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Strategies for Testing Drug Release from Nano-Sized Forms of Therapy in Vitro: A Review

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Abstract: *The techniques for establishing an IVIVC and studying real-time drug release from nanoparticulate drug delivery devices are included in this paper. Drug release is presently measured using a range of approaches, including sample and separate (SS), continuous flow (CF), dialysis membrane (DM) methods, and a combination of these, in addition to cutting-edge methods like voltametry and turbidimetry, since there are no compendial standards in place. The fundamentals of each approach are covered in this overview, along with their benefits and drawbacks, including difficulties with setup and sample. The SS method's straightforward setup requirements enable direct monitoring of drug release, although sampling is laborious. Sampling is simple when using the CF approach, although setup takes some effort. The DM makes setup and sampling simpler, but it may not be appropriate for medications that attach to membranes. Although such approaches may only be able to monitor drug release in real time for certain kinds of medications, they may provide an opportunity. Dialysis has been used to acquire Level A IVIVCs among various techniques, either by itself or in conjunction with a different procedure and a sample. The creation of mathematical models that explain drug release processes and aid in the construction of dose forms at the nanoscale should be the main goals of future research.*

Keywords: Testing drug

I. INTRODUCTION

Since studies demonstrating the effectiveness of polycyanoacrylate and poly-ε-caprolactone nanocapsules for ocular administration were released more than 20 years ago, a number of articles have emphasized the advantages of using nano-sized dosage forms for imaging and medicinal applications. Benefits from nanoparticulate preparations, including better drug solubility and stability, greater performance, and higher effectiveness, have in fact been well-established. The design and development of numerous novel dosage forms and complex delivery therapies, including liposomes, nanoemulsions, nanocrystals, polymeric nanoparticles, solid lipid nanoparti-cles, nanofibers, and dendrimers, to treat a range of disease states, has been greatly aided by the growing interest in nanotechnology-based drug delivery systems. For instance, studies have looked at the use of fenofibrate nanoparticles to treat hypercholesterolemia and the use of cyclosporine nanoparticles to prevent cancer. It should come as no surprise that a number of nanoparticulate formulations are now the subject of clinical research for the intramuscular, subcutaneous, oral, and intravenous administration of a variety of therapies, including antigens, antibiotics, and cytostatics.

These formulations may have sizes ranging from 1 to 100 nm, according to the ISO specification. The 10–100 nm size range is thought to be ideal for nanoparticulate preparations because sizes bigger than this are rapidly opsonized by the reticuloendothelial system's macrophages, while sizes smaller than this have a higher tendency for renal clearance and tissue extravasations. Thus, a range of less than 10–100 nm (in at least one dimension) for nanoparticulates seems to be widely recognized for medical and therapeutic purposes, with a few outliers where sizes more than 100 nm may be acceptable. Because of their tiny size, nano-sized dosage forms have an exceptionally high surface-to-volume ratio, which modifies their chemical, physical, and biological characteristics and enables them to pass through cells and tissues. Without fail, in vitro release testing is a crucial analytical instrument used to examine and determine the behavior of products at different phases of medicinal product development and life cycle management. An in vitro release profile, when properly constructed, may provide fundamental insights into the behavior of the dosage form and

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product development. It makes sense that in vitro release testing is more important for complicated dose forms like nanoparticulates.

Although significant progress has been made in the creation of nanoscale dosage forms, there are currently no official or compendial guidelines for conducting in vitro release testing. Despite efforts to modify the medicinal agent's pharmacokinetics and pharmacodynamics by using the current USP equipment for in vitro barriers. This distinct feature of nanoparticulate preparations has been used to target difficult in vivo targets, such as particular cells or organs, with medicines. An additional effect of improved transport to the intended location is an increase in the drug's potency, which carries the risk of increased toxicity from the carrier material and hence diminished safety. As a result, evaluating the product's performance and quality becomes essential when developing nanoparticulate dosage forms.

Similar to the majority of dosage forms, many in vivo and/or in vitro investigations may be conducted to confirm the product's quality and performance. Among them, drug release kinetics is a crucial measure for evaluating the safety and effectiveness of products because it offers important insights on dosage form behavior. A growing number of people are looking at in vitro release as a stand-in test for product performance since it's less expensive, takes less time, labor, and doesn't need human subjects or animals as it does for drug release kinetics data. In fact, in vitro release testing has been widely employed to anticipate in vivo behavior. This has been the case historically for conventional dosage forms such as tablets and capsules (i.e., dissolving), and more recently for new dosage forms such as implants and injectable biodegradable microspheres. The physiological temperature of 37°C is often used for in vitro release studies; however, testing at higher temperatures has sometimes been investigated to describe drug release from a range of dose forms [18, 19]. Some of the key objectives of in vitro release testing are one or more of the following: assessing the effect of formulation factors and manu- facturing methods on the drug product, routine assessment of quality control to support batch release, substantiating product label claims, establishing an in vitro in vivo correlation/relation- ship (IVIVC/R), assuring product sameness under the SUPAC guide- lines, as a compendial requirement drug assessment of nanoparticles, the set-ups were designed primarily for oral and transdermal products and as such pose many challenges during a release study. As a result, a number of compendial and noncompendial in vitro release techniques have been used and documented. In vitro testing for nanoparticulates undoubtedly lags behind the advancements made in the creation of new medicinal products.

