Narrowing the gap between clinical capsule formulations and commercial film-coated tablets

Based on formulation simplicity and blinding capability, hard gelatin capsules are preferrable compared with other oral solid dosage forms, including tablets, in the early clinical phases of drug development. However, as a result of economic and other marketing considerations, most oral solid dosage forms on the market today are tablets. The authors suggest that time could be saved in formulation development if relatively simple, common formulations, suitable for use in both capsule and tablet dosage forms, can be developed in the preclinical phase. Four case studies, with formulae containing model drugs of varying dose and water solubility, were developed to illustrate the concept.

In each case, comparative dissolution profiles of capsules and corresponding uncoated and film-coated tablets showed equivalence *in vitro*.

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The goal of early clinical trials is to establish the safety and proof-of-concept efficacy of a new API.[1] Limited amounts of the API and aggressive development timelines, however, often force formulators to develop simple hard gelatin capsule formulations for early-phase clinical use;[2] the composition of which could be the API alone, or a simple powder blend of the API and a filler. Not only are they useful for simplifying formulations, hard gelatin capsules are also useful for masking the taste and odour of the active blend as well as for blinding marketed products. The positive comparators can easily be blinded as tablets-in-capsules or capsule-in-capsules.

While hard gelatin capsule formulations for early-phase studies have many desirable features, they are not commercially viable most of the time.[3,4] The reason for this is that the manufacture of early clinical formulations cannot usually be transferred to large-scale production equipment and, as such, the development of a second drug product for late-phase clinical studies that can be manufactured on a large-scale and is chemically compatible, stable and bioavailable, is necessary. Based on economic and certain marketing considerations, tablets are most often formulated for late-stage clinical trials and commercialization; they are more tamper-resistant than hard gelatin capsules and may be compressed

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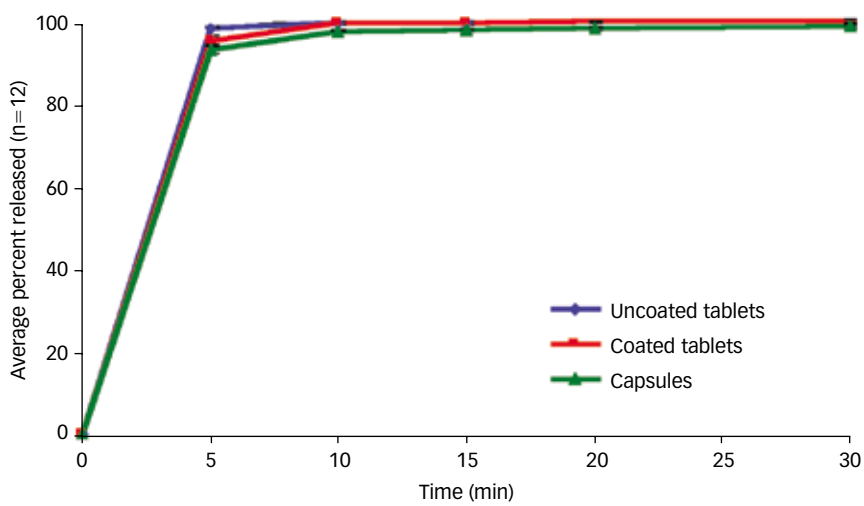
in a myriad of shapes. Tablets are preferentially film coated to obtain a vast array of aesthetic images and these film coatings may also provide a vehicle for anti-counterfeiting measures (brand security), brand identification, functional characteristics such as odour, oxygen and moisture vapour barriers, and enhancing ease of swallowing. The preference for tablets is borne out by approval statistics from the FDA: from 1996 through to 2006, a total of 10139 tablets and 2700 capsules were approved by the FDA, which corresponds to an approximate 4:1 preference of tablets versus capsules.[5]

The Capsule-to-Tablet formulation concept, owned by Colorcon Inc. (PA, USA), is proposed to reduce the amount of work required to develop capsule and tablet formulations. Ideally, the same formulation would be used in capsules for early clinical phases and, subsequently, in tablets for commercialization. As the excipients are identical, the stability of the clinical capsule formula and commercial tablets should be similar. By using a common formulation, the amount of excipient compatibility testing can be reduced, which would lead to corresponding decreases in analytical testing and report writing. Realizing that the amounts of APIs may be very limited, it is suggested that starting Capsule-to-Tablet formulations be developed based on model drugs that have the same dose and solubility characteristics of the APIs if they are in short supply.

The feasibility of the Capsule-to-Tablet concept was initially demonstrated using cyclobenzaprine hydrochloride as a model drug.[6] The objective of the present study was to further support this concept by extending the work to four different model drugs of varying dose and solubility. All the products were tested for their physical properties, content uniformity and dissolution profiles to demonstrate the similarity in product performance between capsules, uncoated tablets and film-coated tablets.

