

The Effect of Overencapsulation on Disintegration and Dissolution

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Abstract

Overencapsulating tablets can provide several benefits such as maintaining blinding during clinical trials. Scientists have wondered, however, whether the technique affects tablets' in vitro or in vivo disintegration or dissolution. The authors examined the disintegration and dissolution profiles of propranolol and rofecoxib tablets overencapsulated with standard hard-gelatin capsules and with capsules specifically designed for double-blind clinical trials.

Keywords

Hard-Gelatin Capsules, DBcaps capsules, BCS Classes 1 and II, Encapsulation, Dissolution, Double-Blind Dosing, Clinical trials

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1. Introduction

In the past decade the number of comparative clinical trials has increased considerably. Overencapsulation, (i.e., encapsulating tablets in hard-gelatin capsules) is used as a quick and low-cost technique to blind investigators and volunteers in a clinical study and to meet the challenging timelines for providing clinical material. Overencapsulation eliminates the need to outsource a matching placebo and complex double-dummy study design. Although standard hard-gelatin capsules (HGCs) are widely used for overencapsulation of materials in double-blind clinical trials, they might not always provide the features required for the clinical-trial design and comparator products.

DBcaps, two-piece hard-gelatin capsules designed for double-blind clinical trials, were developed to overcome these limitations for certain trials. Each capsule body is completely covered by the elongated design of the cap. This design makes it virtually impossible to open the capsule without causing clearly visible damage, thereby alerting investigators of blind breaking and bias. The wide diameter of DBcaps capsules contains several shapes and sizes of tablets relatively easily while the short length facilitates ease of swallowing. Whole tablets can be filled directly into DBcaps capsules without needing to be broken or ground, thus eliminating concerns about inaccurate dosage or modification of the drug's intended performance. Standard two-piece HGCs also can be used for blinding tablets for clinical trials, but their smaller diameter (compared with that of DBcaps capsules) limits the size of tablet that can be filled into the capsule.

It is legitimate to ask whether overencapsulation can affect dissolution, absorption, or bioavailability in clinical trials. In comparative pharmacokinetic trials, overencapsulating an esomeprazole multiple-unit-pellet-system with HGCs did not influence the rate (C_{max}) or extent of absorption in a study involving 49 volunteers¹. Other *in vivo* studies have shown the equivalence of *in vivo* disintegration time using gamma scintigraphy and therapeutic-effect onset time between encapsulated and nonencapsulated sumatriptan tablets². Although some studies have shown that overencapsulation may not affect *in vitro* dissolution studies, it could delay the absorption and *in vivo* efficacy of drugs that are intended to have a fast onset of action.


This delay was demonstrated in an open-trial design in which patients scored a migraine drug's response to headache pain³. Dissolution could also be affected by low capsule-fill weight, type of filler, and drug solubility^{4,5}. Using the right capsule size and excipients (or backfill) similar to those in the tablet formulation could reduce the effect on dissolution. The solubility of the drug should be factored into the blinding trials. This article focuses on overencapsulation's effect on disintegration and dissolution.

Propranolol, a highly soluble, highly permeable, Biopharmaceutics Classification System (BCS) Class I chiral drug marketed as a racemic mixture, exists in two polymorphs. Crystallization solvents, grinding, and compression have can cause change in the crystalline state and, thus, differences in dissolution performance^{6,7}. Although propranolol is not hygroscopic, the presence of moisture in the backfill could cause interparticle surface interaction that could affect the performance of the encapsulated tablet. Rofecoxib, a low-solubility and high-permeability BCS Class II drug, is susceptible to oxidation and photolysis⁸. The influence of moisture on the disintegration and dissolution of the encapsulated tablets has not been studied for either class of drugs.

The model-independent similarity factor (f_2) may be used to compare the dissolution profiles of two drug products (see Equation 1). This equation measures the similarity in the percent dissolution between the two curves. An f_2 greater than 50 implies that two dissolution profiles are similar⁹. The US Food and Drug Administration recommends using only one sample beyond 85% dissolution because the value of f_2 is sensitive to the number of sampling points used in the following equation^{10,11}:

$$\text{Eq. 1: } f_2 = 50 \times \log\left\{1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2\right\}^{0.5} \times 100\}$$

in which R_t and T_t are dissolution values of the reference and test batches, respectively, at time t , and n is the number of points. The dissolution profiles can be determined using the traditional approach of high-performance liquid chromatography (HPLC) or the data can be acquired in real time using a fiber-optic diode-array probe or system (FOPS). Bijlani and Adeyeye used the latter method to monitor the dissolution of a multiparticulate ibuprofen system. They found that it was much faster and more accurate than the HPLC method¹².