Over the past ten years, a number of international in vitro release workshops have been co-sponsored by the US FDA (Food and Drug Administration), FIP (Federation International Pharmaceutique), AAPS (American Association of Pharmaceutical Scientists), and several other scientific groups and agencies in response to the pressing need for improved product safety while maintaining the quality of novel dosage forms like nanoparticles. With a widespread agreement that dissolution or in vitro release testing was a crucial technique in pharmaceutical development and quality control for a multitude of dosage forms, both classic and innovative, the workshop results were published as position papers. The attendees also emphasized how novel and special dosage forms differ greatly from traditional formulations in terms of their characteristics, such as the site and mode of administration. For this reason, careful consideration should be given when choosing the apparatus, release medium, agitation (flow rate), and temperature. The workshops determined, in summary, that nanoparticulate preparations were classified as those “dosage forms requiring more work before a (disso- lution) method can be recommended,” along with a few other innovative dosage forms.

In a different project, the US FDA's Center for Drug Evaluation and Research (CDER) Nanotechnology Risk Assessment Working Group released a regulatory statement detailing the risk assessment and management procedure for a fictitious oral nanomaterial medication. The Working Group determined that "dissolution/release rate" in this instance is a risk factor that might affect the assessment of the drug product's quality, safety, and effectiveness that contains nano-sized drug, i.e., during ingestion and in vitro release/dissolution. Therefore, it is impossible to overlook the value of in vitro release testing from both a regulatory and therapeutic product development perspective.

Thus, the goal of this study is to provide the reader an overview of the advantages and disadvantages of the current in vitro release techniques for nano-sized dosage forms. This paper is intended to function as a manual for creating appropriate methods for evaluating experimental formulations, commercial and clinical dose forms, and creating an in vitro in vivo correlation (IVIVC).

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In Vitro Release Methods

A great deal of effort has gone into creating equipment that is appropriate for evaluating in vitro release from nanoparticulates. Nevertheless, it is impossible to ignore other factors like agitation, release media selection, and so forth. Selection of release media for nano-sized dosage forms will depend on the site of administration as well as the site of action of the formulation; therefore, simulation of in vivo conditions may be challenging, in contrast to oral dosage forms where release media typically mimics pH of the gastrointestinal tract. The choice of release medium for the manufacture of nanoparticulates is typically determined by the technique, test sensitivity, and drug solubility and stability. Non-sink conditions have been used, even though maintaining sink conditions is preferred. Agitation will vary depending on the equipment employed. Agitation is often used to prevent dosage forms from aggregating during an in vitro release study. Similarly, the kind of in vitro procedure used determines the strategies for sampling and buffer replenishment (full or partial).

Therefore, one of the three categories—sample and separate (SS), continuous flow (CF), and dialysis membrane (DM) methods—can be used to evaluate drug release from nano-sized dosage forms. More recently, there have also been reports of devices that integrate the concepts of the SS and DM or the CF and DM. Finally, several new techniques using voltametry, turbidimetry, and other similar techniques are spoken about. A short summary, modifications, extra factors, benefits, and drawbacks are given for each of these approaches.

Sample and Distinguish. Using the SS technique, the drug release is measured by taking a sample of the release medium (supernatant or filtrate) or the nanoparticles after the nanoparticulate dosage form is added to the release media, which is kept at a steady temperature. Numerous modifications to the SS method have been documented in the literature; these variations include variations in setup, container capacity, agitation mechanism, and sample strategies.

Set-ups such as USP I (basket), USP II (paddle), or vials are often documented and typically rely on the amount of release medium used in the in vitro release investigation [7, 38–40]. For example, in vitro release vessels were utilized with greater quantities (600–900 mL) of release fluid, whereas vials were used when the amount was less (1–15 mL).

Container size affects not only the kind of setup but also the agitation technique used in an in vitro release investigation using the SS method. Agitation of the release medium is essential to the in vitro release process of tiny sized dosage forms such as nanoparticles because it improves wetting and decreases the possibility of aggregation, both of which have an adverse effect on the in vitro release rate [38]. While the USP I or USP II apparatus is a convenient tool for agitating release media, other methods have been used to agitate the media contained in vials. For instance, although Prabha et al. reported using orbital shakers with DNA nanoparticles, Danhier et al. and Li et al. employed magnetic stirrers with Paclitaxel and BSA nanoparticles, respectively.

