SPDS
Society for Pharmaceutical Dissolution Science

e-Disso
NEWSLETTER

September 2019

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,

With great pleasure, and after a bit of a gap, we bring you one more edition of e-DISSO under the auspices of DISSO INDIA-NIPER 2019 conference being held at Chandigarh!

In this issue we have a mixed fare of interesting articles from international Experts as well as from Research Students and Faculty.

The first article is a thought provoking one "Past, Present, and Future of Pharmaceutical Dissolution Testing: A Disciplined Reflection and Synthesis" by Dr. Ajaz Hussain, in which in a lucid style, he has shared his experiential learnings on selected aspects of pharmaceutical "dissolution failures" and its relevance to human behavior and professional development.

The second article "Application of 'Joshi Capsules' Concept for the Sublingual Slow Delivery of "Drugs – Dissolution Aspects of Orally Dissolving Capsules" is from Dr. Hemant Joshi, who has written about his new patented concept in hard capsules, and its application for developing slow release mouth dissolving capsules; he has also dealt briefly on *in vitro* release study methods and IVIVC issues of such systems.

Another article by Dr. Harita Desai gives us glimpses of future dissolution technologies and equipments, like Teflon Flow through cells and Microfluidic approach in her article, "Methods in Drug Release Testing -Issues and Updates".

Dr. Hema Nair with her student, Ms. Nazia Begum has compiled a review on "*In vitro* drug release testing methods for *in situ* depot forming injectable formulations," for which no standard compendial methods are available.

Last article is a compilation by the research students of my group, Mr. Pankaj Sontakke and Mr. Ashish Sangve on "Food Drug Interactions: Factors affecting and *in vitro* methods to study the interactions"

In this issue we have added a new feature – an interview with a leading Professional; "Conversation with Dr. Padma Devarajan - a highly accomplished Researcher"

Additionally, we have the regular feature of News updates featuring the awards and honours received by many members of the SPDS Group.

The Editorial team of Ms. Tejashri Khadilkar, Dr. Ujwala Shinde & myself acknowledge the support from Ms. Bhakti, Ms. Isha & Ms. Hemali.

We invite voluntary participation from Academicians, Pharmaceutical Scientists and Analysts and Chemists to contribute in future. We propose to have one interview to be included in each issue. Another thought is to have a regular feature on "Biopharmaceutics and PK aspects of any one class/individual drug(s)" in future issues, for which we look forward to experts to contribute.

We are sure you will enjoy this issue. Happy Reading ! And look forward to your feedback and suggestions to enhance the forthcoming issues.

Dr. Mala Menon

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Past, Present, and Future of Pharmaceutical Dissolution Testing: A Disciplined Reflection and Synthesis

This paper shares a disciplined synthesis of the author's experiential learnings on selected aspects of pharmaceutical "dissolution failures" and its relevance to human behavior and professional development. Experience means practical contact (professionals have) with materials and events in the "real world," and it also means the feelings (of emotions) generated by contact with events. The experience thus has both objective (materialistic) and subjective (emotional) aspects; the main difference between the two – the objective is quantitative and subjective is qualitative. To be objective, experiential learning should account for, but not disregard, subjective feelings, specifically to mitigate the risk of biased memories, and recollections. Contemporaneously recorded notes and transcripts (e.g.; US FDA & Advisory Committee) can be valuable to ensure objectivity. Within this context this paper attempts an "experiential knowledge transfer" on essential aspects of "suitability and capability" of dissolution test methods pertinent to quality by design (QbD) and investigations of "dissolution failures" such as Out of Specification (OOS) observations, product recalls, warning letters and import alerts. The question - why the professional community should expect and plan for significant changes in practices related to dissolution testing in the 21st-century is explored in the context of "real-time release," continuous manufacturing, patient-centric drug development, and "real-world" evidence. A pedagogical narration writing style is developed to encourage critical thinking and encourage detection of dogmas and blind spots in practices.

Introduction

Drug exposure-response relationship is a foundational tenant of modern pharmacology. The rate and extent of dissolution of drugs in relevant physiological fluids is a causal mechanism for generating drug exposure in patients taking medicines in which a drug is in an undissolved (e.g., solid) state. It is desirable that the rate of drug dissolution be optimally calibrated for the intended therapeutic objective, be repeatable and reproducible.

