Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method

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Abstract

Dissolution testing is an essential requirement for the development, establishment of in vitro dissolution and in vivo performance (IVIVR), registration and quality control of solid oral dosage forms. The objective of the present study was to investigate the effect of delivery system positioning in accordance with the USP 23-recommended dissolution methods and the proposed modification on drug release from controlled release systems having different operating release mechanisms, namely, swellable floatable, swellable sticking and osmotic pump. The delivery systems were evaluated by placing each dosage form either in the dissolution vessel in accordance with the USP 23 methods or over/below a designed ring/mesh device for achieving full surface exposure to the dissolution medium for sticking or floatable systems respectively. Results indicate that the overall release profiles from the sticking and floatable systems of theophylline are sensitive to their positioning in the dissolution vessel ($P<0.05$). Furthermore, release of diltiazem hydrochloride from the sticking system also demonstrated sensitivity ($P<0.05$). In contrast, the floatable dosage form of this latter drug with the application of a helical wire sinker, or when it was placed below the ring/mesh assembly, or by allowing the dosage form to float, did not show sensitivity ($P>0.05$) for the overall release behavior. This was attributed to the greater solubility of diltiazem hydrochloride (50% solubility in water at 25°C) in comparison to theophylline which is a sparingly soluble drug (0.85% solubility in water at 25°C). Drug release from the osmotic pump appeared to be identical under the given experimental conditions ($P>0.05$). Statistical analysis of data was performed by comparing the $t_{50\%}$, $t_{70\%}$, $t_{90\%}$; mean dissolution times (MDT$_{50\%}$, MDT$_{70\%}$, MDT$_{90\%}$); the “difference factor, $f_1$” and “similarity factor, $f_2$”. It is concluded that the results derived from the application of the “similarity factor, $f_2$” are superior to the individual time points (e.g. $t_{\%}$) and MDT,% values in differentiating between overall release patterns or the border line release profile differences. It also became apparent that in the case of the swellable sticking systems full surface exposure to the dissolution medium results in greater release rate. For the osmotic pump the required osmotic pressure threshold necessary for constant rate drug delivery appears to have reached independent of the hydrodynamic conditions. A successful and more accurate evaluation of dissolution data can be derived when full surface exposure is considered and this can be accomplished by dissolution method modification with the aid of the designed ring/mesh assembly. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: In vitro dissolution testing; Controlled release system; Swellable sticking and floatable systems; Osmotic pump; Dissolution method modification; Similarity factor application

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1. Introduction

Dissolution testing is used as a quality control procedure in pharmaceutical production, in product development to assist in selection of a candidate formulation, in research to detect the influence of critical manufacturing variables such as binder effect [1], mixing effect [2,3], granulation procedure [4], coating parameters [5,6], excipient type [7] and/or in comparative studies of different formulations [8], in vitro–in vivo correlations [9–12] and possibly as an in vivo surrogate under strictly defined conditions [13]. Therefore, sensitive and reproducible dissolution data derived from physicochemically and hydrodynamically defined conditions are necessary in order to compare various in vitro dissolution data and be able to use such results as a surrogate for possible in vivo bioavailability, bioequivalence testing and in vitro–in vivo correlations (IVIVC). The influence of technological differences and process variables involved, during manufacturing, on dissolution rate often complicates the decision making process in the selection of the appropriate dissolution method and subsequent data interpretation. Skoug and coworkers [14] stress that this consequence is the reason why dissolution studies and the defined specifications so often generate strong interest during regulatory review of solid oral dosage forms. As a result the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) has recently released guidelines called Scale-Up And Post Approval Changes, commonly referred to as SUPAC [15] and Extended Release Solid Oral Dosage Forms: Development, Evaluation And Application Of In vitro/In vivo Correlations, commonly known as IVIVC [16], to be used by the pharmaceutical sponsor in quality assurance and specific post approval changes and to demonstrate that the “dissolution profiles of pre-change product and post-change product are similar”. The impact of the process and establishment of an in vitro and in vivo performance (IVIVR) as a critical stage in the development of oral controlled release products has been further highlighted in the recent work by Devane and Butler [17].

