SPDS
Society for Pharmaceutical Dissolution Science

e-Disso

QUARTERLY NEWSLETTER

October - December 2015

Society for Pharmaceutical Dissolution Science was formed on 16th July 2012 in Mumbai with the objective of promoting science and technological development in the field of dissolution among pharmaceutical professionals, academia, students, regulatory bodies, etc.

SPDS is the only professional body dedicated to Dissolution and its application worldwide.

Vision :

To be one of the most prominent professional body focusing on Dissolution Science among the Pharmaceutical Industry and Academia

Mission :

To dissipate science & advancement taking place in the field of dissolution related to clinical application and methods.

Dear Readers,

It is great pleasure and honor for me to be Chief Editor for "eDisso". My sincere thanks to Dr. Ramswamy, Mr. Vijay Kshirsagar, Dr.Nandkumar Chodankar, and all the managing committee members of SPDS – Society for Pharmaceutical Dissolution Science for their support.

SPDS has Mission to dissipate the science and advancement taking place in the field of dissolution related to clinical applications and methods. As a pharmacist and pharmacologist, I believe there will always be a lot to understand and practice science, art and craft of dissolutions studies.

We have planned launch of eDisso in Goa during International symposium. This is going to be a quarterly publication and will be available to SPDS members on the website. "eDisso" aims to be a platform to young apprentice scientists and veterans of the dissolution field to interact with each other not only locally but also on a global scale. In the evolving scientific, regulatory, intellectual property and most importantly therapeutic mileu of pharmaceutical products, dissolution science holds a prime place. A thorough attention and care needs to be given to the field.

We are extremely delighted and honored to have Dr. Vinod Shah, Founder Chairman, SPDS in International Scientific Committee. He is so enthusiastic about "eDisso"that he sent his article even before the editorial was conceptualized.

It is also a great pleasure to have Dr. Umesh Banakar with us. It was indeed great opportunity for me and many to attend a workshop concluded by Dr. Umesh Banakar recently in Mumbai in the month of June 2015. Well revised was the concept that Dissolution is pivotal in understanding of intrinsic dissolution, dosage form development, quality control, quality assurance and prediction of clinical performance of product. The audience learnt a lot many tips on how to develop a discriminating method, that there can be different methods during development and for the purpose of quality control, how objectively to develop a method for dissolution, choice of USP apparatus, etc. In the second workshop in the series, Dr. Banakar emphasized on the importance of biorelevance of Dissolution testing and thinking out of the box - rather vessel). During development guidelines do play an important role, but they need not limit imaginations and approaches of the development scientist. Instead of getting a Q number specified in monograph or pharmacopoeia, it is necessary to understand and devise a dissolution profile keeping in mind the impact of several factors including physicochemical properties, physiological environment dosage form exposed to, patient factors, target in-vivo profile, etc.

We will witness presence of stalwarts from national and international borders such as Mr. Samir Hadouchi, France, Mrs. Vatsala Nageswaran, USA, Dr.Sandip Tiwari, USA, Dr. Mangal Nagarsenker, Dr.Padma Devarajan, Mr. Vijay Kshirsagar, Dr.Vinay Nayak, Dr. L. Ramaswamy, Dr. Mala Menon, Dr. Abha Doshi, Dr Nandkumar Chodankar, Dr. Suhas Yawle, Dr. Raghunandan, Mr. Anant Naik, Dr.Sengupta, Dr.Vijay Bhate, Dr. Vivek Jadhav, Dr.Prashant Dikshit, Dr. Krishnapriya Mohanraj.

Dr. Mala Menon and Dr. Smita Nayak agreed to be Assistant Editors and I extend my sincere thanks to them international borders including Mr. Samir Haddouchi. We have Mr. Santosh Mohite, Mr. Manoj Vishwakarma as Editorial Assistants. I invite both young and experienced scientists to share their views, experiences, problems and solutions with everyone in SPDS community.

Again happy science art and craft of dissolution studies. Hope to see many members, writers and contributors.

Best wishes
Dr. Prashant Bodhe

Exploring the Limits of Dissolution Science

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No doubt, drug dissolution, or better addressed as in vitro drug release to include all novel dosage forms, has reached a new height in its applications, not only in quality control area but also in drug development and in regulatory arena.

