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Development of Near Zero-Order Release Dosage Forms Using Three-Dimensional Printing (3-DP™) Technology

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ABSTRACT Three near zero-order controlled-release pseudoephedrine hydrochloride (PEH) formulations demonstrating proportional release rates were developed using 3-Dimensional Printing (3-DP™) technology. Mixtures of Kollidon SR and hydroxypropylmethyl cellulose (HPMC) were used as drug carriers. The release rates were adjusted by varying the Kollidon SR-HPMC ratio while keeping fabrication parameters constant. The dosage forms were composed of an immediate release core and a release rate regulating shell, fabricated with an aqueous PEH and an ethanolic triethyl citrate (TEC) binder, respectively. The dosage form design called for the drug to be released via diffusional pathways formed by HPMC in the shell matrix. The release rate was shown to increase correspondingly with the fraction of HPMC contained in the polymer blend. The designed formulations resulted in dosage forms that were insensitive to changes in pH of the dissolution medium, paddle stirring rate, and the presence/absence of a sinker. The near zero-order release properties were unchanged regardless of the dissolution test being performed on either single cubes or on a group of eight cubes encased within a gelatin capsule shell. The chemical and dissolution properties of the three formulations remained unchanged following 1 month's exposure to 25°C/60% RH or 40°C/75% RH environment under open container condition. The in vivo performance of the three formulations was evaluated using a single-dose, randomized, open-label, four-way crossover clinical study composed of 10 fasted healthy volunteers. The pharmacokinetic parameters were analyzed using a noncompartmental model. Qualitative rank order linear correlations between in vivo absorption profiles and in vitro dissolution parameters (with slope and intercept close to unity and origin, respectively) were obtained for all three formulations, indicating good support for a Level A in vivo/in vitro correlation.

KEYWORDS Three-dimensional printing, Zero-order release, Multichamber drug delivery system, Diffusion, in vivo/in vitro correlation

INTRODUCTION

For the past two decades, it has been demonstrated by pharmaceutical researchers in the area of drug delivery that zero-order release kinetics can be judged to be favorable for a significant proportion of bioactive agents. Various

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diverse approaches have been proposed to develop zero-order release formulations for compounds of varying solubility in the past. For example, Alza's osmotic pump technology has been extensively used for over-the-counter and prescription products exhibiting extended duration of action (Venkatraman et al., 2000). Drug is released from the osmotic pump device through one or more laser-drilled holes in the outer semipermeable coat. The driving force is generated by osmotic pressure derived from the drug-containing osmotic core (elementary osmotic pump) or the osmotically active polymeric push compartment ("Push-Pull" System) on ingress of water. Because the release kinetics is governed by the osmotic pressure generated within the dosage form, performance is minimally affected by the microenvironmental conditions of the gastrointestinal tract. An alternative system is SkyPharma's Geomatrix, in which tablets are constructed with multiple layers, each with a different rate of swelling, gelling, and erosion, to achieve the desired drug release rate. Consistent release is accomplished by increasing the surface area available for drug release through swelling of the tablet's core region. Other approaches for zero-order or near zero-order release include, but are not limited to, nonuniform drug distribution in a matrix (Scott and Hollenbeck, 1991); swelling/erosion systems combining ionic and nonionic polymers as drug carriers (Rao et al., 1988; Padmalatha-Devi et al., 1989); geometric modification of dosage forms (Narasimhan & Langer, 1997; Qiu et al., 1998; Danckwerts et al., 1998); and modulation of matrix swelling behavior by inclusion of electrolytes (Pillay & Fassihi, 2000).

Notwithstanding the diverse technologies currently available, the development of zero-order sustained release dosage forms has remained a significant challenge to pharmaceutical scientists. The primary difficulties in maintaining a consistent release rate include retardation of the initial dose burst, loss of the driving force to maintain the target release rate within the desirable time course due to the increased path length for drug release, and untimely changes in the properties of polymeric carrier, such as chain relaxation and disentanglement.

Many of the approaches to achieving zero-order release dosage forms are either difficult to manufacture or are overly material sensitive (i.e., linked to the specific interactions between drug and drug carrier system). The pertinent limitation for a material-dependent system is the need for substantial efforts in formulation modification when one active is substituted for another. Hence, a fabrication technology that provides control over dosage form microstructure and flexibility toward application of materials might show promise in effectively eliminating such formulation and fabrication deficiencies.

The 3-DP™ process is a novel fabrication technique based on a solid free-form fabrication (SFF) technology. Dosage forms are fabricated in a layer-by-layer fashion using ink-jet printing technology. The procedure allows precise spatial placement of active within predetermined areas in the dosage form along with other pharmaceutical materials to provide control over the release of active from the assembled structure. The drug release kinetics is determined by the spatial arrangement of the active within the dosage form, the materials used for construction, and the geometry and micro- and macro-architecture of the dosage unit. The application of the technology in release control of dosage forms has been extensively discussed in the literature (Wu et al., 1996; Katstra et al.; 2000; Lee et al., 2003; Rowe et al., 2000, 2002). Because of its high flexibility in spatial arrangement and microstructure, the 3-DP™ process is capable of constructing dosage forms with heterogeneous or asymmetric configurations to achieve preferred release characteristics.