New modified release formulation technologies and diversity in dosage form design necessitates the development of new procedures or appropriate modification to the existing apparatus as alternative dissolution measurement methods [18,19]. For example, in dissolution studies of low density swellable floatable controlled release drug delivery systems, often position of the dosage form appears to be close to the paddle shaft and liquid surface as illustrated in Fig. 1A (in both schematic and photograph). On the other hand, when a sinker such as the USP-recommended [20] “wire helix”, is wound around the delivery system, position of the dosage form will vary within the vessel (inconsistent hydrodynamics) and its free three dimensional swelling process would be adversely affected and difficult to control [21]. Furthermore, and contrary to floatable dosage forms, many drug delivery systems having high density, tend to adhere (stick) to the bottom of the dissolution vessel as illustrated in Fig. 1C (in both

Fig. 1. Schematics and photographs of drug delivery system positioning within a dissolution vessel: (A) floatable system close to the paddle shaft; (B) floatable system under the ring/mesh assembly; (C) sticking system adhering to bottom of dissolution vessel; (D) sticking system placed over the ring/mesh assembly.
schematic and photograph). Under these conditions the lower surface of the dosage form is not exposed to the dissolution medium and drug release is limited to the exposed surfaces only. Similar phenomena are unlikely to occur in the human gastrointestinal tract. More recently, it has been shown that the complex hydrodynamics and three dimensional fluid flow pattern produced by the USP paddle within different regions of the dissolution vessel varies significantly with a relatively more stagnant region at the bottom portion of the vessel [22,23]. Consequently, in order to mimic and more closely reflect the possible in vivo dosage form surface exposure, have reliable dissolution data and be able to discriminate between release behavior of various modified release formulations, a better understanding of the role of hydrodynamics, delivery system and release mechanisms together with the development of alternative dissolution methods is apparent [18,19]

The present study considers, among the time taken for x% drug release (t, %) and mean dissolution time (MDT, %) parameters, the “similarity factor, f12” [24,25] as a tool for dissolution data interpretation under different hydrodynamic conditions for dissolution behavior of swellable floatable, swellable stick-ing and osmotic pump delivery systems containing low and highly water soluble drugs. Specifically, in this article strategies are used to compare and demonstrate the possible existence of similarities and differences in drug release from three different delivery systems, generated by changes in dissolution hydrodynamics and dosage form positionings within the dissolution vessel. The following approach was adopted:
2. Materials and methods

Procariad XL® 30 mg (nifedipine product based on osmotic pump) was obtained from Temple University Hospital (Philadelphia, PA). Anhydrous theophylline powder (Amend Co., Irving, NJ), nifedipine powder and diltiazem hydrochloride powder (Sigma Chemical Co., St. Louis, MO), hydroxypropylmethylcellulose (HPMC, Methocel K4M PREM CR, Dow Chemical Co., Midland, MI), gas-forming salts and lactose NF anhydrous (Sheffield Products Division, NY) were used as received. Spectrophotometric grade 1-octanol (Aldrich Chemical Co., WI) was purchased for modified dissolution testing. All other reagents used were of analytical grade.

2.1. Formulation of HPMC matrix tablets

Hydrophilic swellable matrix-type tablets were prepared by blending the appropriate quantity of inactive ingredients with the polymer (HPMC) in a V-shape blender for 15 min. On obtaining a homogeneous powder mix, the respective active ingredient was finally added and mixed for an additional 15 min. Tablets were produced on a Carver Press (model C, Fred S. Carver Inc., IN) using a 10mm die and flat-faced punch employing a constant pressure of 2000 lbs. The die wall was lubricated with 1% w/v suspension of magnesium stearate in acetone. Table 1 depicts the actual quantities of ingredients used for each tablet formulation.

The physical properties of the tablets were acceptable and well within the specified limits set by the USP 23 [20]. Content uniformity for drug was similar for all tablet batches (100±3%).