Dissolution / In vitro drug release testing over the last half a century has emerged as a highly valuable and powerful tool for assurance of drug product quality and drug product performance. Dissolution basically started as a tool to test the quality of a solid oral dosage form such as tablet. However, the dissolution testing has now expanded to all areas in the pharmaceutical industry, drug development as well as quality control. Its applications and usefulness has clearly expanded in regulatory arena of bioequivalence, to provide biowaiver and to reduce regulatory burden in drug approval process, and maintaining the product quality and performance.

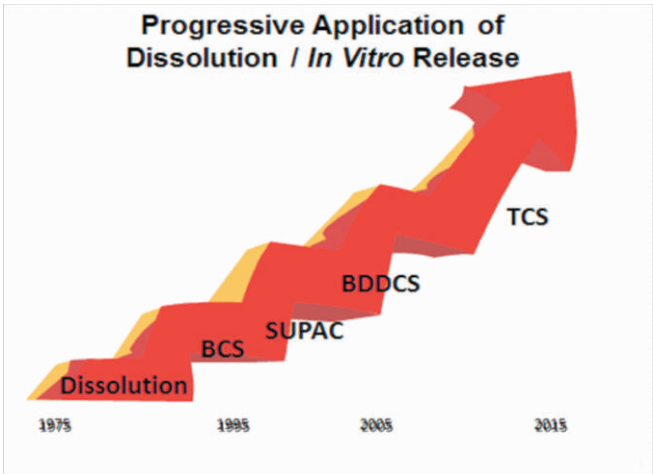
Field of dissolution is dynamic in nature. The dissolution testing is constantly improving and is growing. This has been primarily possible because of the advancing knowledge of dissolution science and technology and also improvement in design of dissolution equipment. Progress have been made to describe dissolution testing for oral dosage forms, tablets and capsules, novel drug delivery systems such as semisolids and transdermal patches. Dissolution test is considered as the most important performance test for almost all types of pharmaceutical dosage forms. More attention, with appropriate changes and adaptation in dissolution testing procedures are being considered for novel dosage forms such as nanoparticles and liposomes.

Research in dissolution has expanded globally for all types of pharmaceutical dosage forms. It is hoped that academia, industry, pharmacopeia and regulatory authorities will work together globally in enhancing and harmonizing dissolution regulatory requirements.

Importance and role of dissolution testing in regulating pharmaceuticals can be easily summarized into following three key points:

- Increasingly in vitro dissolution testing is relied on to assure product performance
- An appropriate dissolution test procedure is a simple economical method that can be utilized effectively to assure acceptable drug product quality.
- Appropriate dissolution test can be used as a surrogate marker for bioequivalence.

Progressively dissolution applications have expanded from quality control test established in 1975 to manufacturing process control, predicting in vivo performance, assuring product sameness after SUPAC related changes and to Biowaivers in 2000 based on BCS. BCS has further led to the development of BDDCS in 2005. The principles of dissolution can be further expanded to reducing the regulatory burden and providing biowaivers without sacrificing product quality. Applying SUPAC-SS principles and in vitro drug release test, a topical drug classification system, TCS, is proposed that can also provide biowaiver for certain topical drug products. The dissolution / drug release is a very powerful tool, and we have not yet reached the limits of its application (Figure 1), it is still growing.



SPDS, the society for pharmaceutical dissolution science, is dedicated to understanding and advancement of dissolution science, provides an ideal platform to discuss the advances in dissolution science. SPDS newsletter is definitely a welcome addition, and it is anticipated that dissolution scientists from different walks of life, academia, industry and regulatory, will join to keep the dialogue moving and spreading the knowledge of dissolution science.

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Pharmaceutical Drug Development Process: Role of Dissolution Testing

Pharmaceutical product design and development is still considered more of an art than science ! Nonetheless, a clear and comprehensive understanding of the multitude of factors influencing formulation design and development including evaluation, both in vitro and in vivo, are pivotal to succeed in the development of a pharmaceutical formulation. The constant quest of a pharmaceutical scientist and, formulation scientist in particular, is to implement appropriate steps during the development process such that the resultant formulation (product) meets the preset criteria for bioefficacy and ultimately clinical efficacy.