In a study of pharmacokinetics when drug dissolution (or release from dosage form) process is rate-limiting, its rate and profile shape systemic drug concentration profiles and can be deconvoluted to estimate *in vivo* dissolution and correlated with dissolution measured *in vitro* (1, 2). Correlations, *in vitro* to *in vivo*, must be validated, and it must be recognized that these are "formulation specific" (3, 4).

Correlations are not causal, and hence there is "uncertainty" in the use and interpretation of *in vitro* dissolution tests. Both "uncertainty" and "validation" co-exist in the reality of pharmaceutical "Good" laboratory and manufacturing practices. The "Good" in practices, among other things, refers to validated lot-lot reproducibility (of calibrated dissolution rate for the intended therapeutic objective demonstrated to be repeatable during drug development). Note that the terms calibrated, repeatable, and reproducible are used here in a context which will be elaborated as this narrative is unfolded.

Knowledge (to know the ledge separating certainty and uncertainty), along with technology, is transferred from research and development (R&D) to operations and it is also gained via experience, especially when there is a need to ask Why many times (e.g., as in 5 Why) to investigate "dissolution failures" such as Out of Specification (OOS) observations. However, inability to get to the "root cause" of failure, repeatedly assigning the cause of "failure" to "human error," and to effectively correct and prevent its recurrence is an indicator of inadequate knowledge and development of professionals and quality management systems. On an extreme, breaching assurances of data integrity to "test into compliance" is BAD-I.

Information is not knowledge. Information is a source of knowledge which is necessary, but not sufficient to prevent "failures". The understanding gained via experiential knowledge leads to wisdom, which is in good practices and a path to professional development. The past, present, and future of dissolution testing provide an opportunity to illustrate the authors learning. At a high level, it is encapsulated in the phrase "care is research, knowledge is power, and wisdom is in practice."

This paper narrates his experiential learning; it does not provide a checklist to follow. The readers are invited to use the ensuing narrative to identify dogmas and blind spots in their practices while exploring the interrelationship between – uncertainty or knowledge (to know the ledges), validation and good (practices) in their context. It is anticipated that the paper will help readers to collect and connect the dots needed to solve the problem they may be confronting. The paper begins with a look towards the future – where are we going?

The Future

The exponentially increasing costs of disease care are bankrupting many nations, including the world's most prosperous nation. Amid the political turmoil, each nation is seeking to secure its supply of pharmaceuticals. In the USA, the 21st Century Cures Act, among other things, mandates US FDA to place emphasis on patient-centric development, real-world evidence, and encourage and fund research on continuous manufacturing of pharmaceuticals.

In the 21st Century Assurance context, the future of dissolution testing can be envisioned as providing a higher level of assurance than in the past via - (a) effective correction and prevention when "failures" occur, (b) demonstratable evidence (e.g., in regulatory application) capability to prevent "dissolution failure", (c) alternate "real time" control and release in batch or continuous manufacturing, and (d) bed-side or patient verifiable assurance of (personalized) pharmaceutical quality and performance attributes via a App.

In the future, the primary source of affordable pharmaceuticals – the generic drugs – can be expected to struggle more to provide the assured quality patients need. A recent "Open Access" publication entitled "Pharmaceutical "New Prior Knowledge": Twenty-First Century Assurance of Therapeutic Equivalence" describes these challenges in more detail (5).

Alongside, the regulators can be expected to utilize non-contact and non-destructive technologies to verify optimal calibration, repeatability, and reproducibility of dissolutions and other critical to quality attributes and detect BAD-I practices. As a former regulator, the author had in 2004 envisioned and developed a prototype artificial neural network to detect unusual patterns in (metoprolol tablet) dissolution data in FDA submissions. It is illustrated in Figures 1 and 2, below. These figures are from his 2004 presentation in Japan (6).