The objective of the study reported herein was to develop formulations capable of controlling release of highly water-soluble pharmaceutical compounds at predetermined rates following zero-order or near zero-order kinetics using 3-DP™ technology, as well as to characterize the in vivo performance of such formulations. It was anticipated that the drug release characteristics of such formulations could be reproduced when the active is replaced by another with similar physical chemical properties, and only minor modifications of the formulation would be needed. This approach is envisaged to be used as a drug-screening tool to effectively shorten the costly product development process. The formulations were also designed to be independent of the pH and the hydrodynamics (e.g., paddle stirring rate) of the dissolution medium.

MATERIALS AND METHODS

Dosage Form Design

The three formulations in the current study were all designed to incorporate a cubic core-shell structure as shown in Fig. 1. The core region of each dosage form

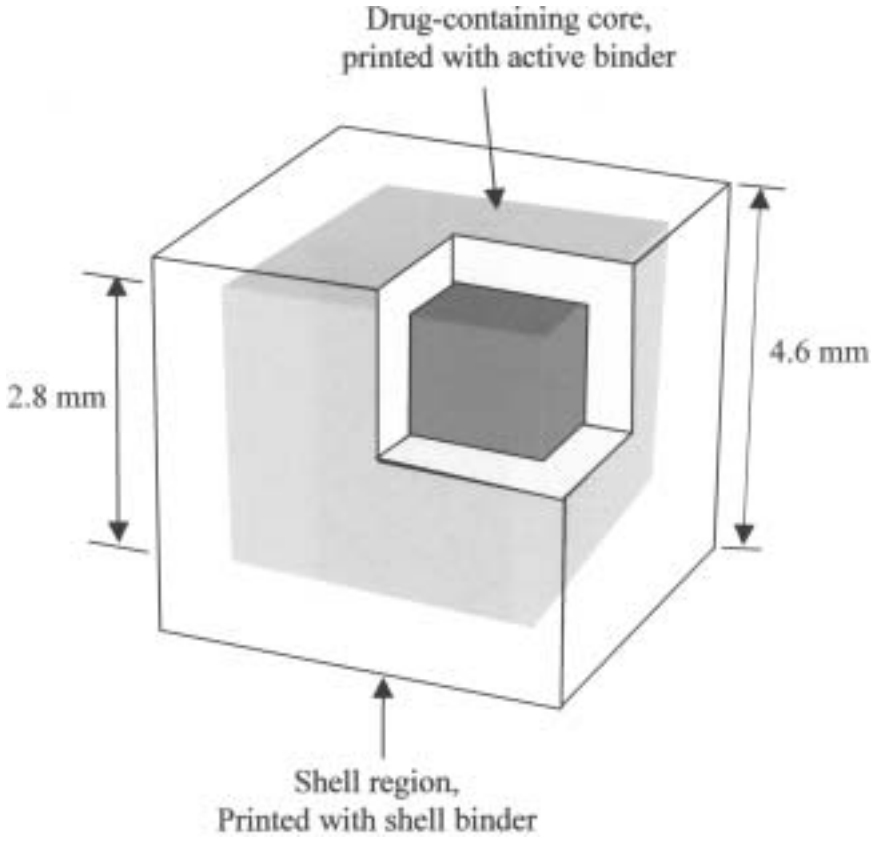

FIGURE 1 **Schematics of the cubic core-shell structure of the dosage form. To facilitate visualization, a corner of the shell has been cut out to reveal the core region inside.**

unit was a cubic matrix with side length of 2.8 mm. The core contained 7.5 mg active and was surrounded by a 0.8-mm-thick shell matrix. The dosage form was designed as a simulacrum of a multichamber drug delivery system, so that multiple subunits can be assembled to provide a therapeutic dose with each subunit releasing drug independently. The rationale for the multichamber pharmaceutical dosage forms has been elaborated in the literature and will not be discussed in this article.

Eight subunits totaling 60 mg of active were assembled for clinical testing in the current study. The powder substrate was composed of Kollidon SR (BASF Corp.) and hydroxypropylmethyl cellulose, substitution type 2910 (Pharmacoat 603, Shin-Etsu Chemical). Kollidon SR is a mixture of 80% polyvinyl acetate (PVAc) with a molecular weight of 450,000, 19% polyvinylpyrrolidone K30 (PVP K30), and trace amounts of sodium lauryl sulfate and silica as stabilizers. These two materials were used as received and were mixed using a twin shell blender for 15 min before fabrication. The release rates of the formulations were adjusted by variation of Kollidon SR-HPMC ratio, as shown in Table 1.

Two different binders were used to fabricate the core and shell regions of the dosage forms. An aqueous binder containing 50% (by weight) of PEH was used to fabricate the core region to form an immediate release matrix containing 7.5 mg of active. Trace amounts (0.1%) of Tween 20 (Spectrum Chemicals) and 5% PVP K17 (BASF Corp.) were added to the binder to achieve desirable surface tension and specific viscosity parameters, respectively, for reliable dispensing performance. A drug-free ethanolic binder containing 15% triethyl citrate (TEC, Spectrum Chemicals) was delivered to the shell region to form the release-controlling matrix. The solvent system of

TABLE 1 **Powder Compositions of Three Test Formulations**

Formulation	Kollidon SR (%)	HPMC (%)
8-h	60	40
12-h	70	30
16-h	80	20

the shell binder was composed of 75% (by weight) ethanol and 25% water. TEC was added to the dosage forms as a plasticizer to increase the flexibility of PVAc to facilitate formation of a continuous drug release control barrier.

