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IN VITRO RELEASE TESTING

The Issues & Challenges Involved in In Vitro Release Testing for Semi-Solid Formulations

By: Qiuxi Fan, PhD; Mark Mitchnick, MD; and Andrew Loxley, PhD

INTRODUCTION

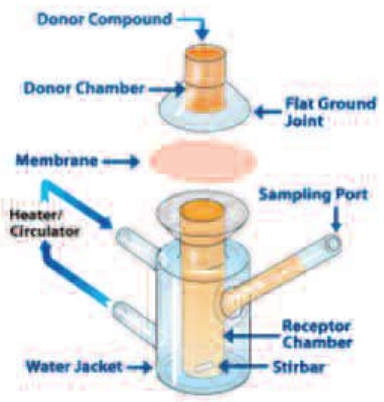
The use of an in vitro release test (IVRT) to evaluate drug release from semi-solid formulations has become the routine test for topical product development. Like the dissolution test for solid dosage forms, IVRT for semi-solid dosage has become increasingly important. As FDA Guidance puts it, "In vitro release is one of several standard methods that can be used to characterize performance characteristics of a finished topical dosage form (ie, semi-solids like creams, gels, and ointments)… A variety of physical and chemical tests commonly performed on semi-solid products and their components (eg, solubility, particle size, and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, IVRT has shown promise as a means to comprehensively ensure consistent delivery of the active component(s) from semi-solid products. An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between pre-change and post-change products… Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug(s) it contains should show up as a difference in drug release."[1]

Based on FDA Guidance, the IVRT method for topical dosage products is built on an open chamber diffusion cell system like the Franz diffusion cell system (Figures 1 and 2) with a synthetic polymeric membrane.[2] The membrane separates the donor part containing test product from the receptor part filled with medium (usually PBS buffer). Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor medium. At predetermined time points, an aliquot of medium is removed from the receptor part for drug content analysis either by high pressure liquid chromatography (HPLC) or other analytical technique, and the same amount of fresh medium is refilled into the receptor to keep constant volume. Theoretically, release is proportional to the square root of time, ie, a straight line in the release profile.[1]

This paper discusses different IVRT set-ups for different systems (one-phase and two-phase systems) of topical products and their respective release profiles, as well as highlighting the challenges involved in collecting useful data and how to overcome them.

FIGURE 1

Franz Diffusion Cell



ONE-PHASE SYSTEM

There are two one-phase systems to be discussed: a water-based system, such as hydroxyethyl cellulose (HEC) gel with peptide as the API, and oil-based systems, such as 1-octanol solution or light mineral oil suspension of either antibiotic or low molecular weight agents like lidocaine or caffeine as the API.

Water-Based System

Two HEC gels with different concentrations of a peptide API, and a poloxamer gel with the same peptide, all containing Transcutol® as a penetration enhancer have been tested

using the IVRT method at Particle Sciences Inc. Because of the relative simplicity of the water-based formulations, IVRT was carried out without modification from the FDA Guidance, using the experimental configuration presented in Table 1, and the release profiles obtained from the three formulations are shown in Figure 3.

It is obvious that for water-based one-phase systems, the regular IVRT method works well with no need for modification, and differences between formulation types and API loading within a formulation type are clearly observed.

Oil-Based System

Fan et al investigated the controlled release of an antibiotic drug (doxycycline HCl) from its solution/suspension in an organic solvent through a porous membrane.[3] When formulated as a simple system of API solution/suspension in 1-octanol/light mineral oil, IVRT results were also dependent on API concentration in the formulations: 5 mg/ml (Sol. 1) or 10 mg/ml (Sol. 2). A similar IVRT procedure was performed as for the water-based formulations, except that a hydrophilized polyvinylidene fluoride (PVDF) membrane (Millipore, 0.1-micron pore size) was used instead of a nylon one. Table 2 shows the permeation data, and Figure 4 presents the release profiles.[3]

From these two IVRT examples of different one-phase semi-solid systems, it is not difficult to observe that one-phase systems pose little challenge for the IVRT method mainly because (as the name "one phase" indicates) either a simple diffusion or partitioning is the major mechanism for API transport through the polymeric membrane. Therefore, different formulations are easily distinguished.