The objective of the study was to investigate the effect of overencapsulating on the *in vitro* disintegration and dissolution of tablets of a BCS Class I drug (i.e., propranolol) or Class II drug (i.e., rofecoxib). The authors compared DBcaps capsules with HGC, in the presence or absence of backfill. The authors performed dissolution using the Delphian FOPS method and examined the long-term stability of the overencapsulated products.

2. Materials and Methods

2.1. Materials

Propranolol hydrochloride, *US Pharmacopeia* tablets (blue color), 20 mg, and rofecoxib (Vioxx) tablets (yellow color), 25 mg, were purchased from Pliva (East Hanover, NJ), and Merck & Co. (Whitehouse Station, NJ), respectively. DBcaps capsules (DBcaps Size B) and standard gelatin capsules (HGC size 00) were supplied by Capsugel (Peapack, NJ). Microcrystalline cellulose (Avicel PH102) was donated by FMC Biopolymer (Philadelphia), and Foremost Farms (Baraboo, WI) supplied anhydrous lactose. A Vankel dissolution apparatus and a Delphian fiber-optic dissolution-monitoring system from Delphian (Woburn, MA) were used.

2.2. Experimental Design

Two blocks of 2 x 2 x 2 randomized full-factorial design were used to determine the effect of three independent parameters. Two levels (i.e., two drug types, propranolol and rofecoxib), two capsule types (i.e., DBcaps and HGC), and two filler levels (i.e., microcrystalline cellulose-lactose 1:1 mixture and no filler) were used in the design.

2.3. Capsule Backfilling

A predetermined weight of a 1:1 physical mixture of anhydrous lactose:microcrystalline cellulose was filled into the capsule body. The tablet was placed on the backfill, and the capsule cap was snapped on to lock in place. When backfill was not required, only the tablet was filled into the capsule.

2.4. Weight Variation

Twenty capsules from each batch were weighed, and the average weight, standard deviation, and percent relative standard deviation (RSD) were computed. To

remove bias, the hand filling of the capsules was blinded from the analyst who conducted the weight-variation experiment. The samples were also coded.

2.5. Disintegration Test

A Vankel disintegration apparatus, running at 30 dips per minute (dpm), and simulated gastric fluid (pH 1.2) without pepsin was used for the disintegration test. Two randomly selected capsules from a batch were tested at a time. This was repeated three times, making a total of six capsules from each batch. The average disintegration (D-time) was computed. Two capsules were run at a time to allow a video camera (MDS 100, Kodack, Rochester, NY) to capture the process of capsule disintegration.

2.6. Dissolution Analysis

The Vankel dissolution apparatus and Delphian RAINBOW dynamic dissolution-monitor system, consisting of six photodiode-array probes with a cell length of 10 mm, were used. Simulated gastric fluid (pH of 1.2) without pepsin, degassed at 40°C, was used as the medium at 37°C.

A spectrophotometric linearity test was performed to test each individual probe for linearity and reproducibility. Using the blank dissolution medium, the fiber-optic system first acquired the 100% transmittance. This step was followed by calibration, which involved collecting the transmittance from three replicates of six standard solutions. The percent difference and percent RSD were calculated, and the linearity was determined.

The dissolution of propranolol was determined using the USP Apparatus I (or basket method) at 50 rpm in 900 mL of simulated gastric fluid. A filtered solution of 20 mg propranolol in 900 mL of simulated gastric fluid was used as the standard. Peak absorbance wavelength and baseline correction wavelength were 288 nm and 370 nm respectively.

For rofecoxib, the USP Apparatus II (or paddle method) was used at 50 rpm in 900 mL of simulated gastric fluid. A filtered solution of 25 mg of rofecoxib in 900 mL of simulated gastric fluid was used as the standard. The peak absorbance wavelength and baseline correction wavelength were 268 nm and 370 nm, respectively. Replicates of eight batches were tested making a total of 16 runs.

2.7. Statistical Analysis

The f_2 similarity factor (see Eq. 1) was used to compare the dissolution profiles. Six and 16 time points were used for propranolol and rofecoxib, respectively, because of differences between the two drugs' dissolution rates. When comparing the dissolution profiles for encapsulated and unencapsulated tablets, the data were normalized for a lag time of 2 min¹³. The significance of individual parameters' effects and their influence on disintegration time and dissolution were determined using a least-squares regression model (p -value < 0.05).