Fabrication

The dosage forms were fabricated using a laboratory scale 3-DP™ machine as described previously (Lee et al., 2003). The core and shell binders were delivered to the powder bed through a motion-controlled printhead to "bond" the powder particles together. The core and shell regions were fabricated concomitantly but independently. The area on the powder bed to be printed was determined by the computer-aided design (CAD) model of the product, which was stored in the computer connected to the 3-DP™ machine. The powder bed was lowered after each printing pass, and additional powder was spread to repeat the printing process to realize another new layer. The process was repeated until the dosage form was completely built. The drop spacing, line spacing, and layer thickness were all maintained at 400 μm throughout the study. The active binder flow rate was controlled at 2.1 g/min to deliver a target dose of 7.5 mg to the core region. The shell region was fabricated with a shell binder flow rate of 1.8 g/min. Other shell binder flow rates were tested, and 1.8 g/min was found to provide sufficient saturation to form a contiguous shell matrix. The printed dosage forms were oven dried at 50°C for 12 h and dedusted using a sieve to remove any excess unbound powder particles.

In Vitro Dissolution Study

Dissolution studies were performed in an eight-station dissolution test apparatus (VK 7000, Vankel Industries, Inc.) using a USP Apparatus II method and water as the dissolution medium. Unless specified, the temperature of the dissolution medium and the paddle speed were controlled at 37 ± 0.5°C and 50 rpm, respectively. Single-dosage units were used for dissolution studies except for the tests performed for in vivo/in vitro correlation, in which eight dosage units encapsulated in two #0 gelatin capsules (Capsugel, NJ) were used. Dissolution vessels of 200 mL and 900 mL were used for studies with single-dosage units and eight-dosage units, respectively. The dosage forms were placed in a stainless steel cage (sinker) in the dissolution vessels to prevent floating. Other dissolution media, including 0.1N HCl solution and pH 6.0 and 7.4 phosphate buffers, were used to evaluate the pH sensitivity of dosage form release.

Stability Study

The dosage units were placed in 20-mL clear glass vials (11 units/vial) and stored in stability chambers controlled at 40°C/75% RH and 25°C/60% RH under open container condition for 1 month. Samples were assayed and dissolution studies were conducted using single-dosage units.

In Vivo Study

The in vivo study was conducted at Biopharmaceutics Research Institute, Rhodes University, Grahamstown, Republic of South Africa. Four dosage units of each formulation were manually inserted into a #0 capsule. Two capsules were administered to each subject for each test formulation. Sudafed Tablets (Glaxo Wellcome, South Africa) containing 60 mg PEH were used as the immediate-release reference formulation.

The in vivo study was a single-dose, randomized, open-label, four-way crossover study. Ten normal adult male subjects between the ages of 21 and 28 and within ±15% of their ideal body weight according to the 1983 Metropolitan Height and Weight table were enrolled in this study after medical screening. The subjects were admitted to the clinic site for each phase at least 12 h prior to dosing and were discharged after the 36-h postdose blood samples were taken.

The dosing schedule of the four formulations was determined using a random number table. Each subject was randomly assigned to one of the four sequences to receive a single dose of 60 mg PEH after fasting for 10 h. The subjects continued to fast until 4 h after dosing, and then a standard lunch was served. During each phase of the study, 7-mL venous blood samples were collected from each of the subjects immediately prior to drug administration (0 h) and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, 20, 24, 30, and 36 h after administration. The samples were transferred immediately into precooled Li-Heparin-containing test tubes. After centrifugation at 2000 rpm for 15 min, plasma samples were harvested and stored

at −80°C until analysis. The pseudoephedrine plasma concentrations were analyzed using a validated LC/MS/MS method with an LOQ of 1.55 ng/mL.

Pharmacokinetic Analysis

The plasma pseudoephedrine concentrations above the LOQ were used for pharmacokinetic analysis. Pharmacokinetic parameters were calculated using the SAS System Statistics program (SAS Institute Inc., Cary, NC, USA) with the TPD (Therapeutic Products Directorate of Canada) macro PKVARM.SAS. Ninety percent confidence intervals for ANOVA comparison of C_{max}, the area under the plasma concentration-time curve from time 0 to t, $AUC_{(0-t)}$, and from time 0 to infinity, $AUC_{(0-\infty)}$, were calculated for all formulations using SAS with the TPD macro ANOVSM.SAS. The $AUC_{(0-t)}$ was calculated using the trapezoid method. $AUC_{(0-\infty)}$ was obtained by extrapolating $AUC_{(0-t)}$ to time infinity by the following equation:

$$AUC_{(0-\infty)} = AUC_{(0-t)} + C_{(t)} / K_e$$

where $C_{(t)}$ is the plasma concentration of pseudoephedrine at time t, and K_e is the elimination rate constant, calculated as the negative value of the slope by linear regression of the terminal phase of the semilog plasma drug concentration-time profiles. The relative bioavailabilities (F_{rel}) of the test formulations were the ratios of their $AUC_{(0-inf)}$ values to the $AUC_{(0-inf)}$ of the reference formulation. The F_{rel} values were derived for each subject, and the arithmetic mean of 10 subjects was used to represent the F_{rel} of each test formulation.