Physically isolating the nanoparticles from the release medium and analyzing either one is how drug release is tracked. The tiny size of the nanoparticles has required the employment of high energy separation methods such as centrifugation, ultracentrifugation, and ultrafiltration. Nevertheless, some publications have reported the use of syringe filters to accomplish physical separation between the release medium and nanoparticles. Filtration: Syringe filters with particle sizes up to 0.45 μm have been employed to remove supernatant in order to track the release of tiny compounds, such Celecoxib, into the medication. High energy separation methods, on the other hand, have been documented for use with bigger macromolecules such as DNA, BSA (bovine serum albumin), and insulin. Following separation, drug release is often observed by taking a sample of the supernatant or periodically decanting the whole supernatant content [7, 49]. In other cases, the separation process was followed by a destructive method study of the nanoparticles. Following the sampling process, the setup is replenished with an equivalent volume of new release media or buffer to ensure sink conditions are maintained throughout the in vitro release investigation.

The SS technique, in general, offers a straightforward way to track medication release. Most sample setups, agitation modes, and sampling methodologies are quite easy and simple to use using this approach. However, a number of real-world issues have been brought to light by the tiny size of nanoparticulate dose forms. Aggregation of nanoparticles during in vitro release, for example, seems to be a major issue. Furthermore, while filtration and other sample approaches appear plausible in theory, reports of drug adsorption on filters, filter clogging during the sampling process, and other issues have been made [50]. In fact, some of the difficulties often seen during sampling include persistent drug release throughout the high energy separation process, difficulties in physical separation even using high energy approaches, and so on [38, 45]. Nonsink circumstances have been shown to be more discriminating with poorly soluble

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medicines, despite the fact that sink conditions are advised when using the SS technique [51]. However, the SS technique provides researchers with an easy-to-use tool for monitoring in vitro release from nano-sized dosage forms, much as with microparticulate dosage forms.

There are very few instances of the CF approach for nano-sized dosage forms that have been published, in contrast to the extensively utilized SS method. For instance, the CF method and other techniques listed below were used to assess the release patterns of amorous nanoparticles and an unprocessed crystalline version of Cefuroxime Axetil, a BCS II cephalosporin antibiotic:

USP I (basket): 900 mL buffer at 100 rpm;

USP II (paddle): 900 mL buffer at 100 rpm;

USP IV (flow through cell): 900 mL buffer at a flow rate of 1.6 mL/min (peristaltic pump, closed loop) through a cell (internal diameter = 25 mm) and 0.2 μm membrane disc filter;

Dialysis bag (MWCO 12 kDa, inner volume = 7 mL) placed into a USP II (paddle) in vitro release tester (outer volume = 900 mL, paddle rpm = 100).

The findings showed that only the USP II paddle and USP IV equipment could produce full drug release, with the release profiles from the USP IV approach being clearly distinct.

It was believed that the immobilization of the nanoparticles was a contributing element to the USP IV apparatus's discriminating findings.

Similar to this, two techniques were used to achieve in vitro release in an experiment using nano- and microparticle laden strip films of Griseofulvin, another BCS II medication:

USP I (basket): 500 and 900 mL media at 50, 100, and 150 rpm;

USP IV (flow through cell): 100 mL media at flow rates of 4, 8, and 16 mL/min (peristaltic pump, closed loop) through a cell (internal diameter = 22.6 mm) and 0.2 μm membrane disc filter with the strip film loaded in 6 different configurations.

Results with configurations of the cell without round glass beads and C (strip film sandwiched between round glass beads) of USP IV at the highest flow rate were more discriminatory than all the other release profiles obtained in the in vitro study, even though complete release was only observed with USP I and configuration B (strip film positioned in the cell on top of round glass beads) of the USP IV method.

There is a dearth of research on the use of USP IV methodology in nanoparticulate dosage forms, but the CF method's application in microparticulate dosage forms suggests numerous important characteristics of the technique. For instance, the CF method's flow rates depend on the kind of pump (peristaltic vs. syringe) and filters (membrane vs ultrafilters). One major contributing factor to the sluggish or partial release from dosage forms has been identified as low flow rates. Generally speaking, the CF approach has made regular media replacement and sampling in closed (recirculating media) and open (nonrecirculating media) loop systems easier with the advent of automated equipment. However, there are a number of drawbacks to the CF approaches, including as high instrument costs, difficulty setting up, clogged filters, adsorption to the filter and glass beads, and difficulties maintaining a steady flow rate that leads in a large range of variability.