2.2. Dissolution studies

Dissolution studies were performed on a fully calibrated dissolution apparatus using the paddle method (Apparatus II, Vankel Dissolution Apparatus, model VK 7000). The degassed dissolution media (1 l) were maintained at 37±0.5°C. Where necessary, a ring/mesh stainless steel device, which fits precisely under the paddle into the lower portion of the standard dissolution vessel, was employed (see Fig. 1). A more detailed description of the above device can be found elsewhere [26,27]. Drug release was measured spectrophotometrically at 238 nm for nifedipine (see the next paragraph for detailed method development) and diltiazem hydrochloride and at 268 nm for theophylline (HP diode array UV spectrophotometer, 8452A). All dissolution studies were performed in triplicate.

2.3. Method for nifedipine release measurements

Due to the low water solubility of nifedipine (<10 µg/ml) and in order to establish suitable sink conditions, dissolution studies on Procariad XL® were conducted in 1 l of a two phase solvent system at 100 rpm. The high agitation speed was employed to assure complete drug transport into the organic phase. The lower phase consisted of 750 ml phosphate buffer pH 7.5 (in accordance with the USP 23) and the upper phase consisted of 250 ml 1-octanol.
The drug release characteristics of the osmotic device was tested in two separate dissolution designs. In one study the tablet was dropped into the dissolution medium (see Fig. 1C; in both schematic and photograph) while in another study the tablet was placed above the ring/mesh assembly (see Fig. 1D; in both schematic and photograph). To avoid exposure of the tablet membrane to the organic phase, this phase was added to the vessel immediately after the introduction of the tablet to the phosphate buffer (i.e. the lower phase). In each dissolution study 5 ml samples were manually withdrawn from the 1-octanol phase at specific time intervals using 10 ml glass syringes over a period of 35 h and immediately read. An equal volume of fresh, drug-free 1-octanol was replaced in each vessel. Manual sampling had to be employed since prior testing using automated sampling demonstrated that the 1-octanol caused hardening of the dissolution tubing through the process of de-plastisization. Both dissolution studies were conducted under dark conditions due to the light-sensitive nature of nifedipine.

2.4. Drug release measurements from swellable floatable matrices

Dissolution studies on the formulated swellable floatable tablets were conducted in deionized water (1 l) at 75 rpm for theophylline and 50 rpm for diltiazem hydrochloride using an automated sampling system as follows:

(i) dropping the tablet into the dissolution medium (Fig. 1A); and
(ii) placing the tablet below the ring/mesh assembly (Fig. 1B); and
(iii) restricting the floatation of the tablet with the aid of a helical wire sinker (USP 23 method).

The agitation rates of 75 and 50 rpm for theophylline (0.85% solubility in water at 25°C) and diltiazem hydrochloride (50% solubility in water at 25°C) respectively, were found to be optimum and discriminatory based on the earlier work [28].

2.5. Drug release measurements from swellable sticking matrices

Dissolution studies on the swellable sticking system consisted of:

(i) dropping the tablet into the dissolution medium (Fig. 1C); and
(ii) placing the tablet above the ring/mesh assembly for full surface exposure (Fig. 1D).

2.6. Treatment of dissolution data

Dissolution data were subjected to two categories of model-independent analyses (i.e. time-point and pairwise approaches) in order to determine the release profile similarity and concomitant dissimilarity where applicable. Model-independency was previously described by Rescigno [29]. Such an approach generates results for which the values do not depend on the selection of the specific parameter for fitting the data, but are dependent on the sampling times \( t_1, t_2, \ldots, t_n \) and on an appropriate coefficient \( w_j \) representing the weight that the sampling time \( t_j \) has in the determination of the specific fitted functions.

In the time point approach the \( t_{50\%}, t_{70\%} \) and \( t_{90\%} \) values as well as the mean dissolution times (MDT\( _{50\%}, \) MDT\( _{70\%} \) and MDT\( _{90\%} \)) were calculated for each formulation in each of the triplicate dissolution measurements. Application of MDT provides more accurate drug release rate as compared toapproach and is determined as the sum of the individual periods of time during which a specific fraction of the total dose is released [30]. The mean values and corresponding standard deviations are presented in Table 2.