The development of pharmaceutical dosage forms often requires a multidisciplinary approach taking advantage of sound science and the technical skills required to combine these approaches. While the primary target of formulation development is to meet the preset and/or expected requirements of bioavailability (bioefficacy), each and every formulation cannot be evaluated for bioavailability for obvious reasons of cost, time and availability of limited resources. Hence, there are numerous prospective tests, such as in vitro dissolution tests, presumably biorelevant, are employed to screen the formulations during the various stages of drug development process. In so doing, the potential for success of the various formulations designed, developed and evaluated can be substantially enhanced if such surrogate tests are appropriately used. As a result, a bioefficacy centered pharmaceutical product design, development and evaluation, especially focusing on the role of dissolution testing in the drug product development is of paramount significance.

Role of Dissolution Test(ing)

Dissolution testing of pharmaceutical formulations/dosage forms, of course, is a regular quality control procedure in good manufacturing practice. Whether or not its numbers have been correlated with biological effectiveness, the standard dissolution test is a simple and, perhaps, an inexpensive indicator of the physicochemical consistency of the product. Dissolution data are also useful in the early stages of drug development and formulation. In the early stages of development, the researchers take steps to optimize drug and dosage form characteristics that will influence subsequent data concerning biological availability. In this sense, the dissolution test can be employed prospectively – while developing a formulation with appropriate drug release characteristics, and retrospectively – to assess whether a dosage form is releasing the drug at prescribed/predetermined rate and extent. The common principal assumption underlying these two uses of this test is that the dissolution test is able to adequately represent, if not predict, the biological performance, i.e., bioavailability, of the drug.

As of date, in vitro dissolution tests seem to be the most reliable predictors of in vivo availability. Although official test have great practical value, the fact that there is still a need for test more directly related to bioavailability has been recognized. While the bioavailability of drug substances and drug products in humans can provide a confirmatory evidence of a potential relationship between dissolution and physiological availability, it is often impractical to perform extensive and expensive human testing.

Challenges and [Innovative] Solutions

Numerous attempts have been made to understand, develop and potentially quantify the correlation between dissolution and bioavailability. Several compendial descriptions and regulatory guidelines are available that provide assistance and direction in establishing and demonstrating such correlations. However, a comprehensive understanding of the breadth of IVIVC from concept to development and demonstration along with its interpretation and applications in the drug development process is not readily available.

More importantly, "is it possible to simulate in vivo conditions within the in vitro dissolution test in the laboratory ?" proves to be often challenging. As a result, the understanding of the physiological/biological, i.e., in vivo conditions is of paramount importance to design an appropriate biorelevant dissolution test. The quest for such a dissolution test continues !!!

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A review of Dissolution and Dissolution Testing - From Noyes Whitney to the present.

In early formulation development, the major focus was on organoleptic aspects, compatibility and stability; the basic evaluation and Q.C. tests also measured only the parameters reflecting these attributes. However, in early 20th century the realisation that oral bioavailability is closely related to drug dissolution led to a new field of Biopharmaceutics and dissolution testing of drugs and dosage forms, and became an important area in Pharmaceutical Quality Assurance.

- **Origins of Dissolution testing (1897 – 1960)**

The study and experimentation to understand dissolution process and its rate, as a science was initiated in physical chemistry way back in the late 19th century. The pioneers were Noyes & Whitney, who in 1897,studied the dissolution of two sparingly soluble solids-benzoic acid and lead chloride. They used a simple apparatus consisting of glass cylinders submerged into vessels containing water. The cylinders were rotated at constant speed and held at constant temperature. From these studies, the basic Noyes Whitney equation and law evolved (Fig 1):

$$dC/dt = k(Cs-C) \quad \text{.....eq.1}$$

The basic mechanism of dissolution is attributed to a thin diffusion layer surrounding the solid surface/particles, through which the the molecules diffuse to the bulk aqueous phase.

Other contributors to basic dissolution research were Erich Brunner and Stanislaus von Tolloczko; their experiments investigated more parameters, and concluded that the rate of dissolution depends on the exposed surface, the rate of stirring, temperature, structure of the surface and the arrangement of the apparatus (Bruner and Tolloczko, 1900), and a proposed model was developed from basic Noyes Whitney equation, by letting k = k1S.Thus this modified equation is:

$$dc/dt = k1S(CS - C), \quad \text{.....eq.2}$$

where S is the surface area.