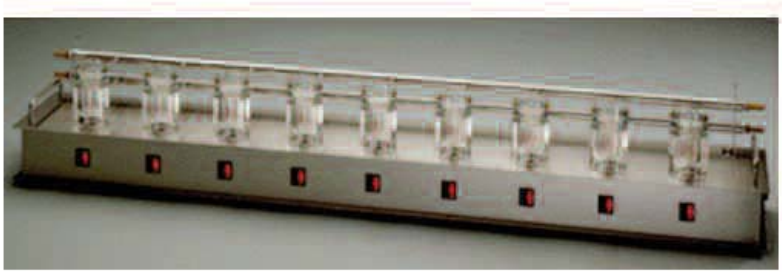
TABLE 1

IVRT Configuration

Diffusion cell	PermeGear®9-station Franz cell stirrer
Weight of sample gel	~ 0.3 grams
Membrane	GE®, Megna, Nylon membrane, 0.45-micron pore size
Receptor medium	PBS
Sampling aliquot	300 microliters
Sampling time	0.5, 1, 2, 4, 6, and 24 hrs

FIGURE 2

9-Station Franz Cell Stirrer



TWO-PHASE SYSTEM

Two-phase systems are more complex than one-phase systems because many more factors are involved, such as API solubility in the two phases, API partitioning between the two phases, interactions within the system and between the emulsion, and membrane interface. And these factors might pose challenges for IVRT to differentiate formulations or even to achieve a reliable release profile.

Oil-in-Water (O/W) System

The O/W emulsion is the most widely applied system in semi-solid dosage products because of its fast API release, and its relative stability and ease of application to the skin. In most cases, because the API is dissolved in the aqueous continuous phase, there is no major barrier to the API's transport through the formulation and into and through the polymeric membrane during the IVRT experiment.

At Particle Sciences Inc., several formulations containing the oil propylene glycol (PG), water, and a low molecular weight microbicide as the API have been tested using regular IVRT conditions. The same IVRT configuration was used except that the receptor medium was a mixture of PBS and ethanol because of this particular API's low solubility in PBS alone. As shown in Figure 5, formulations of the same concentration of API dissolved/dispersed in different phases were easily distinguished from their IVRT release profiles.

Water-in-Oil (W/O) System Using Peptide as the API

In addition to the O/W system, IVRT of water-in-oil emulsions using a higher molecular weight peptide as the API has also been performed at Particle Sciences Inc. Compared to the O/W system, the peptide emulsion system presented the following several challenges for IVRT:

- The high molecular weight of the peptide (close to 2000 Daltons), high solubility in water, and much lower solubility in the continuous oil phase mean that partitioning from the aqueous internal phase into the non-aqueous continuous phase may not be a strong enough driving force for the peptide to diffuse through the membrane.

- The W/O formulation contains a large volume fraction of aqueous phase to dissolve the API, with a relatively small amount of oil-phase components surrounding it as a continuous phase. Within such a tightly bound structure, the peptide may not diffuse from the water phase through the continuous oil phase and release to the medium.

- If negligible release is observed, the IVRT configuration would need to be changed or reformulation with another selection of oil phase and/or emulsifier be carried out.