3. Results and Discussion

3.1. Weight Variation

The weights of the samples showed no randomness because the contributors to the total sample weight (i.e., drug weight, capsule weight, and filler weight) were fixed with fairly little variation from the mean of the individual parameters. This uniformity was reflected by the low percent RSD (0.49 – 1.31%) that indicated that the process of encapsulation had been accurate and efficient. Rofecoxib had a higher overall weight because the original average weight (200 mg) of the tablets was higher than that of propranolol (110 mg).

3.2. Disintegration

A review of the video of the process of capsule disintegration did not reveal any differences between DBcaps and standard gelatin capsules. On average, the capsules ruptured after 60 s; the range of the lag was 34 s to 70 s.

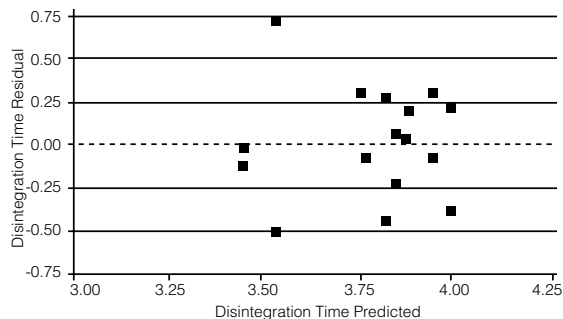


Fig. 1. Residual plot of observed and predicted disintegration times.

Some of the capsules did not rupture; instead the capsule cap separated from the body, thus exposing the content to the medium. The individual parameters (i.e., capsule type, drug type, and filler) showed no effect on D-time (see Table 1). The effects of interactions between parameters on disintegration time also were not significant.

The D-time for rofecoxib was slightly higher than that for propranolol, possibly because of its lower solubility; the average D-times were 3.82 ± 0.28 min and 3.69 ± 0.44 min, respectively. Comparing the capsule effect, the average D-times were 3.85 ± 0.28 min and 3.67 ± 0.43 min for DBcaps and standard gelatin capsules, respectively. These differences were not statistically significant, however ($p = 0.05$). In the case of the filler, average D-times were 3.75 ± 0.36 min and 3.77 ± 0.39 min for presence and absence of filler, respectively. These times indicated that the filler had no effect on disintegration time.

Table 1.

Significance of the effects of individual parameters and their interaction on disintegration time, irrespective of capsule type.

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Drug	1	1	0.072900	0.4382	0.5246
Capsule	1	1	0.119025	0.7155	0.4195
Drug and Capsule	1	1	0.297025	1.7856	0.2143
Filler	1	1	0.000225	0.0014	0.9715
Drug and Filler	1	1	0.030625	0.1841	0.6780
Capsule and Filler	1	1	0.000900	0.0054	0.9430

Note: DF is degrees of freedom, F ratio is F-statistic for testing that the effect is zero, and Nparm is the number of parameters associated with the effect.

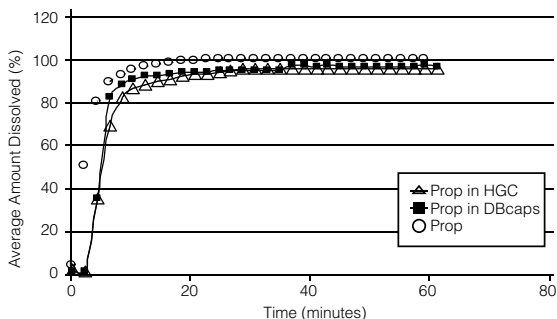


Fig. 2. Dissolution profiles of propranolol tablets (prop) alone, in hard-gelatin capsules (prop in HGC), and in DBCaps capsules (prop in DBCaps).

As expected, the D-time for encapsulated tablets was greater than that for plain tablets. D-times for unencapsulated tablets were 1.80 min and 1.93 min compared to 3.69 min and 3.82 min for the overencapsulated propranolol and rofecoxib tablets, respectively. This difference resulted from the time lag required for the capsules to rupture and expose their content to the disintegration medium. All the samples passed USP specification of D-time of less than 30 min. The residual plot (see Figure 1) was random without any trend, thus indicating that the parameters had no effect on disintegration time.