The absorption profiles for each individual subject were deconvoluted using Wagner-Nelson methodology (Wagner & Nelson, 1964):

$$\%Absorbed = \frac{C(t) + K_e AUC_{(0-t)}}{K_e AUC_{(0-\infty)}} \times 100$$

In Vivo In Vitro Data Correlation

The in vivo/in vitro correlations were established using the mean dose absorbed and the mean cumulative drug dissolved data. Linear regression was used to examine the extent of the correlation.

RESULTS AND DISCUSSION

Multiple adjustable parameters are available to the pharmaceutical scientist using 3-DP™ technology to manipulate release kinetics, as previously reported in the literature (Katstra et al., 2000; Rowe et al., 2000). In the current study, the fabrication parameters (i.e., drop spacing, line spacing, layer thickness, and binder flow rate), as well as geometry were kept constant, thus permitting drug release to be tuned primarily by composition of the dosage form matrix. Furthermore, because the dosage forms were designed to include an immediate-release drug-containing core, the drug release rate was modulated by the drug-free shell. The immediate-release nature of the cores of the three formulations is exemplified by the release profile obtained from printing a Kollidon SR-HPMC (80:20) powder blend (for 16-h formulation) with the aqueous PEH binder only, as shown in Fig. 2. The immediate-release core results from the poor solubility of the main polymer ingredient, PVAc in the aqueous PEH binder. Without compression, the association of Kollidon SR and HPMC particles after fabrication with the aqueous binder was not impervious enough to maintain a sustained-release monolithic matrix. Based on the immediate release nature of the formulations previously obtained in this laboratory with high viscosity HPMCs, the core regions for 8-h and 12-h dosage forms can reasonably be anticipated to possess similar immediate-release characteristics.

The in vitro release profiles of the three formulations are demonstrated in Fig. 3. The overall in vitro release rates of the three formulations were close to

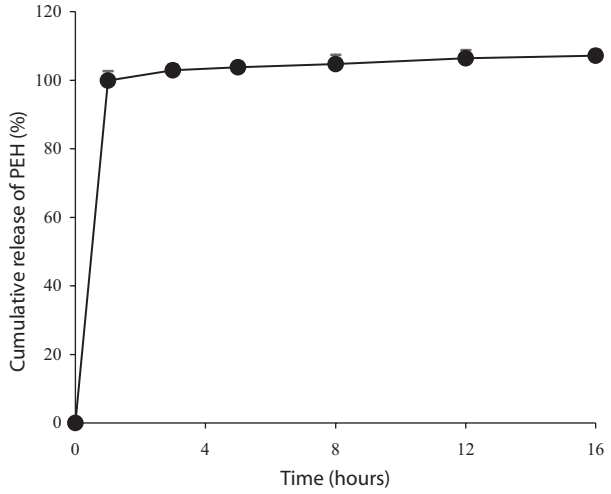

FIGURE 2 **Immediate release of PEH from core-only dosage forms.**

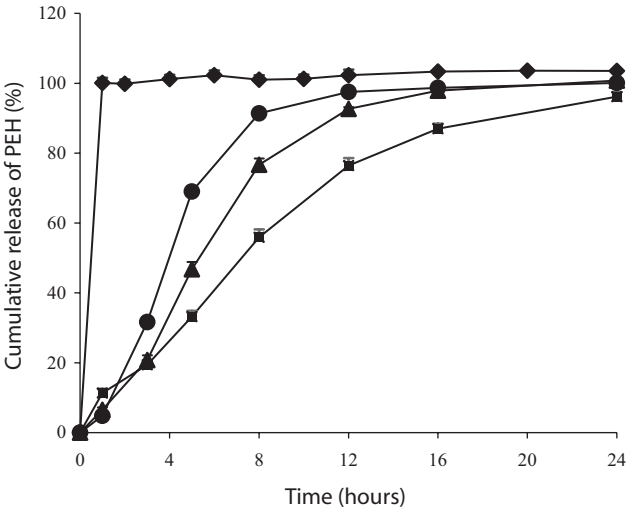

FIGURE 3 **Dissolution profiles of three test formulations and reference formulation. (●) 8-h, (▲) 12-h, (■) 16-h, and (♦) reference formulation.**

TABLE 2 **Comparison of Observed Release Rates to Target Release Rates**

Formulation	Overall mean release rate (%/h)[a]	Target release rate (%/h)	F2 statistics
8-h	12.0	12.5	61%
12-h	8.41	8.33	64%
16-h	5.9	6.25	65%

[a]Obtained by linear regression of dissolution profiles. The R^2 values for 8, 12, and 16-h formulations were 0.983, 0.983, and 0.911, respectively.

their corresponding target release rates, as shown in Table 2. The F2 statistics, used to compare the observed release profiles to the target profiles, were higher than 50 for all of the three formulations, demonstrating the similarity between the observed and target zero-order release profiles. Furthermore, every data point in the dissolution profiles of the three formulations deviated from the corresponding target release by less than 10%, except for the 16-h data point for the 16-h formulation, as displayed in Table 3.

