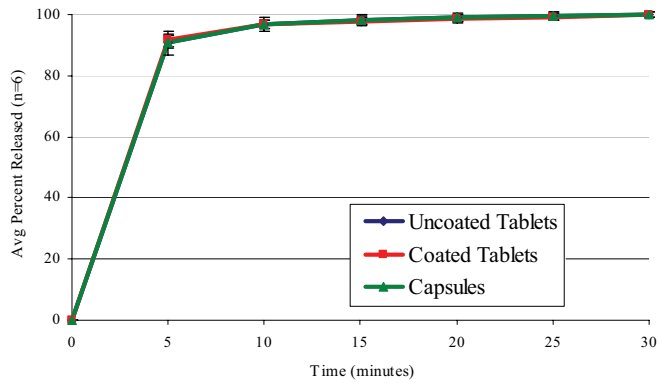
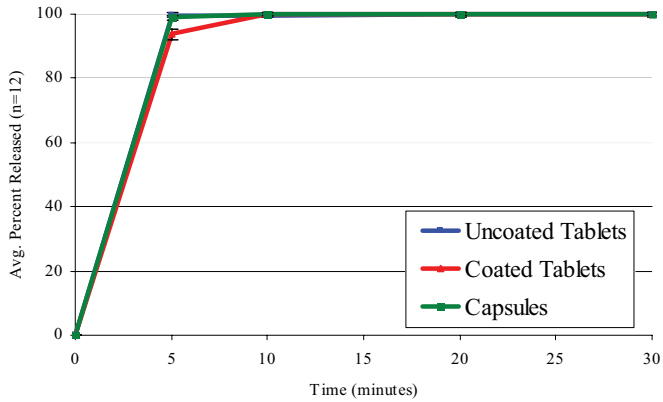


Figure 4. Comparative Dissolution Profiles of Caffeine Capsules, Uncoated Tablets, and Film Coated Tablets (deionized water)



The drug content uniformity was tested to ensure the uniformity of active concentration in the finished products, i.e., filled capsules and film-coated tablets. The potency assay of individual capsules or tablets lie within the acceptable range of 85-115% of the label claim, and the RSD is not greater than 6%. All the capsules and tablets passed the content uniformity test against the acceptance criteria specified in the USP XXXI, where an acceptance value of less than 15 is required (Table 5).

Table 5: Content Uniformity of Capsules and Film Coated Tablets

Statistics (n = 10)	Amlodipine Besylate		Theophylline		Gabapentin		Caffeine	
	Caps.	Tab.	Caps.	Tab.	Caps.	Tab.	Caps.	Tab.
Average potency assay (%)	102.2	98.5	99.1	101.2	103.2	104.4	101.3	98.3
Min. potency assay (%)	100.7	96.2	97.9	99.2	100.9	102.4	99.8	96.2
Max. potency assay (%)	103.5	99.8	100.4	102.8	106.2	106.8	103.1	99.8
RSD%	0.83	1.0	1.0	1.2	1.73	1.15	0.90	1.0
Acceptance value	2.0	2.5	2.3	2.9	6.0	5.7	2.4	2.5

CONCLUSIONS

Single formulae were successfully developed for the manufacture of hard gelatin capsules and film coated tablets. The concept was applied to drugs covering a wide range of dose and solubility characteristics. The manufacturability of the products was demonstrated with satisfactory physical test results and content uniformity. The *in-vitro* performance between capsules and film coated tablets also was proven similar with comparative dissolution profiles.

REFERENCES

1. Drug @ FDA - FDA Approved Drug Products http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu; accessed July 7, 2008.

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First published 11.2008

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