3.3 Dissolution

All the six Delphian fiber-optic probes had good linearity (the range of R^2 was 0.986-0.998, where R^2 was the coefficient of determination) for propranolol and rofecoxib. The time taken for 80% of the drug to dissolve (T_{80}) also

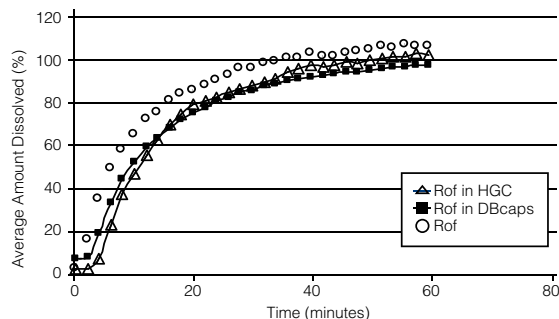


Fig. 3. Dissolution profiles of rofecoxib tablets (Rof) alone, in hard-gelatin capsules (Rof in HGC), and in DBCaps capsules (Rof in DBCaps).

was used to compare the results of dissolution profiles statistically. The significance-of-effects table (Table 2) showed that the drug had an effect on T_{80} ($p < 0.0001$). Although the interaction between drug and capsule appeared significant ($p = 0.0219$), this significance is of no consequence for formulation because the drugs belong to two different BCS classes.

The effects of the filler ($p = 0.5716$) and type of capsule ($p = 0.7614$) were not significant. The average T_{80} times were 14.39 min and 13.80 min for presence and absence of filler, respectively. The differences were not statistically significant. The same weight of backfill was used for all capsule types although the DBCaps size B capsules were smaller in volume than HGC size 00 capsules. Differences in T_{80} for the two capsule types were not significant, thus the volume of the fill did not have an effect on dissolution profile.

Table 2.

Significance of the effects of individual parameters and their interaction on dissolution T_{80} , irrespective of capsule type.

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Filler	1	1	1.3631	0.3447	0.5716
Capsule	1	1	0.3875	0.098	0.7614
Drug	1	1	838.8264	212.1287	<0.0001
Drug and Capsule	1	1	30.2775	7.6568	0.0219
Capsule and Filler	1	1	6.4643	1.6347	0.2330
Drug and Filler	1	1	0.5006	0.1266	0.7302

Note: DF is degrees of freedom, F ratio is F-statistic for testing that the effect is zero, and Nparm is the number of parameters associated with the effect, and T_{80} is the time taken for 80% of the drug to dissolve.

3.31 Similarity Factor (f_2)

The dissolution profiles were also compared using the f_2 similarity factor. A lag time of 2 min was observed in the dissolution profiles of encapsulated and unencapsulated tablets, and it was incorporated into f_2 computations¹³. An f_2 greater than 50 indicates that two dissolution profiles are similar. Propranolol attained a dissolution plateau faster than rofecoxib because of differences in the drugs' solubilities in the dissolution medium. For propranolol tablets, the f_2 between standard gelatin and DBcaps capsules was 60.67, thus indicating that the dissolution curves of the two were similar (see Figure 2). The f_2 between unencapsulated propranolol tablets and DBcaps capsules was 59.48. The f_2 between unencapsulated propranolol tablets and standard gelatin capsules was 53.94. The similarity factor between rofecoxib tablets encapsulated in DBcaps and HGC capsules was 62.48 (see Figure 3). The f_2 between unencapsulated rofecoxib tablets and DBcaps capsules and that between unencapsulated rofecoxib tablets and standard gelatin capsules were 56.97 and 54.92, respectively.

3.4 Long-term Stability

After storing the encapsulated tablets at room temperature and humidity conditions for one year, the authors found no differences in the dissolution profiles of propranolol and rofecoxib tablets encapsulated using DBcaps or standard gelatin capsules. This observation implies that the double-walled DBcaps capsules could be used for blinding drug candidates for a clinical study.

4. Conclusion

Although encapsulation resulted in a lag time of 2-3 min in disintegration compared with the unencapsulated tablets, the disintegration and dissolution of propranolol and rofecoxib were the same whether tablets were encapsulated in DBcaps capsules or standard gelatin capsules. It can thus be expected that *in vitro* drug release will not be influenced by the type of capsule used for overencapsulation in the double-blind clinical study. The bioequivalence between the unencapsulated and encapsulated tablet is not inferred in this study; however, the *in vivo* disintegration data of unencapsulated and overencapsulated tablets reported by Wilding et al. suggest that the *in vitro* disintegration lag time is negligible *in vivo*².

Nevertheless, it is important to use DBcaps capsules for test and comparator dosage forms to correlate *in vitro* data, especially for the highly soluble drugs (e.g., those of BCS Class I). The presence or absence of backfill had no significant effect on disintegration or dissolution. In effect, capsules offer an easy and inexpensive way of blinding clinical trials and pose no threat to studies that compare the performance of two drugs. DBcaps-type capsules allow for the overencapsulation of tablets with large diameters and make blind breaking in clinical trials virtually impossible.

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