The release rates of the dosage forms were successfully modulated by the ratio of the two polymers, Kollidon SR and HPMC, in the matrix by keeping the fabrication parameters constant. The overall release rates increased with the HPMC content in the powder blend in a near-linear relationship, suggesting that HPMC was the key release-regulating material. The major polymeric component, PVAc, in the shell region matrix was fused by the ethanolic shell binder with the flow rate used in this study due to its high solubility in ethanol and the plasticizing effect of TEC. The subsequent 50°C/12-h drying process effectively cured PVAc, which has a low Tg (35°C) in its unplasticized state, to form a nonporous polymeric network to completely block the drug release. Although a significant amount (19%) of water-soluble PVP K30 is present in Kollidon SR, no release from the dosage form fabricated with pure Kollidon SR was observed within 24 h, suggesting that the role of PVP K30 in facilitating the drug release with the current design was minimal, and the major release-controlling ingredient was HPMC.

HPMC is known to control drug release via both diffusion and erosion mechanisms. For the dosage form design in the current study, HPMC is randomly embedded in the dosage form to form a three-dimensional "mosaic" with Kollidon SR. When exposed to the

TABLE 3 **Observed Release Rates vs. Target Release Rates**

	1 h	3 h	5 h	8 h	12 h	16 h
8-h formulation						
Target release (%)	12.5	37.5	62.5	100	—	—
Observed release (%) ± SD (%)	7.58 ± 2.23	32.71 ± 1.30	67.80 ± 1.34	92.51 ± 0.55	—	—
Deviation from target (%)	–4.92	–4.79	5.30	–7.49	—	—
12-h formulation						
Target release (%)	8.33	25	41.67	66.67	100	—
Observed release (%) ± SD (%)	6.30 ± 4.45	20.78 ± 5.02	43.70 ± 6.25	76.00 ± 5.57	95.88 ± 2.88	—
Deviation from target (%)	–2.03	–4.22	2.04	9.33	–4.12	—
16-h formulation						
Target release (%)	6.25	18.75	31.25	50	75	100
Observed release (%) ± SD (%)	7.85 ± 4.48	14.65 ± 2.90	27.15 ± 1.80	50.80 ± 1.61	74.80 ± 1.41	89.81 ± 1.47
Deviation from target (%)	1.60	–4.15	–4.10	0.80	–0.20	–10.19

dissolution medium, it is postulated that the HPMC hydrates to form a gel due to conversion from a glassy to a rubbery state. The gelled HPMC matrix regulates the drug release via both diffusion and erosion mechanisms. However, because only one side of the HPMC matrix was exposed to dissolution medium, the surface area available for erosion to occur was limited. As a consequence, the drug release was predominated by the diffusion mechanism. The minor role of the erosion mechanism was confirmed by the minimal change in dissolution pattern when the paddle speed was increased from 50 to 150 rpm for the 8-h formulation (Fig. 4). This observation uniquely discriminates the release control mechanism of HPMC in the current dosage forms from traditionally coated dosage forms. Literature points out that HPMC typically leaches out to leave behind water-filled pores in the films for film-coated formulations containing more than 20% HPMC (Hjartstam et al., 1990; Lindstedt et al., 1991).

The 8-h and 12-h formulations released nearly 100% of drug within the target time. For 16-h formulation, the drug was released following near zero-order kinetics up to approximately 75% at the 12th h. However, the release rate between the 12th and the 16th h was unclear because no sample was taken during this interval.

The shell regions of the dosage forms in this study were 0.8-mm thick, much thicker than that typically obtained from traditional film-coating processes. As a result, it takes a longer time for the HPMC matrix to complete the hydration process to transition from glassy to rubbery state for the active to diffuse out of the dosage forms. This time-dependent hydration process effectively eliminates the initial burst of release commonly observed with conventional reservoir type sustained-release dosage forms. This seems to apply particularly to the 8-h and 12-h formulations, which had lower-than-expected initial release rates.

The dissolution of PEH from the dosage forms was insensitive to the change in the pH of dissolution medium, as shown in the dissolution profiles obtained by using media of various pH values for the 8-h formulation shown in Fig. 5. The other two formulations were not characterized but would be anticipated to possess similar pH insensitivity because of the pH-insensitive nature of the two polymers in the formulations. The pH insensitivity of the dosage forms also led to the decision to use water as the dissolution medium for the in vitro drug release study.

The insensitivity of the dosage form to the change in hydrodynamic stress was further confirmed by performing the dissolution test on the 16-h dosage form with and without a sinker. Because of its low density, the dosage form floated on the surface of the dissolution medium throughout the study when the sinker was not used. However, the presence/absence of the sinker did not result in any difference in release characteristics, as shown in Fig. 6. In another study, the dissolution test was performed using eight 16-h dosage units in capsules (4 cubes/capsule × 2) and large volume (900 mL) vessels and compared with the results obtained with single-dosage units in 200-mL vessels.