TABLE 2

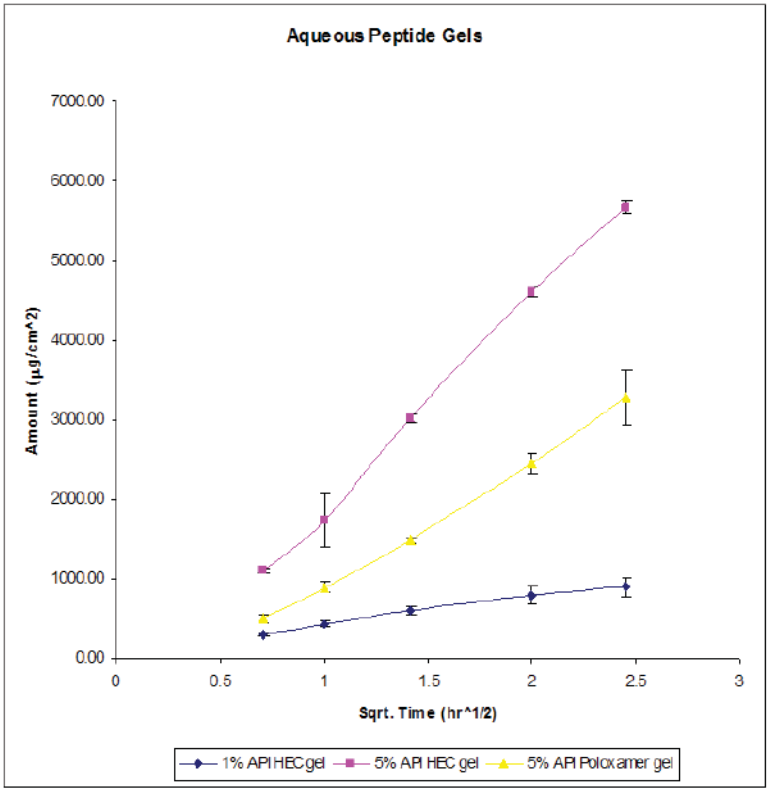
Permeation Data Using 1-Octanol as an Oil-Based System[3]

Diffusion System	Permeability (cm/hr)	Flux µg/cm² hr)	*Q_{24} (µg/cm²)
Sol. 1	0.015 ± 0.003	72.8 ± 12.2	516 ± 146
Sol. 2	0.015 ± 0.002	149.7 ± 21.8	2521 ± 538

*Q_{24}, receptor concentration after 24 hrs.

FIGURE 3

IVRT Release Profiles of Water-Based One-Phase System



Initial IVRT was carried out by the routine se-tup shown in Table 1. As expected, zero release was observed after 24 hrs, which illustrated the challenges previously outlined. Other research groups also indicated that a solubilized drug's delivery from emulsion systems, such as creams, lotions, or ointments, relies on this API's initial concentration, diffusion coefficient in the external oil phase, and partitioning coefficient between the internal water phase and the external oil phase.[4] As for the W/O emulsion system, the preferred partitioning toward the internal water phase would keep the API rarely available in the external oil phase. At the same time, for the API going through the membrane into the aqueous medium, diffusion occurs through the membrane pores filled with medium and is influenced by the partitioning coefficient of the API between the bulk solvent (ie, the continuous oil phase) and the aqueous solvent in the membrane pores.[5] In this case, as this high molecular weight peptide API has much higher solubility in water (> 100 mg/ml) than in the oil phase (< 10 mg/ml), not surprisingly, partitioning was always favored toward the water phase; therefore, diffusion through the continuous oil phase into the aqueous medium generally was not observed. The major challenge here is that if the continuous phase is different from the aqueous phase containing the API, it would be very difficult for the API to transport through the interface between the carrier fluid and the formulation by diffusion and/or partitioning. In another case, if the API is in a dispersed phase whose continuous phase has a sharp interface with the collection medium, then release will be even lower due to reduction in the diffusion of API through the oil phase, and the fact that the whole formulation will not pass through the membrane.

In order to overcome this delivery challenge, a modified IVRT

configuration was proposed to achieve a measurable release profile from the W/O emulsion system:

- Use a larger pore size (0.8 microns, 1.0 micron) and/or hydrophobic membrane (Celgard® membrane, PTFE membrane) to facilitate the emulsion transportation.
- Increase the concentration of API in the emulsion.
- Add organic component to the receptor medium, such as ethanol, to improve wetting the membrane.[6]

After implementing the new set-up, distinguishable release profiles were observed from different W/O emulsion systems.