Dialysis Procedure. Dialysis Method (DM): The most widely used and adaptable technique for evaluating drug release from nano-sized dosage forms. This technique uses a dialysis membrane to physically separate the dose forms, making it simple to sample at regular intervals. Similar to the previous techniques, a number of DM adaptations with notable variations in setup, container capacity, and molecular weight cut-off (MWCO) have been documented in the literature.

The dialysis bag (regular dialysis) is the most often quoted of the several DM set-ups; additional modifications include the reverse dialysis and side-by-side dialysis set-ups.

It is a very easy and basic approach to examine drug release from a broad range of nano-sized dosage forms, such as nanospheres, liposomes, emulsions, nanosuspensions, and so on, because of how simple and easy it is to set up and sample with the DM. Nevertheless, problems with the standard dialysis technique have been documented. Media and dose form leakage from both sides of the dialysis bag setup is possible if the bag is not sealed appropriately. When equilibration durations are long or nonsink circumstances are present, incomplete release data could be seen [38]. Conversely, the disparity in equilibration durations may be used as a discriminant to differentiate the release characteristics of rapid and slow-releasing dose forms. The fact that medications that bind to the dialyzing membrane

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cannot be used with the DM is another important consideration. According to a review study on microparticulate dosage forms, it is advised that the dialyzing membrane's appropriateness be evaluated before usage.

Combination Methods. A few papers have assessed drug release from nano-sized dosage forms by modifying the setups used in the SS, CF, and DM techniques. To facilitate sampling, the dialyzer is used in conjunction with the SS technique setup in the majority of these reports. The DM and CF setup is used in numerous articles to evaluate the in vitro release from nanoparticulates.

New Methods. In addition to the well documented SS, CF, and DM techniques, many more methods have been used to track drug release. Most of them seem to be directed towards medications that are electroactive. Although the methods may vary in theory or implementation, they have some characteristics, such as the fact that the dose form and release medium do not need to be physically separated. Furthermore, these methods provide the opportunity for real-time measurement.

Modeling Drug Release

Mathematical models for describing drug release patterns from nanoparticulate dosage forms have been used in very few papers. This is not unexpected considering the complexity of nanoscale dose forms and the difficulty of evaluating drug release. Nonetheless, a few writers have explored the significance of mathematical models and tried to describe drug release. To examine the complicated nature of drug release from nanoparticles, for example, Barzegar-Jalali et al. proposed a generic model called reciprocal powered time (RPT). Alternatively, the Weibull and log-probability models were proposed. In a different study, Zeng et al. created a three-parameter model that takes diffusional drug release from liposomes and reversible drug-carrier interaction into account.

There are several benefits to using mathematical models to characterize medication release patterns. It may direct efforts to create simulators and allows for the clarification of medication release processes. Moreover, in vitro release patterns may be represented and contrasted using model parameters. Applying mathematical models to intricate drug release systems, however, requires care.

IVIVC

As per the US FDA, an in vitro property of an extended release dosage form, such as the rate or extent of drug release in vitro, and a pertinent in vivo response, like plasma drug concentration or amount of drug absorbed, are predicted by a mathematical model. Therefore, the value of an in vitro research is increased with the formation of an IVIVC, which is defined as a connection between in vitro release and in vivo behavior. An IVIVC will lessen the regulatory burden by reducing the number of in vivo investigations required for product approval, according to a 1997 FDA guideline paper. It also encourages the establishment of in vitro release standards that are therapeutically relevant.

Additionally, IVIVCs are divided into three tiers in the FDA regulation. The in vitro and in vivo release patterns are represented by a linear or nonlinear point-to-point relationship in Level A. Appropriate modeling or scaling is necessary if the connection is nonlinear. Level A, the most often used IVIVC level to get a biowaiver, describes the strongest connection among the three. A Level B correlation, on the other hand, compares summary metrics like the mean residence time (MRT) or the mean in vitro dissolution time with the mean in vivo dissolution time. Level B correlations are appropriate for an IVIVC but less selective than Level A correlations since many in vivo curves will have a comparable MRT value or mean in vitro disintegration time. A Level C correlation denotes the link between a pharmacokinetic measure (like $C\max$) and an in vitro release parameter (like % dissolved at a certain time). A Level C correlation is, however, seldom used and does not fully describe the nature of the in vivo release profile.

II. CONCLUSION

When it comes to innovative dosage forms such as nanoparticles, which lack regulatory or compendial norms, in vitro drug release evaluation becomes even more important as a means of evaluating the quality and effectiveness of the product. Numerous techniques have been used, each with pros and cons concerning quick buffer change, sample ease, and setup ease. An in vitro release technique should ideally mimic in vivo circumstances and release pathways, as well as facilitate the creation of an IVIVC. The development of appropriate mathematical models to forecast drug release

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behavior and release mechanisms that can be applied to a variety of nano-sized dosage forms should be the main goal of future research.

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