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Susan D'Souza
Sunovion Pharmaceuticals Inc.

Jabar A. Faraj
Fresenius Kabi USA

Stefano Giovagnoli
Università degli Studi di Perugia, Italy

Patrick P. DeLuca
University of Kentucky, ppdelu1@uky.edu

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Research Article

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Susan D’Souza,1 Jabar A. Faraj, 2 Stefano Giovagnoli, 3 and Patrick P. DeLuca 4

1 Sunovion Pharmaceuticals Inc, Marlborough, MA 01752, USA
2 Fresenius Kabi USA, Skokie, IL 60077, USA
3 Department of Chemistry and Technology of Drugs, Università degli Studi di Perugia, Via del Liceo 1, 06123 Perugia, Italy
4 University of Kentucky College of Pharmacy, Lexington, KY 40536, USA

Correspondence should be addressed to Susan D’Souza; dr_sdsouza@yahoo.com

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In this study, four PLGA microsphere formulations of Olanzapine were characterized on the basis of their in vitro behavior at 37°C, using a dialysis based method, with the goal of obtaining an IVIVC. In vivo profiles were determined by deconvolution (Nelson-Wagner method) and using fractional AUC. The in vitro and in vivo release profiles exhibited the same rank order of drug release. Further, in vivo profiles obtained with both approaches were nearly superimposable, suggesting that fractional AUC could be used as an alternative to the Nelson-Wagner method. A comparison of drug release profiles for the four formulations revealed that the in vitro profile lagged slightly behind in vivo release, but the results were not statistically significant (P < 0.0001). Using the four formulations that exhibited different release rates, a Level A IVIVC was established using the deconvolution and fractional AUC approaches. A nearly 1:1 correlation (R^2 > 0.96) between in vitro release and in vivo measurements confirmed the excellent relationship between in vitro drug release and the amount of drug absorbed in vivo. The results of this study suggest that proper selection of an in vitro method will greatly aid in establishing a Level A IVIVC for long acting injectables.

1. Introduction

Establishing an IVIVC (in vitro in vivo correlation) remains a challenge for non-oral dosage forms like long acting injectables. One reason for the lack of IVIVC is the dearth of in vitro methods that are simple to set up and use, while suitably mimicking in vivo conditions. The benefits of establishing an in vitro in vivo correlation (IVIVC) have been enumerated in numerous pharmaceutical publications spanning the last three decades. Indeed, IVIVC has remained a topic of constant discussion with several dosage forms, especially solid orals, since the publication of an IVIVC guidance by the FDA in 1997 [1]. The goal of an IVIVC is to establish a relationship between the in vitro dissolution behavior and in vivo performance of a drug product. An IVIVC is generally described by a linear relationship between parameters derived from the in vitro and in vivo experiments as quantified by the Pearson correlation. As defined by the FDA guidance, these correlations have been classified under four categories.

(i) Level A, the highest correlation, is a point to point correlation between in vitro dissolution and in vivo absorption over time. With a Level A correlation, the in vitro dissolution profiles are generally superimposable with in vivo absorption curves or may be made superimposable by use of an appropriate scaling factor.

(ii) Level B is a correlation between summary parameters such as in vitro dissolution rate and in vivo absorption rate (e.g., mean dissolution time (MDT) versus mean residence time (MRT)). Though frequently used, a Level B correlation is not a point to point correlation as it does not uniquely reflect the actual in vivo profile due to the fact that several in vivo curves will produce a similar MRT value or mean in vitro dissolution curve.

(iii) Level C describes a single point comparison of the amount dissolved in vitro at a particular time (e.g., T_{50}%) and an in vivo pharmacokinetic parameter.
glycolide (PLGA) polymers [6, 7]. These polymers are FDA
injectable dosage forms formulated using polylactide-co-
marketed over the past decade include polymeric based
[2–4].

(iv) Level D is a rank order correlation that is qualitative
in nature.

Once established, an IVIVC can be used to guide for-
mulation and/or process development changes in the various
stages of drug development and also simplify any scale-up or
post-approval changes.

Additionally, an IVIVC allows setting of clinically rel-
levant in vitro dissolution specifications to ensure product
quality. A particular benefit of an IVIVC is that it can
be used to support the use of dissolution testing as a
surrogate for human bioequivalence studies, which would
reduce the number of human studies needed for drug
applications. A well-described in vitro in vivo relationship
could also be used to set clinically meaningful dissolution
specifications for monitoring drug manufacture. Though
the FDA guidance provides a framework for developing
and establishing an IVIVC, several challenges have been
noted with solid oral dosage forms, particularly, the de-
velopment of an in vitro dissolution method. Among other
variables, including the fact that the gastrointestinal envi-
nronment is highly complex, developing an in vitro dissolu-
tion method to mimic in vivo conditions is not simple or
straightforward.