Further contributions by Nernst and Brunner by basingthe concept of diffusion layer and the Fick's second law, he Nernst–Brunner equation, was derived from Eq. (2) by letting k1 =D/(Vh); Thus Nernst-Brunner equation : dC/dt= [DS/(Vh)] . (Cs-C).,where D is the diffusion coefficient, h the thickness of the diffusion layer and V is the volume of the dissolution medium.

Later, an expression for Swith respect to weight was derived by the researchers, Hixson and Crowell in 1931; Hixson and Crowell Cube root equation which relates time to the cubic-root of weight and in the special case of sink conditions, where small concentrations are considered and the difference(Cs - C) can be considered as constant, the cubic-root law takesa simple form:

$$(W0)1/3 - (W)2/3 = k2t \quad \text{.....eq. 3(W0 is the initial weight and k2 a constant).}$$

These three groups of scientists laid the foundation of dissolution research, based on the dissolution layer model as a physical explanation for dissolution process, where the limiting step is the diffusion of molecules through the stagnant liquid film clinging to the solid surface.

Later models proposed for understanding dissolution were:

a) Wilderman (1909), Zdanovskii (1946), Miyamoto (1933) -the interfacial barrier model, proposing interfacial transport (high activation energy) as the major rate limiting step as against diffusion through the film.
b) Danckwert's model (1951) explains dissolution to be due to constantly renewed macroscopic packets of solvent reaching the solid surface and absorbing molecules of solute and delivering them to the solution. Combinations of above two models were also considered
c) Levich (1962) experimented on rotating disks and improved the theoretical model considering te centrifugal force on diffusion.

The concept of dissolution in pharmaceutical dosage forms was applied extensively only much later, in early 1950s, to replace the disintegration test used.

- **Establishment of relationship between dissolution and bioavailability -(1950 to 1980)**

During this period a lot of researchers have investigated and reported the effect of dissolution on bioavailability of several drugs. Some examples - Edwards (1951) –aspirin; Nelson(1951)-theophylline; Campagna & Levy (1963-64)-several brands of tolbutamide tablets; Martin et al (1968)-chloramphenicol, sodium diphenylhydantoin

and sulfisoxazole brands; Macleod (1972) -several ampicillin products; Lindenbaum (1071)-digoxin. This led to FDA initiatedinvestigations on digoxin and phenytoin products [Fraser et al -1972;Tyrer et al-1970; Chapron et al- 1979; Cloyd et al – 1980). All these studies revealed that in addition to the basic drug dissolution behaviour, excipients and processing methods also can have a marked influence on dissolution-bioavailability relationship.

Theseobservationsraised a lot of concerns and prompted the need for introduction of a better alternative to the disintegrationtest and resulted in the introduction of dissolution requirements in tablet and capsule monographs incompendia. Thus dissolution testing became an important tool for Q.C. and as an indicator of bioequivalence.In 1970, the USP introduced the basket stirred flask as dissolution apparatus(Type I), and 6 monographs required dissolution rate testing. Subsequent to this rapid strides were made in several fronts-

- Dissolution rate test equipment design evolving the various types .
- Research on factors affecting dissolution-stirring rate, media features, temperature, effect of excipients (solubilizers, complexing agents, lubricants)
- Mathematical modelling of dissolution curves to explain the mechanism of drug release, especially applicable to modified release tablets.
- Dissolution – an importantand essential tool for design and assessment of modified release dosage forms (1980)

The late 1970s saw the rapid development of sustained release dosage forms based on retardant coatings and matrix systems, osmotic systems, hydrogels.
These systems have to be designed with great precision and the majorparameter is the release behaviour of thedrug at a predictable rate. The kinetics of drug release from these systems is dependent on the typeand amount ofretardants used and the processing methods. Mechanism of drug release may be diffusion across membranes, diffusion across membranes or hydrophilic gel/swollen gel layer, osmosis, ion exchange etc. Diffusion is the principal release mechanism in most systems, and mathematical modellingand equations to assess these mechanisms have been developed. Important among them are:

- Higuchi's model- is suitable for systems in whichthe drug is homogeneously dispersed in the planar matrix andthe medium into which it is released acts as a perfect sink underpseudo steady-state conditions.Higuchi's equation gives the relationship forthe cumulative amount q(t) of drug released at time t:, which is given as :

q(t)/ q∞ =K t) 1 / 2 . . . . . .eq . q4 (. . .

is the cumulative amount of drug released at infinite time and K is a composite constant with dimension time- 1/2 related to drug diffusional matrix as well as the design characteristics of the system.