Figure 1: Comparative dissolution profiles of theophylline capsules, uncoated tablets and film-coated tablets (deionized water).



Experimental design

Formulation and materials

Four model drugs were selected to represent actives of varying solubility in water. The model drugs and their solubilities in water (mg/mL USP water solubility classification) were:

- amlodipine besylate (3.2; slightly soluble)
- theophylline (7.4; slightly soluble)
- caffeine (22; sparingly soluble)
- gabapentin (>100; freely soluble).

The equivalent volume mean particle diameters (D[4,3]) of the model drugs were 33.6, 81.62, 8.82 and 187.2 μm for amlodipine besylate, theophylline, caffeine and gabapentin, respectively. For the purposes of this study, the doses of the drugs selected were illustrative and not necessarily representative of the actual recommended dose. The compositions and characteristics of the four Capsule-to-Tablet formulae are listed in Table 1.

Table 1: Compositions of capsule-to-tablet formulae.

Formula ID (Source of drug substance)	Ingredient percentage				
	Active	Starch-based excipient	Microcrystalline cellulose	Colloidal silicon dioxide	Magnesium stearate
Amlodipine besylate (Cadila Pharmaceuticals)	3.47	48.04*	48.04	0.25	0.20
Theophylline (Spectrum Chemicals)	40.00	29.75*	29.75	0.25	0.25
Gabapentin (Kemprotec Ltd)	40.00	17.93**	41.83	------	0.25
Caffeine (Spectrum Chemicals)	34.72	21.68*	43.35	------	0.25

Notes: * Starch 1500 ** StarCap 1500

The formulation principle used in all cases was to provide a simple, cost-effective formulation that would enable the manufacture of both capsules and tablets. The excipients selected were:

- microcrystalline cellulose (Microcel102-SP; Blanver, Brazil) as a dry binder
- a multifunctional, starch-based excipient (Starch 1500 or StarCap 1500; Colorcon)
- colloidal silicon dioxide (Cab-O-Sil M-5P; Cabot, MA, USA) as a glidant
- magnesium stearate (Hyqual, Mallinckrodt; MO, USA) as a lubricant.

Colloidal silicon dioxide was not incorporated in the gabapentin and caffeine blends because the flow properties were satisfactory without it. Magnesium stearate was used at a low level *versus* historical industry practices in all cases as Starch 1500 and StarCap 1500 also have lubricant properties.

Manufacturing processes

Blend preparation

The batch sizes of the formulations described in Table 1 were in the 1.5–3.0 kg range for each trial. The API was blended with all excipients, except magnesium stearate, for 10 min in a twin shell V-blender (PK-Liquid–Solids Blender; Patterson-Kelly Co., PA, USA) and sieved through a 40-mesh screen to ensure good distribution of the materials throughout the powder mixture. Magnesium stearate was passed through a 60-mesh screen before dispensing. In the lubrication step, magnesium stearate was added to the powder mixture and blended for 3 min. The same batch of each formulation was used to produce both filled capsules and tablets.

Roller compaction

The active was blended as above with all excipients except magnesium stearate. The powder mixture was then compacted into hard ribbons on a roller compactor (Alexanderwerk WP120; Alexanderwerk Inc., PA, USA) set at 5 rpm roll speed, 30 bar roll pressure, 36 rpm feed screw speed and 2 mm roll gap. The ribbons were milled through a Quadro Comil U5 (Quadro, Canada) set at 1500–2500 rpm impeller speed and using a 0.050–0.079 in. grater screen. The resulting granules were then mixed with magnesium stearate in a V-blender for 3 min.

Encapsulation

Encapsulation was conducted on a tamp-filling machine, In-Cap (Dott. & Bonapace C., Italy), set up for hard gelatin shells size #0 to #3 (Capsugel, NJ, USA), with a dosing disc of 15.5–20.5 mm thickness depending on the target capsule fill weight. The encapsulation speed was set at #1 setting with a throughput of 1500 capsules/h.

Tabletting

The final blends were compressed on a 10-station, instrumented Piccola tablet press (SMI, NJ, USA). A compression speed of 30 rpm was set for all compression runs. Standard, round, concave punch tooling with varying diameters depending on the target tablet weight was used.

Film coating

All tablets were coated to a 3% weight gain in a Compu-Lab (Thomas Engineering Inc., IL, USA), equipped with a 15-in., side-vented, fully perforated coating pan and a VAU spray gun (Spraying Systems Ltd, UK) containing an antibearding nozzle (1.0 mm inner diameter), with Colorcon's film coating formula Opadry II 85F18422 white at 20% solids concentration.