SUMMARY

In the topical pharmaceutical arena, the application of IVRT to investigate drug release rates from emulsion formulations has received increased attention throughout the past decade. This paper analyzed the issues/challenges related to the use of IVRT for different emulsion systems: a one-phase (either oil or water) system and a two-phase (O/W, W/O) system, and whether IVRT can differentiate formulations. One-phase systems and O/W two-phase systems with the API in the aqueous phase (or in the dispersed oil phase but with a non-zero solubility in the aqueous phase) pose little challenge for IVRT with a wide range of membrane choice and medium selection based on API properties. On the other hand, for W/O two-phase systems, the challenges for IVRT are significant and stem from the API solubility issue in the two phases, the API partitioning between the two phases, oil phase membrane-wetting

FIGURE 4

IVRT Release Profiles of Oil-Based One-Phase System

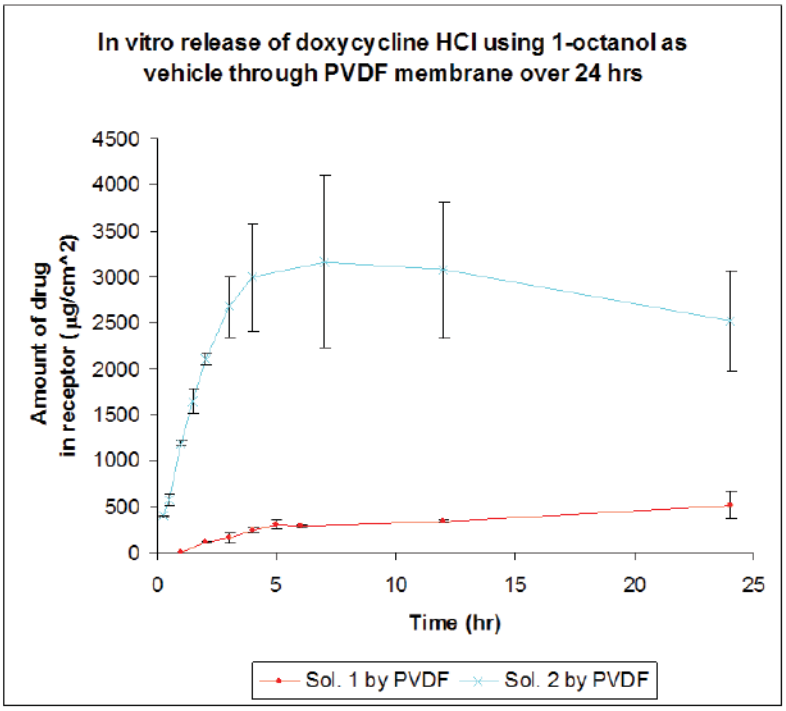


FIGURE 5

IVRT Release Profiles of O/W System

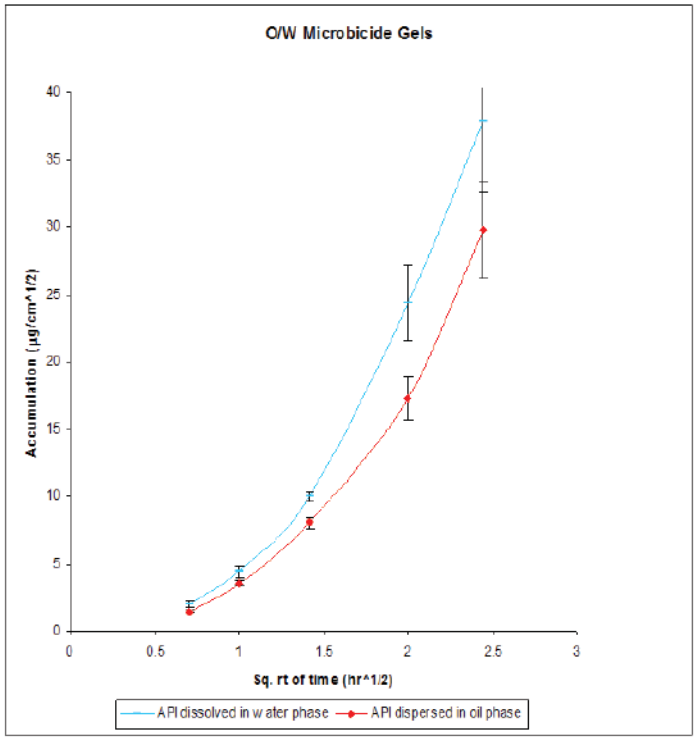
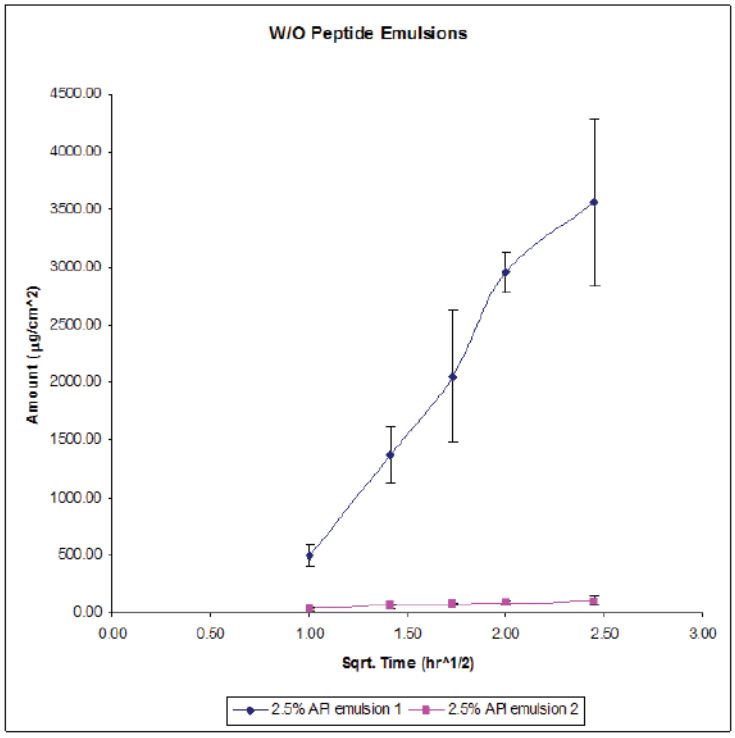


FIGURE 6

IVRT Release Profiles of W/O System



issue, and slow release issue. In the case of O/W/O and W/O/W systems, they behave similarly to W/O and O/W systems, with an additional complicating phase.

Differing from case to case, the regular IVRT set-up may need to be modified to meet the requirements of different emulsion systems as well as different APIs. The present paper used a high molecular weight peptide API in a water-in-oil formulation as an example of how to overcome these challenges.

It is evident that the regular IVRT procedure needs to be modified to meet the requirements of different emulsion systems as well as APIs. The present paper used a large MW peptide as an example of how to overcome those challenges based on our successful IVRT experiences for different emulsion systems here at Particle Sciences Inc. Now that IVRT can be adapted to evaluate all types of formulations, the next challenge is the correlation between in vitro and in vivo release results, which is currently under intense investigation at the company.