- Peppas model-is a a semi-empirical equation whichdescribes drug release from polymeric devices in a generalized way: q(t)/q∞= =K1tn where K1 is a constant reflecting the structural and geometric characteristics of the delivery system expressed in time- n units and n is a release exponent the value of which is related to the underlying mechanism(s) of drug .

- **Dissolution studies as a prognostic tool of oral drug absorption (1980-200)-**

Further to dissolution, the next step is the absorption of drug through the g.i. membranes to reach the required blood levels. Consideration of both the processes, viz. dissolution and permeability,the Biopharmaceutics Classification System (BCS) evolved. According to this system, a substance is classified onthe basis of its aqueous solubility and intestinal permeability, and four drug classes were defined :

Class I- high solubility/high permeability

Class II- low solubility/high permeability

Class III- high solubility/low permeability

Class IV- low solubility/lowpermeability

Using this system, the properties of drug substance can be combined with the dissolution characteristics of the drug product, to predict and get some insight intoin vitro–in vivo correlations, and thus dissolution could be used as a predictor of in vivo behaviour.A lot of efforts have been directed to develop biorelevant media which simulate the g.i. fluids including the fasted and fed states, as well as hydrodynamic conditions. However, we are still far away from the goal of using dissolution as a tool to predict absorption.

- **Current benefits of dissolution testing—**

a) Q.C. tool

b) Since 2000-Dissolution in theframework for BCS-Biowavers -Based on the BCS classification, the FDA in 2000 has provided regulatory benefit for highly permeable drugs that are formulated in rapidly dissolving solid immediate release formulations. The guidance classifies a substance to be highly soluble when the highest dose strength is soluble in 250mL or less of aqueous media over the pH range 1–7.5, while a drug product is defined as rapidly dissolving when no less than 85% of the dose dissolves in 30

min using USP Apparatus I at 100 rpm in a volume of 900mL in 0.1N HCl, as well as in pH 4.5 and 6.8 buffers. Thus, petitioners may request biowaivers for high solubility-high permeability substances (Class I) formulated in immediate release dosage forms that exhibit rapid in vitro dissolution.

c) In Quality by Design approach- Dissolution tests are an important and powerful Critical Quality attribute(CQA) in drug and dosage form development , which reflectsseveral material and process inputs.

- Challenges and Future directions-
- Dissolution testing of Novel systems, for routes other than oral require a lot of optimization and regulations and guidelinesare by far limited. A uniform and standard method as well as equipmentsneeds to be developed.
- Minituarizing the dissolution testing- involves small volume dissolution testing, which would be applicable to preformulation studies and new drug development, wherin the amount of samples are small. These can help the developer to screen and select initial molecules and polymorphic forms exhibiting best dissolution behaviour.
  This could also help understand supersaturation and precipitation tendencies.
- Development of equipments which can combine /mimic all the PK aspects, namely ADME.

References-

1) AristidesDokoumetzidisa, PanosMacheras,"A century of dissolution research: From Noyes and Whitney to theBiopharmaceutics Classification System" Int. J. Pharmaceutics, 321 (2006), 1-11.
2) Martin Kuentz,"Analytical technologies for real-time drug dissolution and precipitation testing on a small scale" J. Pharmacy and Pharmacology, 67, 2014, 143-159
3) TiinaHeikilla, "Miniaturization of Drug Solubility and DissolutionTestings" Academic dissertation, University of Helsinki, 2010
4) ShirzadAzarmi, Wilson Roa ,RaimarLo ¨benberg" Current perspectives in dissolution testing of conventional and novel dosage forms"Int. J. Pharmaceutics, 2006, doi:10.1016/j.ijpharm. 2006.10.001
5) Patrick J. Marroum,"History and Evolution of theDissolution Test"Dissolution Technologies, Aug 2014.