Development of an IVIVC with non-oral dosage forms
is even more complex. With the increasing number of
such dosage forms being developed and commercialized
in recent years, development of an IVIVC has gained
additional significance. As such, the FDA guidance is cur-
rently applicable only to oral extended release products
and not for non-oral dosage forms like transdermals or
long acting injectables. However, a few publications have
attempted to establish an IVIVC from non-oral dosage
forms using the fundamental principles in the guidance
[2–4].

Some of the most successful non-oral dosage forms
marketed over the past decade include polymeric based
injectable dosage forms formulated using polylactide-co-
glycolide (PLGA) polymers [6, 7]. These polymers are FDA
approved for surgical sutures and implantable devices and
have excellent safety, tolerability, and toxicity [8, 9]. Further,
they are known to be biodegradable and biocompatible as
they undergo biodegradation over weeks to months
resulting in the formation of lactic and glycolic acids that
are cleared by the Krebs cycle. Several reports have doc-
umented the incorporation of a wide range of complex
therapeutics like peptides and proteins into PLGA to form
micron sized dosage forms called polymeric microspheres
[10–14]. Key advantages of delivering therapeutics using poly-
meric microspheres include sustained drug release, reduced
dosage, and fewer systemic side effects. Additional bene-
fits of using polymeric microspheres are the improvement
in patient compliance to drug therapy, primarily due to
reduced frequency of administration of the slow degrading
dosage form that releases the therapeutic in a sustained
fashion [15–19]. For this reason, long acting microsphere
dosage forms of several molecules like Risperidone (atyp-
cal antipsychotic to treat schizophrenia) and Leuprolide
(LHRH superagonist against prostate cancer) have been
developed and have achieved significant commercial success
[20–23].

Despite the advances in development of long acting
injectables, literature on the IVIVC with these dosage forms
continues to remain sparse. A major challenge cited for
the lack of IVIVC is the absence of a standardized or compendial
method to assess in vitro drug release from long acting
injectables [7]. A few authors have attempted Level A, B,
and C correlations, albeit with different methods and varying
degrees of success [2, 4, 24]. Of the methods available
to assess in vitro drug release, a dialysis based method
offers the most advantages in terms of simplicity in set-up,
ease of sampling, and reproducibility. With dialysis based
techniques, the dosage forms are entrapped inside a dialysis
bag containing media (inner media, non-sink conditions).
This dialysis bag is subsequently immersed inside a larger
vessel containing a large volume of the same media (outer
media, sink conditions), thus enabling a physical separation
of the dosage form from the outer media. As drug is
released from the dosage form and into the inner media,
it diffuses through the dialysis membrane into the outer
sink. This scenario mimics in vivo conditions where the
long acting injectable is immobilized upon subcutaneous or
intramuscular administration and surrounded by a stagnant
layer leading to slow drug diffusion due to non-maintenance
of sink conditions [25, 26]. Several adaptations of the dialysis
based techniques (e.g., dialysis bags) have been evaluated,
including the modified dialysis method that was successfully
used to study drug release from large molecules like peptides
[27].

In a previous publication by the same group, long act-
ing injectable formulations of Olanzapine (a second gen-
eration atypical antipsychotic) were prepared using four
PLGA polymers with the aim of improving effectiveness
and patient compliance for this drug. Subsequently, these
formulations were administered to rats to assess in vivo
performance and were successfully shown to provide sus-
tained in vivo levels of Olanzapine for 7 to 15 days [5]. In
the current study, the Olanzapine PLGA formulations were
further characterized for in vitro release behavior, using a
modified dialysis method, with the goal of achieving an
IVIVC.