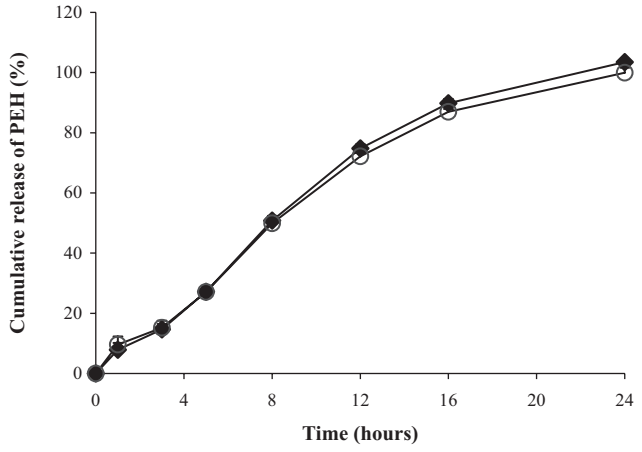

FIGURE 4 Dissolution profiles obtained from single cubes (♦) and 8 cubes encapsulated in 2 capsules (○) of the 16-h formulation.

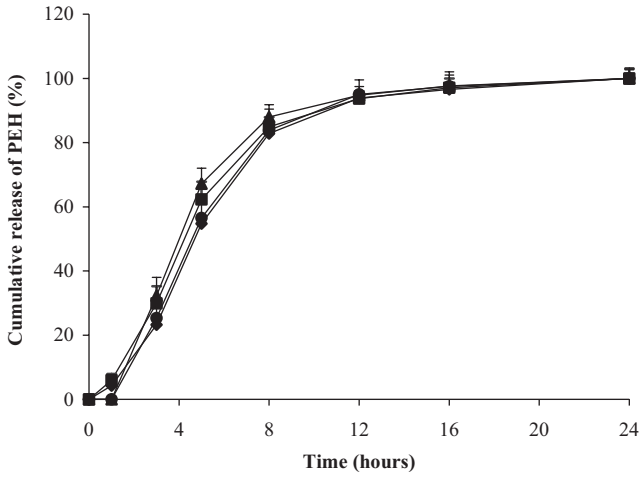

FIGURE 5 Dissolution profiles obtained using dissolution media of different pHs for 8-h formulation. (♦) Water, (■) pH 6.0, (●) pH 7.4, and (▲) pH 1.2.

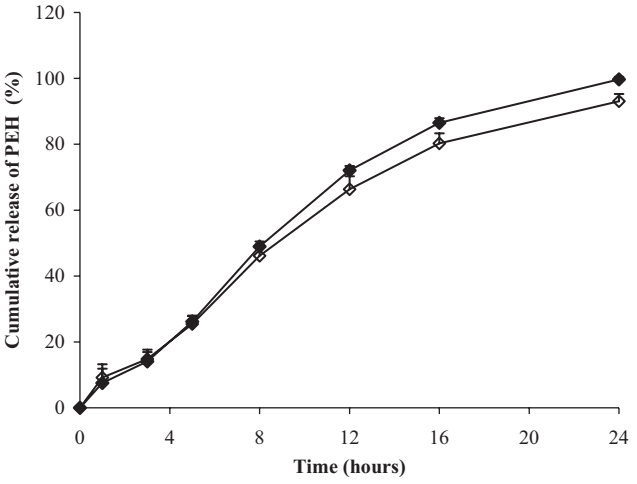

FIGURE 6 Dissolution profiles obtained from 16-h formulation with (♦) and without (◇) a sinker.

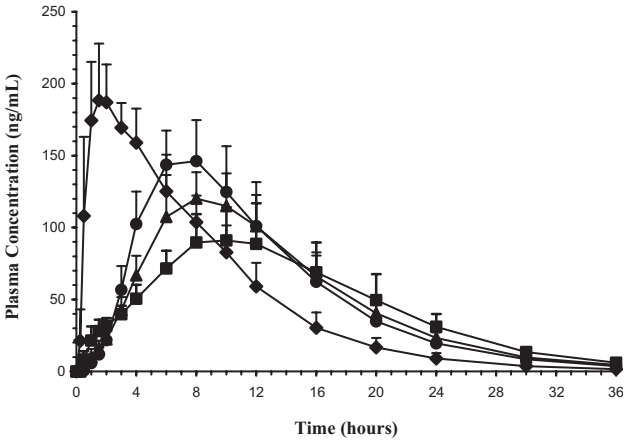

FIGURE 7 Plasma concentrations of three test formulations and reference formulation. (●) 8-h, (▲) 12-h, (■) 16-h, and (♦) reference formulation.

No significant difference in release pattern was observed. As could be expected, the release rate variability was lower for the eight-cube test.