UPCOMING COURSES

COURSE III [19-20 October, 2015]
DISSOLUTION AND BIOAVAILABILITY: Fundamentals and Applications of IVIVC

COURSE IV [21-22 December, 2015]
IVIVC, BIOWAIVERS AND CLINICAL - APPLICATIONS OF IVIVC

COURSE V :
QbD in Dissolution Method Development:
QTTP, Critical Method Attributes, Discriminatory Method. DOE's, Method Finalization

OTHER EVENTS

Disso Europe 2016
May 5 & 6, 2016 at Turkey

Disso America 2017

Dr. L. Ramaswamy
Managing Director,
Soatx India Pvt Ltd, Mumbai

For any professional body to interact and communicate among the members, industry, and other prospective members, it is very important to have a communication media such as a news letter. I would even compare the media as equal to the Blood or body fluid or volume of distribution in our body. Perhaps it is the only unique substance or material which always flow and keep our life through out. I feel eDisso can do the same function at SPDS.

I wish to congratulate all SPDS office bearers, the Editorial board of eDisso, and mainly the Chief Editor, Dr. Prashant Bodhe who has initiated this movement of a news media with a name eDisso. Let it go and touch every Pharmaceutical Research &Analytical Scientist/Pharmacy Faculties/Students /college Libraries/Regulatory officer' stable once in three months from now.

Today is only a start and it has miles and miles to travel till it reaches the sky. Every Pharma professionals contribution in which ever forms has to be accepted which can add quality and value to eDisso.

Let us all commit to ourselves and SPDS that when any one receives the eDissocopy , the same has to be circulated to all his/herPharma Industry/academia/ regulatory contact with a cc to the Contac @SPDS.in so that next time the SPDS shall incorporate those mail id in the circulation list of eDisso.

My distant vision for eDisso is to make as an index journal so that it has its value globally. This means every one working on eDisso has to think, breath, and live with this long term vision of achieving the goal which is a dream today.

I may be unrealistic to some of you or over ambitious , that can we make eDisso as the window of Dissolution Science and its applications to the world of Pharmaceuticals which The nature has achieved over the years where every research scientists hows his hunger and thirst to get his paper/article published in The nature.

eDisso should invite posters/papers/articles related to Dissolution Science across the globe and the editorial board should evaluate the quality and publish this new media once accepted for publication.

I also would suggest to have awards and appreciation for the best papers/articles/posters published by SPDS. It can be even in the form of certificate, cash prize or a free registration to our seminars and symposiums.

I wish the entire editorial board all success in this initiative and assure my unconditional support and assistance required at any point of time to improve the quality of eDisso and circulation.

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Institute of Chemical Technology, University Under Section-3 Of UGC Act-1956,
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Dissolution Testing for Nanopharmaceuticals : A Continuing Challenge

INTRODUCTION: The past few decades have witnessed accelerated developments in nano technology applications in medicine. Various nano drug delivery syste msincluding liposomes, lipid and polymeric nanoparticles, nanosuspensions / nanocrystals, nanoemulsions and many other nanopharmaceuticals have been developed to improve physicochemical, as well as pharmacokinetic and pharmacodynamic properties of therapeutics. Nanosuspensions or nanocrystals are known to improve dissolution of poorly water soluble drugs and hence oral bioavailability. Targeting to various specific organs and cells becomes possible through nanotechnology. Nanoparticles of <100 nm are readily targeted to tumour cells by enhanced permeability and retention (EPR) effect, while nanocarriers of >200nm find application in targeted delivery for infectious diseases.

The nanodrug delivery explosion emphasises the need for standardised quality parameters to ensure product performance and quality, one critical parameter being in vitro dissolution. In vitro dissolution testing an important analytical tool during various stages of drug product development, can often serve as a screen for in vivo performance of drug delivery systems. When designed appropriately an in vitro release profile can reveal vital information on the behaviour of a dosage form, as well as details on the release mechanism and kinetics, enabling a rational and scientific approach to drug product development(1-3).