2. Materials and Methods

2.1. Materials. Olanzapine was purchased from Cipla
Ltd., Bombay, India. PLGA having molecular weights
15, 30, 82, and 131kDa was purchased from Boehringer
Ingelheim (Ingelheim, Germany) and Alkermes (Cambridge,
MA, USA). Spectra/Por Dialysis membranes (MWCO
300,000 Da) were purchased from Spectrum Labs, Inc.,
CA. All the other chemicals were obtained commercially as
analytical grade reagents.
2.2. Preparation of Microspheres. Olanzapine PLGA microspheres were prepared by a solvent extraction/evaporation method and recovered by filtration [5]. Briefly, a solution of drug and polymer was injected into an aqueous continuous phase under stirring with a Silverson L4R mixer (Silverson machines, MA, USA) at predetermined speeds. Subsequently, the solvents were removed by stirring after which the microspheres were recovered by filtration, suspended in a suitable vehicle, filled into vials, and freeze dried. Briefly, the four formulations prepared were as follows:

(a) Formulation A (15 kDa, 75:25 lactide:glycolide),
(b) Formulation B (30 kDa, 50:50 lactide:glycolide),
(c) Formulation C (82 kDa, 65:35 lactide:glycolide),
(d) Formulation D (131 kDa, 75:25 lactide:glycolide).

2.3. Drug Content. Olanzapine content in the microspheres was analyzed by a reverse phase HPLC method using a HPLC C-18 column at a flow rate of 1.5 mL/min. in a gradient mode. The mobile phases were 0.1% TFA (trifluoroacetic acid) aqueous solution and Acetonitrile with 0.1% TFA. Measurements were performed in triplicate. Drug content (%) was expressed as the “weight of drug in microspheres/weight of microspheres × 100” and was determined to be 26, 30, 40, and 40% for Formulations A, B, C, and D, respectively [5].

2.4. In Vitro Release. In vitro release (n = 3) was performed using a modified dialysis method [26]. Briefly, Olanzapine microspheres were accurately weighed and placed in a 7 mL dialysis tube (Tube-O-Dilalyzer, MWCO 300,000 Da) filled with 5 mL 0.5 M PBS (phosphate buffered saline), pH 7.4, containing 0.05% Tween 80 and 0.1% sodium azide (inner media), which in turn was placed in a 50 mL tube containing 40 mL of the same release medium (outer media). The contents of the outer media were continuously stirred with a magnetic stirrer to prevent formation of an unstirred water layer at the outer dialyzing surface. At predetermined intervals, 1.0 mL samples were withdrawn from the outer media followed by buffer replacement and HPLC analysis.

2.5. In Vivo Study. The in vivo release of Olanzapine from PLGA microspheres has been described previously [5]. Briefly, male Sprague-Dawley rats (n = 6) weighing approximately 300 g were used to evaluate in vivo performance of Olanzapine microspheres. The microspheres were injected subcutaneously at the back of the neck at a 10 mg/kg dose (Formulations A and B) or 20 mg/kg dose (Formulations C and D) after reconstitution with water for injection. Blood samples were collected from the tail vein at specific time points. The samples were centrifuged in Microtainer tubes (Becton Dickinson, Franklin Lakes, NJ) and serum was collected. Serum samples were frozen and stored at −20°C until analysis. Serum samples were analyzed at Medtox Laboratories location using a validated method.

2.6. IVIVC. The relationship between % drug released in vitro and the percent absorbed for the four Olanzapine PLGA formulations was assessed using two approaches.

(a) Nelson-Wagner approach: the fraction absorbed (Fabs) was determined from the plasma concentration-time data by deconvolution using the Nelson-Wagner method as described in [28],

\[ F_{abs}(t) = \frac{C(t) + k_e \times AUC_{(0-t)}}{k_e \times AUC_{(0-inf)}}. \]  

With the Nelson-Wagner equation, the pharmacokinetic profile is deconvoluted to obtain the in vivo absorption as a function of time and is plotted alongside the in vitro release data to assess the superimposability of the two profiles. If the two curves are superimposable and a linear relationship is obtained, it suggests a strong correlation between in vivo and in vitro drug release.

(b) Fractional AUC approach: the area under the curve (AUC) was calculated using the trapezoidal rule

\[ AUC(t_1-t_2) = \frac{(C_1 + C_2)}{2} \times (t_2 - t_1). \]

The fractional AUC was determined by dividing cumulative AUC at time “t” with cumulative AUC(0−last), as described in previous publications [3, 29] and plotted along with the % drug released in vitro. In a manner similar to the Nelson-Wagner approach, the superimposability of the in vivo and in vitro drug release was compared.