The following equation (Eq. (1)), was used to calculate the MDT for each percentage point:

\[
\text{MDT} = \frac{1}{\sum_{i=1}^{n} \frac{M_i}{\bar{M}_\infty}}
\]  

where \( M_i \) is the fraction of dose released in time \( \bar{M}_\infty = (t_i + t_{i-1})/2 \), and \( M_\infty \) corresponds to the loading dose.

In the pairwise approach, determination of a “difference factor, \( f_1 \)” [25] and “similarity factor, \( f_2 \)” [15,16,25] (as outlined in the SUPAC and IVIVC guidelines) using the mean percentage released values were performed by using Eqs. (2) and (3). In order to validate the acceptance of the \( f_1 \) and \( f_2 \) fit factors, calculations were performed on the individual dissolution data of each formulation, which
Table 2
Treatment of dissolution data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nifedipine</th>
<th>Theophylline</th>
<th>Diltiazem HCl</th>
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<tr>
<td>Mean Time, $\mu$s</td>
<td>(h)</td>
<td></td>
<td></td>
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<tr>
<td>Over mesh</td>
<td>Without mesh</td>
<td>Over mesh</td>
<td>Without mesh</td>
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<td>6±0</td>
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<td>24±2.12</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$f_1(%)$</td>
<td>19.16, 11.12</td>
<td>reference</td>
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</tr>
<tr>
<td>$f_2$</td>
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<td>81.57</td>
<td>70.17</td>
</tr>
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</table>

Key (a) $* = 35$ h; $h = 50.5$ h; $f = 35$ h; $a = 26$ h; $b = 26$ h; $c = 15$ h; $f = 25$ h; $k = 12$ h; $l = 12$ h.

reflected no statistical difference ($P > 0.05$) to the mean dissolution values.

The recent guidelines by the CDER at the FDA [16] describes the necessary criteria for granting biowaivers for specific changes (i.e. pre-change product or post-change product) in drug product manufacturing. To this end the guidelines and specific published work [25] on extended release solid oral dosage forms, describe the mathematical treatment of dissolution data by comparing dissolution profiles using the “similarity factor, $f_2$” which may be defined as follows:

$$f_2 = 50 \log \left\{ 1 + \frac{1}{n} \sum_{i=1}^{n} w_i (R_i - T_i)^2 \right\}^{-0.5} \times 100$$

(2)

where $n$ is the number of pull points, $w_i$ is an
optional weight factor, $R_i$ is the reference assay at time point $t$ and $T_i$ is the test assay at time point $t$. In the present study, the “reference” and “test” products are identical; however, both products are evaluated under standard USP 23 and modified dissolution conditions. The $f_2$ value between 50 and 100 suggests that the dissolution profiles are similar. The $f_2$ value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases.

In addition, Moore and Flanner [25] in their recent work also describe an $f_1$ fit factor or “difference factor” as follows:

$$f_1 = \left( \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i} \right) \times 100\%$$  \quad (3)

where $f_1$ describes the relative error between two dissolution profiles. “It approximates the percent error between two curves. The percent error is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles”.

The data generated from the application of the above three analytical methods were subjected to statistical analysis ($t$-test) at a 95% confidence level.

3. Results and discussion

Fig. 1 illustrates typical dosage form positionings and dissolution conditions that were developed to evaluate the release potential of the three delivery systems. The respective dissolution profiles are depicted in Figs. 2–6 ($N=3$, standard deviations are not shown because they were smaller than the symbol size). The results of the mathematical treatment of data are presented in Table 2.

3.1. Comparison of dissolution profiles derived from swellable floatable and swellable sticking delivery systems in accordance with the standard USP procedures and the proposed alternative method

The dissolution profiles for theophylline having 0.85% water solubility at 25°C demonstrated that the overall release trend from the swellable sticking and swellable floatable delivery systems are sensitive to their position in the vessel as shown in Figs. 2 and 3.
respectively. Significant differences in drug release profiles were observed from the sticking delivery system when it was placed in the vessel as such or when it was placed over the designed ring/mesh assembly (e.g. theophylline release: \( t_{90\%\text{over mesh}} = 17.5 \text{ h}, \ t_{90\%\text{without mesh}} = 24 \text{ h}, \ P<0.05 \)). Similar

release differences \((P<0.05)\) were also observed for the swellable sticking dosage form of a highly soluble drug, diltiazem hydrochloride (solubility in water \(>50\%\) at \(25\degree\text{C}\)), when the delivery system was placed either in the vessel as recommended by the USP 23 standard method or when it was positioned over the ring/mesh assembly (see Fig. 4). It appears that in the case of the swellable sticking systems full surface exposure to the dissolution medium was essential regardless of drug solubility in order to demonstrate the “true” drug release potential.