United State Pharmacopeia (USP) officially adopted in vitro dissolution testing in 1970 for oral dosage forms, which is an essential and regulatory tool for quality control of products. Over the years seven apparatus are recognised by the USP and extend from oral dosage forms to suppositories, transdermal and dosage forms for other routes of administration. Great strides in the design and development of nanopharmaceuticals dictate an urgent need for design of standard methods which could meet pharmacopeial/regulatory standards for in vitro release testing. The official dissolution apparatus cannot be readily adapted for nanopharmaceuticals due to the unique challenges posed by their size (4,5). This article briefly summarises various approaches evaluated for in vitro release testing of nanopharmaceuticals.

IN VITRO RELEASE METHODS FOR NANO PHARMACEUTICALS : No standard apparatus are defined and methods report various apparatus, media, agitation etc. Broadly four methods are delineated namely:

- Sample and separate method (SS)
- Dialysis membrane method (DM)
- Continuous flow method (CF)
- Continuous flow Dialysis membrane method (CFDM)

Sample and Separate (SS) method: This method involves direct introduction of nanopharmaceutical formulations in to the dissolution media maintained at constant temperature and monitoring drug release by sampling aliquots of the release media. Such studies are reported using various volumes of media, of differing compositions in containers ranging from tubes to beakers to vessels of the USP dissolution apparatus. A limitation was the unpredictable aggregation of nanoparticles in the dissolution medium which severely affected the reproducibility. An even more serious issue was ensuring that the undissolved nanoparticles from the dissolution media were not withdrawn in the aliquots, as normal filters used to withdraw aliquots are not fine enough to separate the nanoparticles. Several methods have been documented for the separation of nanoparticles from the aliquots using specialised syringe filters, centrifugation, ultracentrifugation, and even ultrafiltration(6-8).Nevertheless, although the SS method is a simple and straightforward approach it must be used with caution.

Dialysis Method (DM): This is a more popular method for the dissolution testing of nanopharmaceuticals. The nanoformulation is introduced into a dialysis bag which is sealed with clips or tied and introduced into the dissolution medium in a suitable container. As in the SS method no standard volume or composition of media, or even vessel is evaluated. However this method overcomes the major disadvantage of the SS method namely, separation of nanoparticles from dissolution media as the dialysis membrane limits direct transport of the nanoparticles into the dissolution medium, allowing only drug to diffuse out. An important limitation in this method is selection of a dialysis membrane of appropriate molecular weight cut off (MWCO). Further the unpredictable surface area of dissolution and the possibility of the dialysis membrane being a rate limiting factor in drug release could challenge validity of this approach. Leakage of the contents from the dialysis bag add to the challenge of reproducibility of release data (9).

Continuous flow (CF) method: An attempt to standardise basic parametrs of invitro dissolution testing resulted in the CF method which relies on the USP IV apparatus. The nanoformulation is introduced into the column with continuous circulation of dissolution media through column and drug release monitored. While this

apparatus minimises variables by fixing column size and flow rates the challenge of separation of nanoparticles that may leave the column undissolved as in the SS method described above, is not completely ruled out. Further clogging of filter which leads to slow flow rates and high pressure could produce errors in data (10).

Continuous flow Dialysis membrane method (CFDM): This method introduces a modified holding device with dialysis membrane(Fig 1) adapted to the CF column in USP IV and hence represents a combination approach of CF and DM. This combination overcomes limitations such as filter clogging and also separation as only drug would be released through the dialysis medium. Such an apparatus appears to be the most promising as on date. Advantages of this system include the adaptability to small samples and the use of changing dissolution media and volume at different temperatures and fixed surface area of the dialysis membrane, thereby ensuring better reproducibility. Facility to change the dialysis membrane adds to the versatility of the apparatus (11).