The plasma concentration-time curves for the three test formulations and the reference formulation are displayed in Fig. 7. Consistent with the in vitro dissolution profiles, the plasma profiles demonstrated a clear distinction and a qualitative rank order correlation between the formulations. The low variation of the plasma level data within the same formulation reflected reproducibility of in vivo performance of the dosage forms. The pharmacokinetic parameters, calculated from the plasma concentration-time curves, are shown in Table 4. The C_{max} values of the tested formulations decreased when the duration for drug release was extended, as anticipated. The C_{max} values of different formulations were also significantly different from each other. The T_{max} values for the 12-h and 16-h formulations were not statistically distinguishable. However, both were significantly longer than the 8-h formulation and the immediate-release reference product. The relative bioavailability decreased slightly when the release duration was prolonged from 8 to 12 and to 16 h, probably associated with incomplete in vivo release of a small residual amount of PEH in the 12- and 16-h formulations in vivo.

The cumulative in vitro release profiles of three formulations demonstrated good agreement with their corresponding in vivo absorption profiles, obtained by deconvolution of the plasma concentration-time curves using the model-independent Wagner-Nelson method, as shown in Fig. 8. The in vitro release and the in vivo absorption plots were nearly superimposable for the three test formulations, indicating that the absorption of the active mainly depended on the release rates of the dosage forms. The linear regression analysis of the in vivo and in vitro data also suggested a significant linear in vivo/in vitro correlation (Fig. 9; Table 5). Furthermore, the slopes of the three test formulations are all close to unity, suggesting that the in vivo and in vitro release rates were similar. Alternatively, the release of active from the reference formulation was so rapid as to exceed the absorption rate, as indicated by the lower slope value. The intercepts of the three test

TABLE 4 Pharmacokinetic Parameters of Three Test Formulations and Reference Formulation Mean (% RSD)

Formulation	C_{max}[a] (ng/mL)	T_{max}[a] (h)	$AUC_{(\infty)}$ (ng·h/mL)	$AUC_{(\infty)}$ (ng·h/mL)	K_{el} (h^{-1})	$T_{½}$ (h)	F_{rel}[b] (%)
8-h	149 (18.9)	7.0 (15.1)	1942 (22.2)	1972 (22.2)	0.1425 (16.4)	5.0 (21.2)	99.4 (11.3)
12-h	123 (17.4)	9.2 (18.3)	1775 (17.5)	1808 (17.5)	0.1390 (10.5)	5.0 (10.9)	94.2 (13.5)
16-h	98 (25.5)	9.6 (21.5)	1665 (22.3)	1712 (21.7)	0.1309 (10.7)	5.3 (10.9)	88.5 (11.8)
Sudafed	198 (17.3)	1.6 (37.9)	1831 (18.5)	1849 (18.5)	0.1469 (18.9)	4.9 (17.0)	100

[a] C_{max} for all formulations were significantly different from each other; T_{max} for all formulations were significantly different from each other except for 12-h and 16-h formulations. Data were analyzed at 95% CI using 2-tailed t-test.

[b] Relative bioavailability, obtained from the ratio of $AUC_{(\infty)}$ of the test formulation to $AUC_{(\infty)}$ of the reference formulation.

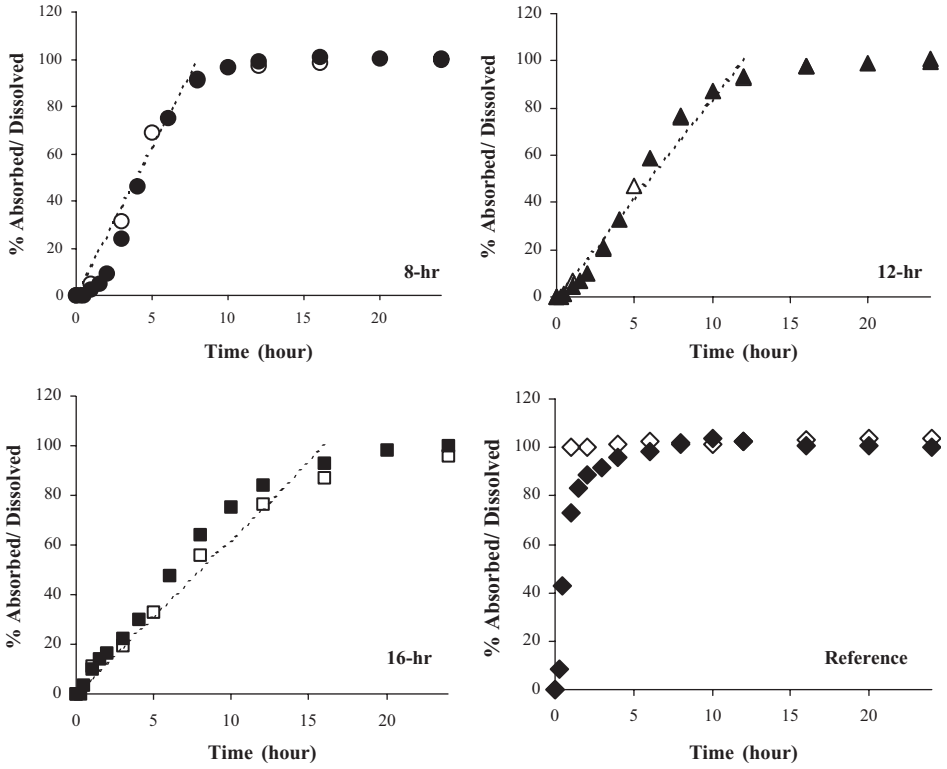

FIGURE 8 **Comparison of in vivo absorption profiles (solid legends) to in vitro dissolution profiles (hollow legends). Dash lines represent target release profiles.**