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BIOGRAPHIES

Dr. Qiuxi Fan joined Particle Sciences, Inc. in 2006 as a Chemist focusing on preformulation and IVRT areas with over 10 years experience in both industrial and academic environments of pharmaceutics and cosmetics. In 2005, Dr. Fan worked at Dermik Labs as a Scientist, the dermatology division of Sanofi-Aventis. He published several papers on a variety of topics from passive transdermal/topical delivery to active iontophoretic delivery to applying intelligent polymers (ie, temperature-sensitive gels for transdermal delivery of antibiotics) in the Journal of Controlled Release, Pharmaceutical Research, etc. He is also the inventor of two pending US patents related to transdermal/topical drug delivery. Dr. Fan earned his PhD from New Jersey Institute of Technology.

Dr. Mark Mitchnick is the CEO of Particle Sciences. Dr. Mitchnick holds approximately 20 issued and pending US and international patents related to nanoparticle production, skin care formulations, self-sterilizing catheters, and encapsulation and stabilization of active ingredients. Dr. Mitchnick earned his BSc in Animal Sciences from Purdue University and his MD from Georgetown University Medical School. He was trained in Paediatrics at The New York Hospital, Cornell Medical Center.

Dr. Andrew Loxley is Manager of Special Projects at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, many based on novel and proprietary nanotechnologies, in fields from HIV vaccine and microbicide development to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he worked as a researcher in the nanotechnology space. British-born, he earned his BSc in Chemistry from the University of Sussex and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol.