Dissolution of a Phosphate Prodrug from Hard Gelatin Capsules: A Case Study

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OBJECTIVE

To compare dissolution of a phosphate prodrug from three capsule shell types.

BACKGROUND

Clinical studies often include an active comparator (an active control) in the specific study design. The respective design compares the standard therapy (comparator) to the test treatment. In the context of solid oral dosage form and in order to provide for patient blinding, overencapsulation of both comparator and test treatment dosage forms has become common place. Hard gelatin capsules, both standard and “double blind” varieties, are used to overencapsulate tablet and capsule dosage forms. In some cases chemical compatibility between one or more components in the comparator or test tablet and the gelatin capsule shell has not been established. Since the overencapulsated comparator and test tablet represent a new dosage form, the two groups are put on stability to support the duration of the clinical study. Stress storage at accelerated conditions (e.g. high heat and humidity) have been known to facilitate a chemical reaction between gelatin shell and/or active pharmaceutical ingredient and excipients (1). In this case study, an overencapsulated phosphate prodrug, which was found to liberate free formaldehyde as one of its degradants, presented an issue of impaired dissolution performance upon stressed stability storage. Two alternative capsule shells were presented as options, and the resulting dissolution performance is presented here.

MATERIALS AND METHODS

Materials

- Active Tablet: Phosphate pro-drug
- Microcrystalline Cellulose (FMC Corporation, Avicel PH102)
- Lactose Monohydrate (Foremost Farms, Fast Flo® 316)
- Gelatin Capsule (Capsugel, Inc., ConiSnap® size 00 clear)
- HPMC Capsules (Capsugel, Inc., V-Caps®, size 00 white opaque)
- NP Capsules (Capsugel, Inc., size 00 white opaque)
- Formalin Solution (Aldrich; 37% w/v)

Analytical Equipment

- Disintegration Apparatus: VanKel 35-1400
- Dissolution Equipment: Hanson SR8+ Test Station
- HPLC: Hitachi L-7000

Analytical Methods

- Apparatus II, 0.1N HCL, 50 rpm, 10 mL sample size
- Column: Atlantis DC18, 3 micron, 4.6 x 100 mm
- Mobile Phase: 60% 10mM sodium acetate buffer 40% acetonitrile
- Column/Autosampler Temperature: 30°C/4°C
- Flow rate: 1mL/min. Injection volume: 10 mL
- Detection: UV, 260 nm. Run time: 10 min.

Formulation Rationale/Experimental

An API (X), possessing two phosphate ester linkages, was formulated with lactose monohydrate, pregelatinized starch, croscarmellose sodium, talc, and magnesium stearate. Initial development batches of tablets which were overencapsulated with gelatin capsules led to observation of capsule crosslinking, when the overencapsulated tablets were stored at 40°C/75% RH in HDPE bottles. As a preliminary experiment, gelatin, HPMC, and NP capsules were exposed to formaldehyde gas inside a glass desiccator (Figure 1). Six capsules of each type were placed on an aluminum screen inside the desiccator and 10µL of formalin solution introduced into the desiccator. Capsules were exposed for 24 hours and removed from desiccator. All 18 capsules were filled with 300 mg of 0.5% (w/w) FD&C Yellow #10 Lake in microcrystalline cellulose. Disintegration times were obtained for the three groups as well as control groups from each capsule type.

HPMC and gelatin were evaluated side by side in an overencapsulation study (Table 1). As a negative control, gelatin capsules were backfilled with lactose because lactose was in the tablet formulation. HPMC capsules were manufactured with and without backfill. Dissolution (DI water) was performed on all groups at T=0 and at T=6 days, after storage at 40°C/75% RH in HDPE bottles. The planned pull at T=10 days was halted due to stability issues of the drug in DI water. A subsequent study (results shown here) was conducted using 0.01N HCl as dissolution media.

A second overencapsulation study comparing NP (pullulan) capsules to gelatin capsules was conducted (Table 2). NP capsules were manufactured with lactose or MCC backfill. Dissolution (0.01N HCl) was performed on each group at T=0, 5 days, 11 days, and 31 days, after storage at 40°C/75% RH in HDPE bottles.

TABLE 1 -HPMC/Gelatin Capsule Overencapsulation Study

Group	Capsule	Filler
1	Gelatin	Lactose
2	HPMC	MCC
3	HPMC	none

TABLE 2 -NP/Gelatin Capsule Overencapsulation Study

Group	Capsule	Filler
1	Gelatin	Lactose
2	NP	MCC
3	NP	Lactose

RESULTS

Simulated Capsule Stressing Experiment

FIGURE 1 –Chamber used to 'stress' hard gelatin capsules

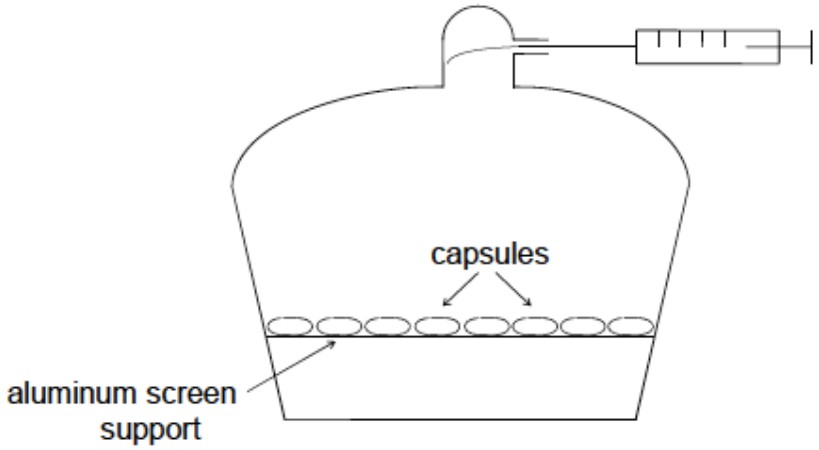
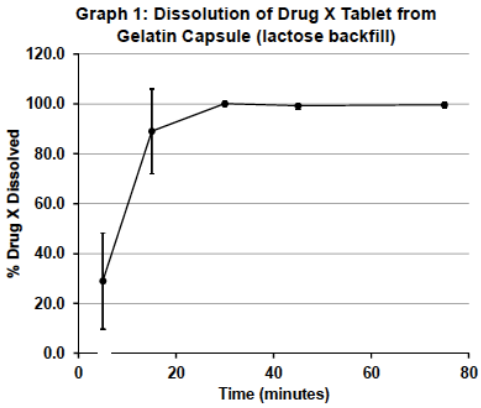


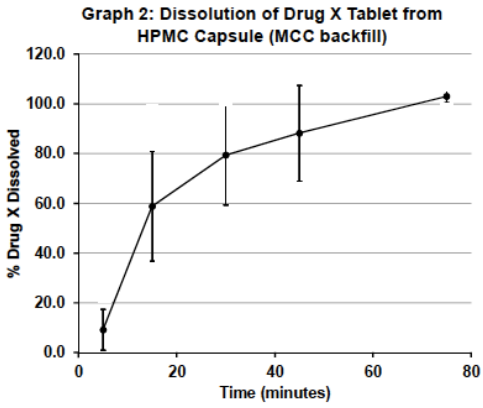
TABLE 3 –Dissolution of Drug X from Capsules (DI water at 37°C)

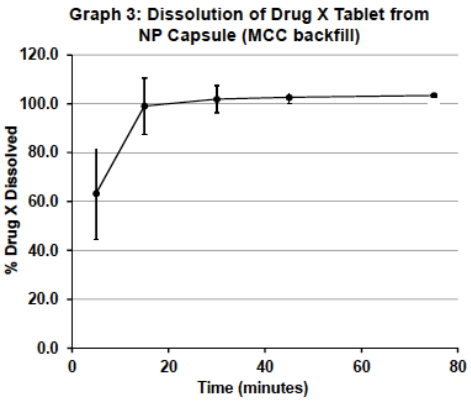
Sample	Disintegration Time (minutes)	Comments
Gelatin (control)	1.5	DT beganat 1.5 minutes; all capsules swelled/melted
HPMC(control)	3.5	DT beganat 1.5 minutes; all capsules swelled/melted
NP(control)	1.0	Capsulesburst around 1 minute and had dissolved within 5 minutes
Gelatin(stressed)	Didnot disintegrate	1capsule leaked at 8 minutes; at 20 minutes, shells still intact
HPMC(stressed)	3minutes	Allsix capsules ruptured at three minutes and at six minutes, shells were dissolved.
NP(stressed)	50 seconds	Allcapsules ruptured within 50 seconds; at five minutes, shells were dissolved.

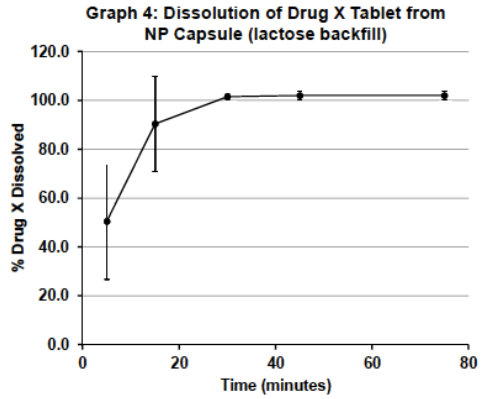
Overencapsulation Studies (0.01N HCl dissolution medium)

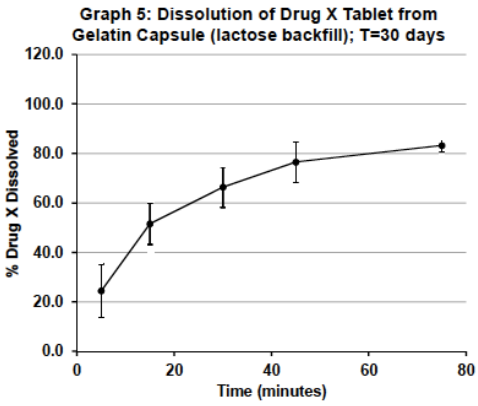
Graphs 1 through 6 show dissolution of an overencapsulated tablet (drug X) using three different capsule types. Error bars are 1 standard deviation unit, with each point being the average of six vessels.