Physical and analytical test methods

Particle size analysis of model drugs

Particle size analysis of the model drugs was conducted using a Malvern Mastersizer-S (Malvern, UK) particle size analyser equipped with a 300RF lens and a MS-1 small volume sample dispersion unit. Approximately 100 mg of sample was placed in a 50 mL glass beaker. A small volume of dispersant (0.2% w/v of Span-85 in hexane) was added to sufficiently wet the sample, which was then mixed to make a slurry with a spatula. An additional 20 mL of dispersant was added and mixed to begin dispersion. The sample was sonicated using an ultrasonic bath for 5 s and aliquots of the sample were transferred to the MS-1 until an obscuration of 10–30% was achieved. The sample recirculated in the MS-1 at 1500 rpm for 1 min prior to analysis. The particle size distribution was calculated using the polydisperse model and the refractive indices were recorded.

Analysis of the final blends

The particle size distribution of the final blends was determined on an ATM Sonic Sifter (Sepor Inc., CA, USA) (5-min test time, amplitude 4, sift-pulse mode) using a sample size of 10 ± 0.1 g. The bulk and tapped densities were determined in accordance with USP Method 1.[7] The geometric mean diameters and standard deviations of the blends were calculated based on a weight cumulative frequency–particle size distribution plotted on a log-probability scale. The mass flow rates of the blends were measured on a Sotax FT 300 powder flow tester (Sotax, PA, USA), and the Loss on Drying (LOD) was measured with a Denver Instrument IR-200 (Denver Instrument, CO, USA) moisture balance set at a temperature of 105 °C.

Physical and dissolution testing of capsules and tablets

Capsules and uncoated tablets were checked for weight variation using an Erweka Multicheck (Erweka, Germany). The uncoated tablets were also tested for crushing strength (Erweka Multicheck), friability (Vankel, NJ, USA) and disintegration time (Erweka ZT 44). Dissolution profiles were generated for capsules, uncoated and coated tablets for a comparison of product performance. For those model drugs that have a USP monograph, the dissolution test was conducted following the method described in USP XXXI.[8,9] For the non-compendial drugs, the FDA-recommended dissolution method was used instead.

There are two separate USP monographs for theophylline tablets and capsules with identical dissolution methods. However, the specification limits for tablets are different from those for capsules; that is, not less than 80% dissolution released in 45 min for tablets and not less than 80% dissolution released in 60 min for capsules.

Similar to the theophylline products, an identical dissolution method was described in the USP monograph of gabapentin capsules and tablets with different specification limits. The tolerances are NLT 80% dissolution of the labeled amount of active dissolved in 20 and 45 mins for capsules and tablets, respectively.

A monograph for caffeine tablets or capsules as a single active product is not currently listed in the USP XXXI. However, the monographs of several combination products that contain caffeine are posted in the USP that can be used as references. In this study, the USP dissolution method for acetaminophen/caffeine combination tablets was utilized for analysing caffeine tablets and capsules. The USP specification limits for acetaminophen/caffeine tablets are not less than 75% dissolution of the label claim of acetaminophen and caffeine to be released in 60 mins.

The dissolution method for amlodipine besylate tablets is not currently posted in the USP XXXI monographs. The dissolution test for the uncoated and coated tablets was performed following recommendations from the FDA.[10] The content uniformity test was conducted 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 (Pharmaceutical Forum: Volume No. 32(3)).

Results and discussion

Amlodipine besylate, theophylline and gabapentin tablets were all readily produced *via* direct compression. StarCap 1500 rather than Starch 1500 was used in the gabapentin formulation, because gabapentin was poorly compressible, and the corresponding formulation required the additional compactibility provided by StarCap 1500. The caffeine formulation was processed by roller compaction prior to encapsulation or tableting because the flow properties were poor. The use of roller compaction enabled the formation of larger, more flowable particles than could be obtained from simple dry blending alone.

Properties of final blends

The properties of the final blends are provided in Table 2. Because the caffeine blend was processed *via* roller compaction, a larger average particle size was obtained *versus* those of the direct compression blends. All four blends had comparable Carr compressibility indices[11] in the 25–30% range. The dynamic flow properties of the blends were also evaluated using a Sotax powder flow tester, with which the flow was characterized by the amount of powder blend passing through a fixed aperture of a funnel in a unit of time. The flow rates of the blends were 4.7 g/s–6.8 g/s, which were indicative of good flow.

Properties of uncoated tablets

Tablet weight variation was low, with average tablet weight in the 99.5–101.4% range of the target weight and low relative standard deviation (RSD) of <1.1% for each tablet type. The tablets had high crushing strengths and low friability values of <0.1%, indicating that the cores were sufficiently robust to withstand the mechanical forces of the film-coating process.[12]

Figure 2: Comparative dissolution profiles of gabapentin capsules, uncoated tablets and film-coated tablets (0.06 N HCl).