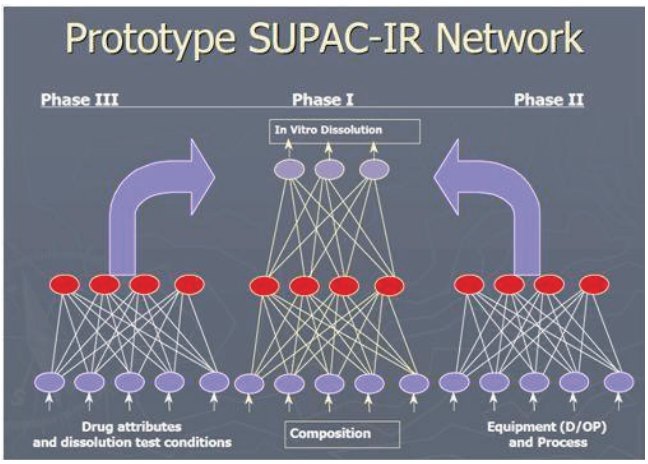


Figure 1: A prototype of an artificial neural network to map the relationships between dissolution and formulation and process variables.

Test Formulation	Prediction Error % : Q(10)	Prediction Error % : Q(30)
ANDA 1	-29	-15
ANDA 2	-2	-2
ANDA 3	13	13
ANDA 4	- 6	- 4
ANDA 5	25	4
ANDA 6	7	2
ANDA 7	14	-5
ANDA 8	- 4	4
ANDA 9	- 14	7
Innovator	6	-7

Figure 2: Prediction error for two dissolution time points in FDA submissions, the high prediction error used as an indicator to flag data that are not consistent within the pattern of dissolution relationships derived from prior knowledge.

The Present

In the present state, efforts are being expended to ensure "clinical relevance" of dissolution testing, for developing and encouraging methodologies for "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development" - the title of a recent workshop (7). Beyond the implementation of clinically relevant dissolution specifications (7, 8), the need to replace conventional dissolution testing with methods that enable "improved life-cycle management," which entails ability for continual improvement, are being sought. Improving process understanding within the context QbD, real-time release testing (RTRT), and continuous manufacturing are "hot" topics of discussion and debate within the community of knowledge.

Meanwhile, in practice, we continue to yearn for "Six Sigma Quality" (9), and we struggle with recurring OOS, high rate of "invalidated OOS investigations,"product recalls, BAD-I Warning Letters and so on. Why?

Why struggle? Does the past hold an answer we may be ignoring?

Perhaps now is the time to unfold an explanation of what was noted in the introduction - *the terms calibrated, repeatable and reproducible are used here in a context which will be elaborated as this narrative is unfolded.* Measurement system adequately "calibrated" and demonstrated as "repeatable" (e.g., same analyst, instrument, laboratory) and "reproducible" (e.g., different analysts, instrument, laboratories) are foundational to ensuring manufacturing process stability or suitability and capability (see "Process Capability Roadmap" on Slide 7 of Ref. 16). This aspect generally remains underappreciated within the community of

knowledge. The community to a more considerable extent is focused on developing research methodology to improve the clinical relevance of dissolution testing. Research methods are often not suitable for routine quality control laboratory applications - for "lot-to-lot" variability.

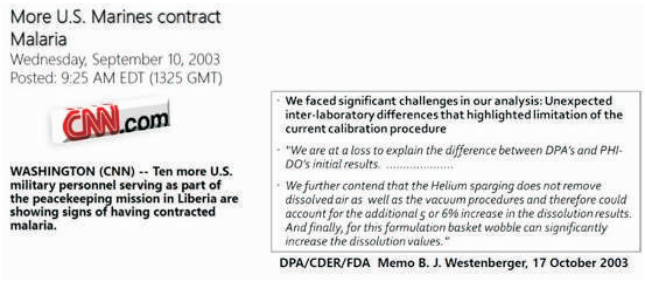
As we can see in Figure 1, the dissolution rate of pharmaceuticals is multi-factorial, and only recently we have begun to truly appreciate multi-factorial aspects in our regulatory submissions (e.g., ICH Q8 Pharmaceutical Development). How we design control strategy and set regulatory specification for dissolution – beyond the "black-box discriminatory test," is evolving slowly. The "black-box discriminatory test" was the only option in the absence of multifactorial information and knowledge, and it placed a heavy emphasis on dissolution test as a surrogate of "pivotal bioequivalence" despite the inherent limitation of the test method; particularly as a quality control (in contrast to research) test. Following regulatory approval, the assumption of "validation" of analytical methods and manufacturing processes by repeating few (e.g., 3) times contributes to undermining the residual uncertainty that must be vigilantly monitored continually to ensure our practices are and remain "good" over a product life cycle (10). The slow evolution of a holistic or systems approach to a "weight of evidence" approach to dissolution specification setting poses a significant challenge. A challenge can be an opportunity which provides a competitive advantage, but for those who are systems oriented in their QbD and regulatory communication strategy.