3. Results and Discussion

3.1. In Vitro Release. Figure 1 shows the in vitro release from Olanzapine microspheres, measured using the modified
dialysis method [26]. An initial burst of almost 10% (day 1) was observed from Formulations A and B after which drug release from these batches was very similar through day 30. In contrast, Formulations C and D exhibited a slight initial burst (day 1) followed by slow release of drug through day 3 to 8, Formulation C demonstrated an increase in drug release from these batches was very similar through day 30, and 82kDa, resp.) with a plateau noted at the high molecular weight PLGA (82 and 131kDa for Formulations C and D, resp.), a classic triphasic release profile was observed; initial burst by day 1 was followed by diffusional release through day 3 and subsequently, erosional release. A faster release rate with Formulation C was not totally unexpected due to a combination of an intermediate polymer molecular weight and the differing lactide : glycolide content in the polymers (75 : 25 in Formulation A and 50 : 50 in Formulation B), in vitro drug release profiles were nearly superimposable for these two formulations, indicating that lower molecular weight was a major determinant of drug release rate. For the higher molecular weight PLGA (82 and 131 kDa for Formulations C and D, resp.), a classic triphasic release profile was observed; initial burst by day 1 was followed by diffusional release through day 3 and subsequently, erosional release. A faster release rate with Formulation C was not totally unexpected due to a combination of an intermediate polymer molecular weight in a 65 : 35 copolymer. On the other hand, a high polymer molecular weight (131 kDa) in a slow degrading copolymer (75 : 25 lactide : glycolide) led to slow release from Formulation D. Obviously, the rate and extent of in vitro drug release depended chiefly on polymer molecular weight than the lactide:glycolide ratio of the PLGA copolymer.

Overall, the drug release profile from the four formulations can be explained as follows. Once formulated as drug-polymer microspheres, it is well known that release of encapsulated drug from a PLGA matrix is controlled by two phases, namely, drug diffusion through the polymer matrix followed by polymer degradation and erosion [30]. During the first phase, release of the encapsulated drug occurs mainly through its diffusion through the polymer matrix while during the second phase, the release is mediated through both diffusion of the drug and the degradation of the polymer matrix. Drug diffusion through the polymer matrix, a slower process, occurs during polymer hydration. Once hydrated, the polymer undergoes bulk hydrolysis that causes rapid polymer degradation, erosion, and loss of mass. Drug release during the hydrolytic degradation phase (erosional phase) occurs at a much faster pace than that during the diffusional phase.

As such, Formulations A and B, manufactured using low molecular weight PLGA (15 and 30 kDa, resp.), released drug rapidly. Clearly, hydration of the polymeric matrix was extremely rapid (within a day) due to low polymer molecular weight leading to a fast onset of polymer erosion. Despite the differing lactide : glycolide content in the polymers (75 : 25 in Formulation A and 50 : 50 in Formulation B), in vitro drug release profiles were nearly superimposable for these two formulations, indicating that lower molecular weight was a major determinant of drug release rate. For the higher molecular weight PLGA (82 and 131 kDa for Formulations C and D, resp.), a classic triphasic release profile was observed; initial burst by day 1 was followed by diffusional release through day 3 and subsequently, erosional release. A faster release rate with Formulation C was not totally unexpected due to a combination of an intermediate polymer molecular weight in a 65 : 35 copolymer. On the other hand, a high polymer molecular weight (131 kDa) in a slow degrading copolymer (75 : 25 lactide : glycolide) led to slow release from Formulation D. Obviously, the rate and extent of in vitro drug release depended chiefly on polymer molecular weight than the lactide:glycolide ratio of the PLGA copolymer.

3.2. In Vivo Results

3.2.1. Fraction Absorbed. Formulations A and B were administered to rats at a 10 mg/kg dose while Formulations C and D were administered at a 20 mg/kg dose as shown in Figure 3 [5]. Using the Nelson-Wagner method (described in Section 2.6), the fraction of drug absorbed was calculated by deconvoluting the pharmacokinetic profile to obtain the in vivo absorption as a function of time [28]. Deconvolution is a numerical method used to estimate the time course of drug input using a mathematical function and is based on a convolution integral. Once deconvoluted, the in vivo curve is plotted alongside the in vitro release data to assess the superimposability of the two profiles. Thus, the deconvolution approach allows comparison of in vivo release profile with in vitro behavior.