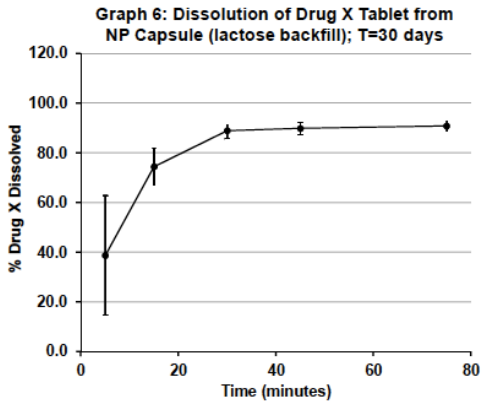












DISCUSSION AND CONCLUSIONS

Based on observations that Drug X, when placed inside a gelatin capsule, showed impaired dissolution after stress storage at 40°C/75% RH (3 months), it was theorized that one of the related substances given off by the tablet on stability was a low molecular weight aldehyde. As aldehydes are known to crosslink gelatin (1), a preliminary experiment was conducted to demonstrate the effect of formaldehyde on three different capsule shell types: HPMC, pullulan (NP), and gelatin. Twenty four hours incubation of each capsule type in a chamber in which formaldehyde was introduced was enough to impair the disintegration of the gelatin capsules (Figure 1 and Table 3). Both HPMC and NP were unaffected.

Since initial clinical data was obtained using Drug X inside a gelatin capsule, with lactose backfill, the 'control' group in all studies used that formulation. The initial study was conducted using the three capsule types and two different fillers (MCC and Lactose; Graphs 1 and 2). Preliminary dissolution results of drug X from HPMC capsules, conducted in 0.01N HClmedia, ruled out the use of HPMC as a backup to gelatin (Graph 2). The HPMC capsules, V-Caps, used gellangum as the gelling agent. With a pKaaround 3.4, any media at orbelow that, will be render the HPMC insoluble.

The second study with Drug X encapsulated in NP capsules, using either MCC or lactose backfill was compared to the gelatin control group, with respect to dissolution (Graphs 3 and 4, T=0). Stressed capsule dissolution data for gelatin and NP capsules are shown in Graphs 5 and 6, respectively. The standard F2 test was employed to compare respective dissolution profiles at T=0, according to the equation:

$$f_2 = 50 \times \log\{[1 + (1/n)\Sigma_{t=1}(R_t - T_t)^2]^{-0.5} \times 100\}$$

Although using the dissolution profile comparison calculation (F2) was not entirely appropriate given that Drug X is rapidly dissolving (i.e., more than 85% in 15 minutes) (2,3), values at 15 minutes were close enough to 85% to give consideration to this approach. Using five time points (5, 15, 30, 45, 75), it was found that backfilling the NP capsules (containing Drug X tablets) with lactose, compared to gelatin capsules (containing Drug X tablets/lactose backfill) gave an F2 value of 50.6, while backfilling the NP capsules with MCC, compared to the gelatin group, gave an F2 value of 38.8 (Table 4). F2 values between 50 and 100 ensure equivalence of performance of the two groups (4).

TABLE 4 -F2 Dissolution Profile Comparison: NP and Gelatin Capsules

Timepoint (min.)	Mean % Released Gelatin (Lactose backfill)	Mean % Released NP Capsule (Lactose backfill)	$R_t - T_t$	$(R_t - T_t)^2$	$\frac{(R_t - T_t)^2}{5} + 1$	f2
5	29.2	50.5	21.3	453.69	94.98	50.6
15	89.1	90.4	1.3	1.69		
30	100.1	101.5	1.4	1.96		
45	99.3	102.0	2.7	7.29		
75	99.7	102.0	2.3	5.29		
Sum	417.4		29.0	469.92		
Timepoint (min.)	**Mean % Released Gelatin (Lactose backfill**	**Mean % Released NP Capsule (MCC backfill)**	**$R_t - T_t$**	**$(R_t - T_t)^2$**	**$\frac{(R_t - T_t)^2}{5} + 1$**	**f2**
5	29.2	63.3	34.1	1162.81	281.03	38.8
15	89.1	99.1	10.0	100		
30	100.1	101.9	1.8	3.24		
45	99.3	88.2	11.1	123.21		
75	99.7	103.0	3.3	10.89		
Sum	417.4		60.3	1400.15		

It must be noted that at the time of this study, HPMC capsules were available only as V-Caps®. In 2009 Capsugel introduced V-Caps Plus®, which do not employ a chemical gelling agent. Hence, the dependence of solubility on pH has been removed. HPMC capsules, (V-Caps Plus®) as a result, would likely be an option or alternative, in this case.

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