Verify assumptions hidden under layers of history

With the finalization of US FDA's Guidance on Process Validation in 2011(10) the path forward is statistical process control which was described in the early 1920s by Walter Shewhart who also noted that - *Both pure and applied science have gradually pushed further and further the requirements for accuracy and precision. However, applied science, particularly in the mass production of interchangeable parts, is even more exacting than pure science in some issues of accuracy and precision.* This quote was selected for a reason in 2004 to conclude an FDA White Paper entitled "Innovation and Continuous Improvement in Pharmaceutical Manufacturing: Pharmaceutical CGMPs for the 21st Century" (11).

Before writing the first draft of the FDA White Paper, an incident occurred in which a "dissolution failure" occurred in the context of national security (12) – two US FDA labs assigned to test sample of mefloquine tablets obtained from US Marines, using their "validated methods", observed dramatically different dissolution results, see Figure 3 below.

Figure 3. A slide from the author's presentation at the USP–India Workshop: Quality of Chemical Medicines: Impact of Impurities and Strategies for Control, 12 June 2015 (13).



In 2010, the US FDA issued final guidance on enhanced "Mechanical Calibration" (MC) of dissolution apparatus I and 2, and it noted - *FDA's current good manufacturing practice (CGMP) regulations require that laboratory apparatus be calibrated at suitable intervals by an established written program of scheduled procedures (21 CFR 211.160 (b) (4) and 211.68). The enhanced MC procedure recommended in this guidance can be used as an alternative to the current Apparatus Suitability procedure for USP Dissolution Apparatus 1 and two described in USP General Chapter Dissolution. The Chapter Apparatus Suitability procedure requires that the dissolution apparatus assembly meet certain MC tolerances and that a performance verification test (PVT) beper formed with specified USP Reference Standard (RS) tablets; however, the MC tolerances specified in USP for the dissolution apparatus assembly are not as comprehensive or as stringent as those in the enhanced MC procedures recommended in this guidance* (14). However, the debate and discussion on the dissolution test "process qualification"–i.e., dissolution behavior of standard material (calibrator tablet) as well as control of the mechanically measurable parameters of the apparatus, continues (15).

It is interesting to note that the typical "DEAR CUSTOMER" letters the USP issues - to regrettably inform on stability issues of calibrator tablets -"It is known that the dissolution of USP Prednisone Tablets RS changes over time"- is no longer accessible, for example at http://www.usp.org/sites/default/files/usp_pdf/EN/referenceStandards/2015-07-10_prednisone_tablets_1559505_r001b0_notice_to_customer_letter.pdf. Does this mean the issues and problems has been resolved? No. As of this writing, NIPTE has proposed to the USP on ways to improve the quality of the "Calibrator Tablet" via continuous manufacturing.

Let us not forget – *in vitro* to *in vivo* correlations are "formulation specific," i.e., dissolution behavior *in vitro* is formulation specific. Regulators forcing all manufacturers to "comply" with one compendial test method is (or should be) now a historical footnote, useful for lessons to be learned. Is it so?

"Back to the Future": A way forward

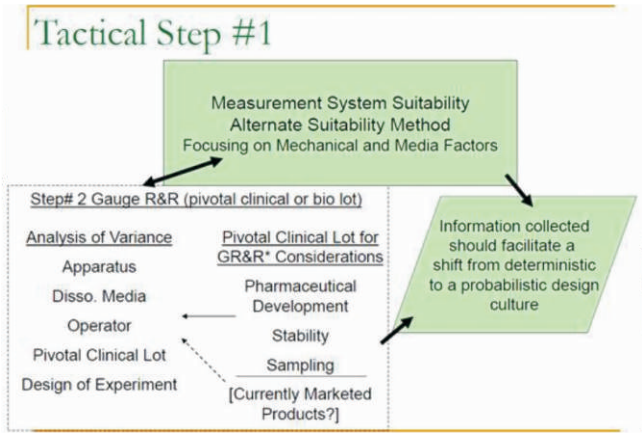
In September 2004 at the USP Annual Scientific Meeting entitled "The Science of Quality" in Iselin, NJ, the author was invited to give a talk entitled "Biopharmaceutics and Drug Product Quality: Performance Tests for Drug Products, A Look Into the Future" in which he noted that *"The future is*