A plot of the fraction of drug absorbed for the four formulations is illustrated in Figure 4. As with Figure 1, the
Four formulations can be instantly discriminated on the basis of rank order. The profiles for Formulations A and B are nearly identical and reveal that drug absorption from both formulations is rapid. A slower absorption profile is noted with Formulation C with the slowest rate of absorption for Formulation D. Indeed, Figure 4 reveals that nearly 10% of Olanzapine was absorbed by day 1 for the rapidly releasing Formulations A and B, while the remaining formulations released only about 3% at the same time point. In a manner similar to that observed with in vitro release, an excellent inverse linear relationship (Figure 2) was observed between initial burst release as measured by the Nelson-Wagner method and polymer molecular weight ($R^2 > 0.99$) for Formulations A–C, with levels demonstrating a plateau for the highest molecular weight microsphere formulation (Formulation D). By day 4, only 7% of Olanzapine was absorbed from Formulation D whereas the value for Formulation C was almost double that amount. Likewise, the fraction of Olanzapine absorbed from Formulation D was five-fold lower than that of Formulations A and B. This trend continued until complete absorption was achieved for all the formulations, albeit at different time points. A noteworthy fact is that the in vivo drug release profiles (Nelson-Wagner method) were triphasic for the four formulations, suggesting a similar mechanism of release (diffusional and erosional) as observed in vitro.

3.2.2. Fractional AUC. A plot of fractional AUC over time is shown in Figure 5 and demonstrates a rank order behavior. Similar to the in vitro results (Figure 1), the fractional AUC profiles for Formulations A and B are nearly superimposable.
and demonstrate that complete release occurs rapidly \textit{in vivo}. On the other hand, a moderate \textit{in vivo} release profile is noted for Formulation C with the slowest \textit{in vivo} profile for Formulation D. As such, the rank order for fractional AUC profile appears similar to the \textit{in vitro} release profile. Of particular note is that fractional AUC values by day 1 are around 11\% for Formulations A and B, and between 2 and 3\% for Formulations C and D are essentially indistinct from those seen in Figure 1. Akin to the inverse linear relationship observed between initial burst release and polymer molecular weight (Figure 2) for \textit{in vitro} release and fraction absorbed (Nelson-Wagner method), a good correlation was observed with fractional AUC ($R^2 > 0.96$). Further, as observed with the \textit{in vitro} release profile (Figure 1), Formulations C and D show slow release through day 3, after which the \textit{in vivo} release rate increases rapidly until approximately 80–85\% is released after which the release rate tempers to achieve complete release by days 30 and 45 for Formulations C and D, respectively. Lastly, the \textit{in vivo} fractional AUC plots for the four formulations were sigmoidal in nature, similar to those seen with \textit{in vitro} drug release profiles, reaffirming that the mechanism of release was unchanged whether \textit{in vitro} or \textit{in vivo}.

3.3. IVIVC. Per the 1997 FDA guidance, three or more formulations of different release rates are recommended for the purpose of establishing an IVIVC [1]. Additionally, the guidance recommends use of the Nelson-Wagner or Loo-Reigelman method to calculate absorption profile of the drug. Since the four formulations used in the current study had varying release rates \textit{in vivo} and \textit{in vitro}, that is, Formulations A and B had the fastest release rate, while Formulation C was intermediate and Formulation D had the slowest release rate, all four formulations were selected for data analysis and to establish an IVIVC.

Of the FDA recommended methods for IVIVC development, the Nelson-Wagner was deemed suitable for the current study as it is appropriate for use in drugs whose pharmacokinetics can be fitted to one compartment model [28]. Once the fraction absorbed is calculated, a correlation may be obtained by comparing \textit{in vivo} behavior with \textit{in vitro} release, to establish an IVIVC. Another approach suggested by Woo et al. is to compare the fractional AUC with \textit{in vitro} release [29]. In the current study, data analysis was performed using both approaches. Figure 4 shows the fraction of drug absorbed \textit{in vivo}, as determined by the Nelson-Wagner method, while Figure 5 outlines the fractional AUC for the four formulations. At first glance, the similarities between Figures 1, 4, and 5 are very apparent. The release rates for the four formulations follow a rank order where Formulations A and B behave similarly and exhibit fast release while Formulation C demonstrates a modest release rate with the slowest drug release rate from Formulation D.

A comparison between \% release \textit{in vitro}, \% absorbed using the Nelson-Wagner method, and fractional AUC is depicted in Figure 6. To determine the \% absorbed by the Nelson-Wagner method, the fraction absorbed was multiplied by 100. A few striking observations are evident in Figure 6.

(i) The \% release \textit{in vivo} curves, as fractional AUC or using the Nelson-Wagner method, are nearly superimposable for the four formulations. Similar findings were reported by Chu et al. in a study on PLGA microspheres containing the alkaloid, Huperzine A [3].