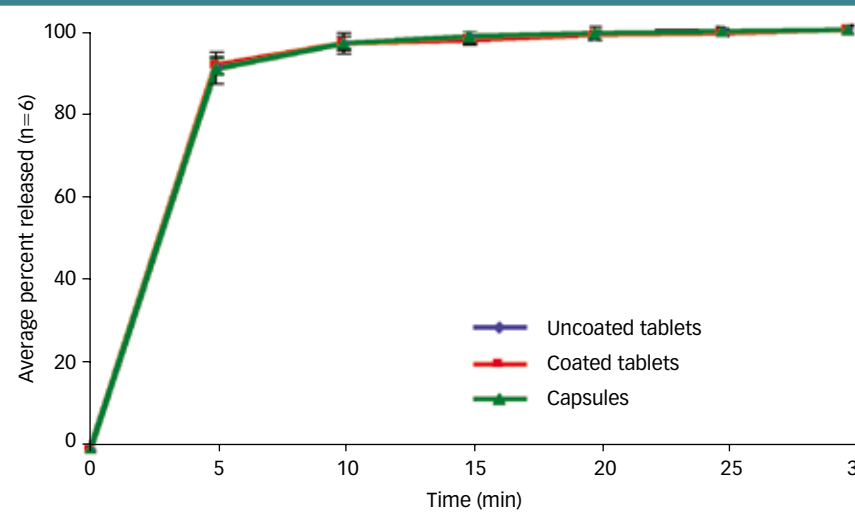


Table 2: Content uniformity of capsules and film-coated tablets.

Statistics (n=10)	Amlodipine b.		Theophylline		Gabapentin		Caffeine	
	Capsules	Tablets	Capsules	Tablets	Capsules	Tablets	Capsules	Tablets
Average potency assay (%)	102.2	98.5	99.1	101.2	103.2	104.4	101.3	98.3
Minimum potency assay (%)	100.7	96.2	97.9	99.2	100.9	102.4	99.8	96.2
Maximum 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	2.8	2.5	2.3	2.9	6.0	5.7	2.2	2.6

Note: Potency assay values expressed as percent (%) of target drug concentration.

All tablets had low ejection forces during compression, demonstrating that the blends were well lubricated by the magnesium stearate and the starch-based excipients.

Properties of capsules

The weights of the empty shells and filled capsules were used to calculate the variation statistics of the capsule fill weight. The individual capsule fill weights were calculated by subtracting the average weight of empty shells from the weights of individual filled capsules. Low RSDs of <2.3% and low spreads of <5% of the means provided strong evidence of satisfactory flow properties of the blends and good uniformity of capsule fill weights throughout the runs.

Content uniformity of capsules and film-coated tablets

The drug content uniformity was tested to ensure the uniformity of active concentration in the finished products. This was particularly important for the amlodipine besylate formula, where a low concentration of active (3.47%) was used. The arithmetic mean and RSD were calculated from individual potency assay results for all capsules and film-coated tablets. All the capsules and tablets passed the content uniformity test against the acceptance value criteria specified in USP XXXI — Uniformity of Dosage Units General Chapter <905>, where an acceptance value of <15> is required. The satisfactory results generated from the physical and content uniformity testing confirmed the acceptable manufacturability of the formulae.

Dissolution of capsules and film-coated tablets

Capsules, uncoated tablets and film-coated tablets were tested for comparative dissolution performance (Figure 1 and Figure 2). For all model products, complete release of the active in all three dosage forms (capsules, uncoated tablets and film-coated tablets) was achieved at the 10-min test point, which was in compliance with the specified dissolution limits for the corresponding commercial drug products. While the dissolution profiles of the three dosage forms for each model drug were very similar in all cases, profile comparisons for rapidly dissolving drug products, with more than 85% dissolved in 15 min or less, are not required by the FDA for post-approval changes and biowaivers.[13]

Conclusions

The feasibility of developing common formulations suitable for both capsules and tablets was demonstrated with four model drugs of varying dose and water solubility. The formulations have all the properties required for the manufacture of hard gelatin capsules and tablets, and satisfactory content uniformity was achieved in all cases because of the good flow properties of the blends and minimal segregation of the actives during processing. In all cases, the *in vitro* dissolution profiles of capsules, uncoated tablets and film-coated tablets were similar with complete release of the model drug in the first 15 mins of the dissolution test. The development of a common formulation for capsules and tablets, ideally by formulating with the API or with a model drug having similar characteristics to the API if the API is in short supply, may save considerable time in the development of a commercially viable dosage form. **PTE**

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Article Excerpted from ©May 2009 issue of
Pharmaceutical Technology EUROPE
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