upon us! The increased importance of physical performance characteristics of drug delivery systems; Complex drug delivery systems; Combination systems (e.g., drug drug-device); Nanotechnology. The Science of Quality — a critical dimension is the ability to understand, control, and manage variability. What can we learn from dissolution or drug release testing experience? (16). What have we learned? Set minds on dissolution testing remain grounded on grounds that are no longer justifiable.

Every challenge is an opportunity for those who care to recognize, acquire the knowledge to exploit it but do so wisely to do good. Not recognizing the challenges and assuming "FDA Approved" and "Validated" makes the analyst on the frontline "accountable" for "dissolution failures" and fear of losing a job can lead to BAD-I.

As we have noted in the "Present" and as in the "Past," the community of knowledge seems to be "going around in circles." To "spiral forward", let us not ignore solutions in plain sight. For example, the US FDA's Advisory Committee for Pharmaceutical Science discussion in May 2005 provides a way forward. Extensive characterize of variance in clinical or bio-lot via a "Gauge R&R" study can, among other things, provide a basis to verify the statistical distribution, obtain and benchmark robust estimate of variance useful to justify appropriate tolerance limits. In this approach, the clinical or the bio-lot instead is the clinically relevant "calibrator" and the characterization study, among other things, a basis to verify the statistical distribution and obtain and benchmark robust estimate of variance useful to set appropriate tolerance limits (18).

Figure 4. Establishing Drug Release or Dissolution Specifications: Topic Introduction by Author. May 3, 2005, FDAACPS Meeting (18).



Cycle for "prior knowledge" and spiral for "new and new prior knowledge."

Increasingly the US FDA review has become more stringent and Complete Response Letters related dissolution rate control have sought to impose additional "dissolution tests as in-process controls." Will this "additional;" dissolution testing in-process improve the stability and capability of the manufacturing process? Will it increase or decrease the rate of OOS?In parallel, the US FDA is also seeking information on "Quality Metrics" (17) and its CGMP inspection focusing on OOS investigations and effectiveness of CAPA. All this is occurring in an environment of drug shortages due to quality and manufacturing issues, and sub-optimal competition resulting in increasing prices of generic drug products.

The extent of the challenges at hand are also reflected in recent media headlines such as "Fed Up With Drug Companies, Hospitals Decide to Start Their Own," "With U.S. Generic Drug Market in Chaos, Indian Upstarts Rise" and "Sen. Elizabeth Warren: U.S. government ought to make generic drugs." Moreover, an alarming signal visible in the noise of the real world is media reports such as "If color or shape of generic pills changes, patients may stop taking them" (5).

The future is "patient-centric," "personalized," and racing to meet the needs of additional assurance via verification of quality at pharmacy, hospital bedside, and, perhaps an App that patients can use home is not just an imagination. Given a choice of products with "variance" from expected values as shown in Figure 2, which would you choose for your self or a family member?

Information is a source of knowledge which is necessary, but may not be sufficient to make the right decisions. The understanding gained via experiential knowledge leads to wisdom. Wisdom is in good practices, and good practices are a path to professional development by asking the "right" questions. The answers needed for leveraging opportunities in what others consider a challenge can be in plain sight but are not listed in a checklist to follow. As a pedagogical narrative, this paper brought on the same page different "dots" that when "connected" should provide patterns that hold many answers. To acquire experiential knowledge, one must experience, ask the "right questions" and begin with the end in mind – the intended use. To do so, one must first ensure the measurement systems of their senses and mind, and in a laboratory and factory floor are suitable and capable – with appropriate calibration and repeatability and reproducibility studies to justify the description of "validated".