(ii) \textit{In vitro} release lagged slightly behind \textit{in vivo} release for the four formulations. However, the \textit{in vitro} curves ramp up with a similar slope and are essentially parallel to the \textit{in vivo} profile. In a separate study, Jiang et al. attributed the faster release rate \textit{in vivo} to the contribution of enzymes and foreign body response [31].

Figure 7 highlights the correlation between \% \textit{in vitro} release using the modified dialysis method and the \% absorption, as calculated by the Nelson-Wagner method. As can be clearly seen in the figure, an excellent linear correlation ($R^2$ values between 0.95 to 0.98, $P < 0.0001$) was obtained for the slow, intermediate and fast releasing formulations. The values of the slope are slightly greater than 1 (1.03–1.18) indicating that \textit{in vivo} release occurred slightly faster than \textit{in vitro} release.

An IVIVC utilizing fractional AUC (\textit{in vivo} drug levels) and \textit{in vitro} drug release over time for the four formulations is shown in Figure 8. Once again, a strong linear correlation was obtained ($R^2$ values between 0.95 and 0.98, $P < 0.0001$) for the four formulations. Values of the slope ranged between 1.03 and 1.18, similar to those obtained with the Nelson-Wagner method and indicated that \textit{in vivo} release proceeded slightly faster than \textit{in vitro} release. These data suggest that fractional AUC could be used as an alternative to the deconvolution approach to obtaining an IVIVC, similar to that reported previously [3].

Figures 9 and 10 highlight the pooled IVIVC for the fast, medium, and slow releasing Olanzapine PLGA formulations. This type of an approach has been recommended by the FDA [1] and has been used by other authors who attempted a Level A correlation with injectable implants having varying release rates [4]. As expected, slopes using the Nelson-Wagner (Figure 9) and fractional AUC (Figure 10) approaches were around 1.10 and 1.12, respectively, once again confirming that \textit{in vivo} release for the fast, medium, and slow formulations followed a similar trend in which there was minimal lag \textit{in vivo}. The results in Figures 9 and 10 demonstrate an excellent correlation ($R^2$ value greater than 0.96) between \textit{in vitro} release of Olanzapine from PLGA microspheres and \textit{in vivo} release, represented by fractional AUC and the FDA approved Nelson-Wagner method. To our knowledge, the results in this study are the first time an IVIVC has been attempted and successfully achieved with Olanzapine PLGA microspheres.
Further, these results suggest that assessment of in vitro release using the modified dialysis method is an excellent predictor of in vivo behavior of a small molecule, Olanzapine, formulated with PLGA of varying molecular weight and copolymer composition. Similar results were reported on peptide PLA and PLGA microspheres. For instance, Woo et al. used the modified dialysis method to evaluate in vitro release from Leuproline PLGA microspheres [29]. In another study, Kostanski et al. used the modified dialysis method with Orntide microspheres formulated with 50:50, 75:25, and 85:15 PLGA and also Orntide PLA microspheres [27].

In addition to being a regulatory requirement, studies on IVIVC are extremely beneficial as they minimize time, labor costs, and expenses needed to perform human or animal studies with conventional or extended release products. Further, having an IVIVC reduces the need for unnecessary use of human subjects or animals to evaluate drug release [7]. While there is plethora of IVIVC studies published on
oral dosage forms, there are fewer reports on this subject with long acting injectables, possibly due to the lack of compendial methods that can be used to assess drug release from extended release injectables. The research presented in this paper has addressed this gap by using a systematic scientific approach to selecting an in vitro release method and establishing its suitability to predict in vivo behavior. The work presented here also confirms that a suitable in vitro method can be used as an indirect measurement of drug availability for complex dosage forms such as PLGA microspheres where formulation factors undergo extensive evaluation prior to selection of a suitable copolymer that can provide a desirable release pattern having clinical relevance.

4. Conclusions

A modified dialysis method was selected to characterize in vitro behavior of Olanzapine PLGA microspheres prepared
using varying molecular weights and copolymer composition. This method was able to accurately discriminate the formulations on the basis of release rates. Rank order of drug release in vitro and release profiles were nearly similar to those obtained in vivo, either by deconvolution (Nelson-Wagner method) or using the fractional AUC method. An excellent 1:1 linear Level A correlation between in vitro and in vivo release was obtained for all the formulations evaluated, suggesting that the modified dialysis in vitro technique was suitable for in vitro release assessment of Olanzapine PLGA dosage forms.

**Conflict of Interests**

The authors declare that there are no conflict of interests.

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