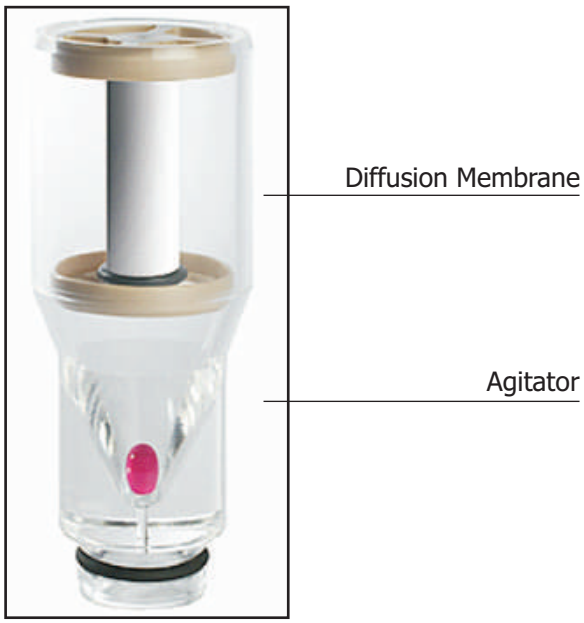

Figure 1: Holding device with diffusion membrane

Thoughts to ponder: Nanopharmaceuticals are developed for varied applications. When designed for oral delivery selection of dissolution media can follow guidelines specified for oral formulations based on the drug property and BCS class. Nevertheless for nanoparticles developed for tumour targeting selection of bio-relevant dissolution media could prove challenging. Would the fate of the nanoformulation in the body be the dictating factor? To mimic possible in vivo conditions should in vitro the release of intravenously administered nanoformulation for tumour targeting be carried out in two phases? Phase 1 to ascertain that there is no release of drug from nanoparticles in plasma/blood pH and Phase 2 monitoring immediate release in acidic environment representing tumour pH. For other indications what could be probable conditions. Developments for in vitro release of nanopharmaceuticals are yet elementary and need to evolve to address such challenges(12).

Scope: The scope for development of in vitro dissolution testing methodologies for nanopharmaceuticals is vast. From newer apparatus designs to challenges on adequate methodologies this field presents a vast arena to explore.

References :

1. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov. 2004; 3(9):785–96.
2. Liu Y, Sun C, Hao Y, Jiang T, Zheng L, Wang S. Mechanism of dissolution enhancement and bioavailability of poorly water soluble celecoxib by preparing stable amorphous nanoparticles. JPharm Pharm Sci. 2010; 13(4):589–606.
3. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul. 2001; 41:189–207.
4. Dokoumetzidis A, Macheras P. A century of dissolution research: from Noyes and Whitney to thebiopharmaceutics classification system. Int J Pharm. 2006; 321(1–2):1–11.
5. United State Pharmacopeia (USP). USP 34-NF 29. ed2011. Dissolution; p. 5091-7.
6. D. Heng, D. J. Cutler, H. K. Chan, J. Yun, and J. A. Raper,"What is a suitable dissolution method for drug nanoparticles?" Pharmaceutical Research, vol. 25, no. 7, pp. 1696–1701, 2008.
7. Y. Zhang, H. Wang, C. Li et al., "A novel three-dimensionallarge-pore mesoporous carbon matrix as a potential nanovehiclefor the fast release of the poorly water-soluble drug,celecoxib," Pharmaceutical Research, vol. 31,pp. 1059–1070, 2014.
8. M. Cetin, A. Atila, and Y. Kadioglu, "Formulation and in vitrocharacterization of Eudragit L100 and Eudragit L100-PLGAnanoparticles containing diclofenac sodium," AAPS Pharm SciTech, vol. 11, pp. 1250–1256, 2010.
9. G. P. Yan, R. F. Zong, L. Li, T. Fu, F. Liu, and X. H. Yu,"Anticancer drug-loaded nanospheres based on biodegradableamphiphilic ? -caprolactone and carbonate copolymers," PharmaceuticalResearch, vol. 27, no. 12, pp. 2743–2752, 2010.
10. L. Sievens-Figueroa, N. Pandya, A. Bhakay et al., "Using USPI and USP IV for discriminating dissolution rates of nanoandmicroparticle-loaded pharmaceutical strip-films," AAPSPharmSciTech, vol. 13, no. 4, pp. 1473–1482, 2013.
11. S. S. D'Souza and P. P. DeLuca, "Methods to assess in vitrodrug release from injectable polymeric particulate systems,"Pharmaceutical Research, vol. 23, no. 3, pp. 460–474, 2006.
12. Xu X, Khan MA, Burgess DJ. A two-stage reverse dialysis in vitro dissolution testing method forpassive targeted liposomes. Int J Pharm. 2012; 426(1–2):211–8.

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