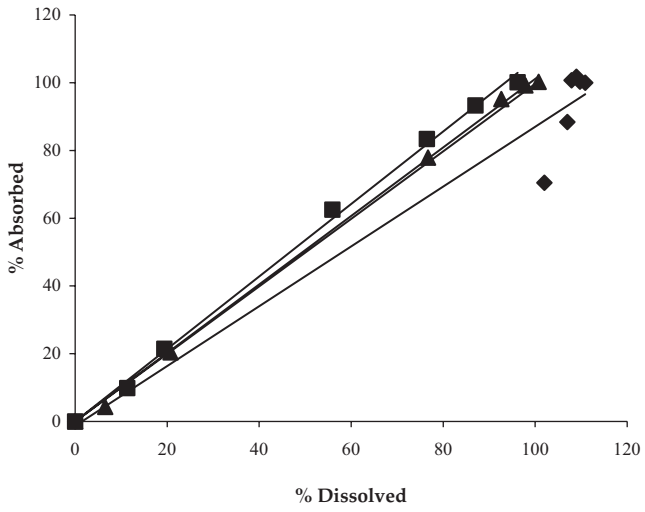

FIGURE 9 **In vivo in vitro correlations of three test formulations and reference formulation. (●) 8-h, (▲) 12-h, (■) 16-h, and (♦) reference formulation.**

formulations were all close to the origin, indicating the immediate absorption of active following administration. The data obtained from linear regression suggested a Level A correlation (Mojaverian et al., 1997) for all three formulations.

TABLE 5 **Parameters Obtained From Linear Regression of In Vivo/In Vitro Correlation**

Formulation	Intercept	Slope	R^2
8-h	–3.25%	1.036	0.997
12-h	–1.03%	1.008	1.000
16-h	0.59%	1.067	0.996
Sudafed	–1.28%	0.883	0.941

A stability test was performed on the 12-h formulation to determine the influence of high temperature and humidity on the dissolution properties. The dosage forms were stored at 25°C/60% RH and 40°C/75% RH in open and closed containers. Assay and dissolution studies were performed on the samples at 1, 2, and 4 weeks. No significant changes in release characteristics were observed after a 4-week storage period for each of the samples in an open container condition, as shown in Fig. 10. The excellent physical s_tability of the formulation may result from the 50°C/12-h drying conditions, which effectively cured the major polymeric component, PVAc. Furthermore, no degradation product of the active was observed, suggesting chemical stability of the formulations. The residual amount of ethanol in the

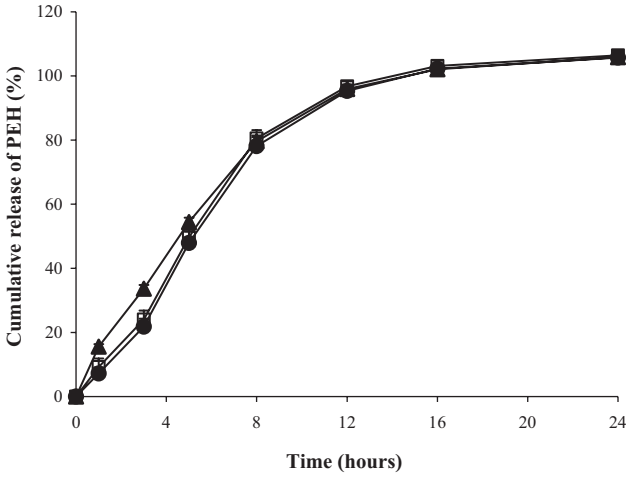

FIGURE 10 **Dissolution profiles obtained from 12-h formulation before (●) and after storing under 40°C/75% RH (▲) and 25°C/60% RH (□) under open container condition for 1 month.**

12-h formulation was also evaluated using a GC method and was found to be 1.2%.

CONCLUSION

This study demonstrated successful development of near zero-order controlled-release formulations for a water-soluble compound using the 3-DP™ technology. By keeping the fabrication parameters constant, the drug release rate was successfully modulated by the ratios of two polymers in a simple material system. The dosage form structure was conceptually similar to the traditional reservoir system derived by film coating. However, the core-shell structure allowed the dosage forms to minimize the erosion role of HPMC and resulted in a diffusion-dominant system. It was concluded that the drug was released via the diffusion mechanism through the hydrated HPMC matrix embedded in the well-fused, impermeable Kollidon SR network.

The current formulations resulted in dosage forms insensitive to both changes in pH and hydrodynamic stress of the dissolution medium. An excellent in vitro/in vivo correlation demonstrated that the dissolution methodology used was both discriminating and predictive. The chemical and dissolution properties of the three formulations maintained performance stability after 1 month's exposure to the stress conditions of 25°C/60% RH and 40°C/75% RH. The results suggest the fundamental formulation design may serve as a model for rapid prototyping of controlled-release formulations of water-soluble compounds.

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