Application of the helical wire sinker to the swellable floatable theophylline delivery system appeared to inhibit the three dimensional swelling process of the dosage form and consequently suppressed drug release from the formulation. In comparison drug release was faster when the floatable delivery system was placed under the mesh (e.g. theophylline release: \( t_{90\%\text{with helix}} = 26 \text{ h}; \ t_{90\%\text{without mesh}} = 18.25 \text{ h}, \ P<0.05 \)). The \(t_{90\%}\) value for the floatable system without application of the ring/mesh device or sinker is the smallest value as shown in Table 2. The cause of such low “\(t\)” value as compared to other “\(t\)” values for the same delivery system can be attributed to floatation, greater mechanical attrition and erosion of the delivery system. As discussed earlier (see Fig. 1A) the floatable system tends to adhere to and detach itself from the
paddle shaft consistently, and constantly rotate around the shaft during the entire dissolution period. This resulted in significant matrix erosion and particle separation as observed visually and consequently greater release rate. In the case of a swellable floatable system containing the highly soluble drug diltiazem hydrochloride, no differences in release were found by employing the helical wire sinker, placing the dosage form in the vessel as such or when the delivery system was fully submerged under the ring/mesh assembly (see Fig. 5). Hence, the nature of drug release behavior from swellable floatable systems depended on both full surface exposure and unhindered swelling as well as drug solubility.

In general, for floatable systems containing a low or sparingly soluble drug such as theophylline (0.85% water solubility at 25°C) full surface exposure (i.e. dosage form positioned under the ring/mesh assembly) resulted in release profiles which are rationally more acceptable. While, for a highly water soluble drug such as diltiazem hydrochloride (>50% water solubility at 25°C) under given experimental conditions (i.e. swellable floatable system) release profiles of the identical delivery systems were alike (P>0.05) irrespective of the position of the dosage form. In contrast, swellable sticking systems of both theophylline and diltiazem hydrochloride demonstrated position sensitivity with significant differences (P<0.05) in release profiles under the given experimental conditions (i.e. with and without the ring/mesh assembly).

3.2. Evaluation and comparison of nifedipine release from the push–pull osmotic pump with changes in the positioning of the delivery system within the dissolution vessel

As described earlier (see Section 2), a modification of the two phase dissolution medium system was adopted for drug release determination from the osmotic pump system [31,32]. 1-octanol was chosen for two main reasons:

(a) its high viscosity in comparison to other partitioning organic solvents reduces the propensity for evaporation during the test; and

(b) the 1-octanol–water distribution coefficient [33] is about 10 000: 1, favoring the “drag” of drug molecules into the organic phase from the buffer solution and hence maintaining sink conditions in the lower aqueous phase.

The commercially available nifedipine osmotic pump (Procardia XL®) was subjected to dissolution studies by either dropping the delivery system into the dissolution vessel or placing it over the ring/mesh assembly prior to adding the organic phase (see Fig. 1C and 1D). Results showed that the drug release profiles over the entire dissolution period (i.e. 35 h) were identical (P<0.05) irrespective of the position of the delivery system (see Fig. 6). For the osmotically-driven system, the required osmotic pressure threshold necessary for constant rate drug delivery appears to have been reached irrespective of full surface exposure.

3.3. Advantages and limitations associated with the time point (t,%), MDT, f, and f approaches

The time point approach (t,%), MDT, f, and f approaches for the interpretation of dissolution data proved to be inadequate for complete characterization of the profiles, since comparison of profiles not following a single path or void of crossover are not uncommon. In the case of the theophylline swellable floatable system random crossover of the profiles was observed (see Fig. 3). Consequently the choice of single data points for the calculation of meaningful dissolution values are questionable. Similarly, the choice of MDT, MDT and MDT may not always provide accurate information when profile crossover is too close. Both these observations are justified for the release profiles shown in the case of the theophylline floatable system with and without the ring/mesh assembly as well as when the dosage form was enclosed within the helical wire sinker (see Fig. 3). In the case of immediate release products such crossover in drug release profiles may not present a major problem since the time scale of the release event is very short often in the range of a few minutes to an hour. On the contrary, such occurrences with controlled release products may have significant implications in both quality assurance during product development and establishment of in vitro–in vivo correlations such as changes in percent in vivo peak-to-trough fluctuations. Therefore, in the characterization of such dissolution profiles, a more
in-depth analysis of data could provide a better description of the overall release profile.

Polli and co-workers [24] recently undertook an extensive study to mathematically and statistically evaluate the various methods available for the comparison of dissolution profiles of conventional metoprolol tartrate dosage forms and demonstration of IVIVC. The application of the “similarity factor, $f_2$” recently proposed by Moore and Flanner [25] and adopted by the CDER at the FDA were also among the selected methods for dissolution testing by these workers [24]. The “similarity factor, $f_2$” was shown to be useful in providing a basis for overall dissolution profile comparisons. While the method appears accurate, one of the main difficulties experienced was the “dependence of metric value on length of dissolution profile”. When the “similarity-difference factor approach” was employed in data treatment (pairwise procedure) it became apparent that the selection and determination of the dissolution end pull points play a critical role in the calculation of the similarity factor value (see Table 2) and the subsequent decision as to whether the test and reference profiles resemble each other or not. This observation is in agreement with the latest addition to the CDER document on the dissolution guidance for immediate release products [34]. However, it should be noted that as yet no limit on the selection of the dissolution end pull points has been released in the case of modified release dosage forms. In Table 2 the footnotes a–i represent the different dissolution endpoint times selected for the calculation of the $f_1$ and $f_2$ fit factors. For example, in the case of the sticking delivery system of theophylline, inclusion of data points up to 30.5 h (corresponding to 96.26% of total drug content) as the dissolution endpoint demonstrated that the profiles of the “test” and “reference” products are dissimilar ($f_2 = 49.85$). However, when the dissolution endpoint was considered to be 35 h (corresponding to 97.81% of total drug content) the overall release profiles were similar ($f_2 = 51.30$). Therefore, marginal differences observed in the comparison of dissolution data between the “test” and “reference” products may result in rejection of the test product as it is currently stipulated in the guidelines. Therefore, the interpretation and selection of the dissolution endpoint for modified release products is critical in the determination of profile similarity/dissimilarity.

4. Conclusions

This work has highlighted the effect of various hydrodynamic conditions and some of the underlying areas of concern, particularly in controlled release drug delivery. The study has revealed that two categories of delivery systems, namely swellable floatable and swellable sticking behave differently and their release capacities depend on system design and their position in the dissolution vessel as well as drug solubility. From the overall analysis of dissolution data, it was found that the application of the “similarity factor, $f_2$” is superior to the $t_{\%}$ and MDT$_{\%}$ values in differentiating the borderline release profiles in each category of delivery systems. The greater flexibility in assessing the overall similarity of dissolution profiles by the application of the $f_2$ fit factor to data analysis may lead to the better recognition of the real difficulties experienced in the comparison of dissolution profiles which so often emerge during product modification and in the IND/ANDA revisions. The confidence in the $f_2$ fit factor is further illustrated by relating the degree of similarity to the $f_1$ fit factor or percent error as was shown in Table 2. A clear mechanistic effect on release behavior caused by variation in delivery system position in the dissolution vessel also became apparent. It is further demonstrated that the relative importance of dissolution method modification by the application of the ring/mesh assembly will depend on the type of delivery system and its sensitivity to hydrodynamic conditions. Finally, the determination of accurate and reproducible dissolution profiles is achievable when full surface exposure is taken into consideration and rationally such dissolution data can be more reliably utilized for IVIVC purposes.

Acknowledgements

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