Let us remember that R&D deal with complex problems; i.e., cause and effect have to be determined with experiments. The QC and manufacturing operations utilize documented procedures that can be complicated, hence "good practices" which require education, training, and experience (21 CFR 211.25) apply, and some procedures can be simple, cause and effect are self-evident – "best practices" apply. B*oth pure and applied science have gradually pushed further and further the requirements for accuracy and precision. However, applied science, particularly in the mass production of interchangeable parts, is even more exacting than pure science in some issues of accuracy and precision. Walter Shewhart.*

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Application of "Joshi Capsules" Concept for the Sublingual Slow Delivery of Drugs – Dissolution Aspects of Orally Dissolving Capsules

"Joshi Capsules,"is a new concept, wherein drug(s) is/are incorporated in the capsule shell matrix. Orally dissolving capsules (ODCs), similar to Orally Disintegrating Tablets (ODTs) are designed to release the drug in the oral cavity. This article gives an insight into the concept of "Joshi Capsule," its merits and an example of Vitamin B12 capsules being developed as an ODC product. Products developed by combining these two concepts can provide several advantages. Details of "Joshi Capsules" concept can also be found on the website – www.joshicapsules.com

Concept

The term "Joshi Capsules" appeared in an article in American Pharmaceutical Review in April 2018. It was coined after the last name of inventor Dr. Hemant N. Joshi, Founder of Tara Innovations LLC. Tara owns three patents for this product - US Patent # 8,728,521 (May 20, 2014), US Patent # 9,884,024 (February 6, 2018) and US Patent # 10,357,461 (July 23, 2019). **Figure 1** & Table 1 depict the details on the "Joshi Capsule" concept and its applications.

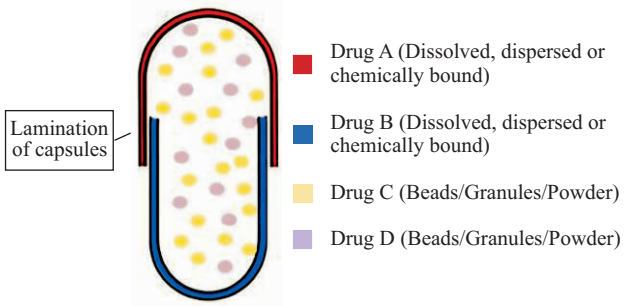

Figure 1-Concept of "Joshi Capsules" depicting many possibilities for drug loading

Table 1: Different variations in "Joshi Capsules" concept

Different types for drug distribution (via location) :

1. Drug A in the cap and drug B in body
2. Drug A in the cap and no drug in the body
3. Drug B in the body and no drug in the cap
4. Drugs A or B in the cap and body
5. Drugs A and B in the cap and body
6. Drug A in the cap and drug B in the capsule core
7. Drug A in the cap and body, as well in the capsule core
8. Drugs A and B in the cap and body and drugs C and D in the capsule core

Additional drug distribution methods :

1. Drugs molecularly dissolved in the capsule shell matrix
2. Drugs physically distributed in the capsule shell matrix
3. Drugs partially molecularly dissolved and partially physically distributed
4. Drugs chemically bound to the polymer matrix
5. Drugs partially chemically bound and partially molecularly distributed

Table 1 describes different aspects of the "Joshi Capsules" concept. The key limitation of "Joshi Capsule" is drug loading. The dose of the drug(s) is limited to 5 mg per capsule or less and the drug(s) should not affect the capsule properties negatively. On the positive note, "Joshi capsules" can produce fixed combination dosage forms and can avoid drug-drug interactions. We can modify the release rate of drug(s) using different methods of drug distribution in the capsule shell matrix. It will also reduce the cost of the drug product. Lastly, there are only a few capsule shell manufacturers and as a result, there is a low probability of competing generic drug products arriving to market.

"Joshi Capsules" for slow release ODC

Tara Innovations recently applied for a patent (US2018/0318226) suggesting that the capsule should not be swallowed, it should be kept in the mouth to dissolve slowly. Tara combined the concepts of "Joshi Capsules" and slow-releasing ODC's using vitamin B12 as the model drug. Initial batches of HPMC capsules in which vitamin B12 was embedded in the shell matrix has been prepared. Each capsule contains 0.5 mg of vitamin B12. Sublingual delivery of vitamin B12 is advocated and ODTs and spray solutions are available in the market. In the ODC patent application, the HPMC capsule, loaded with medicament is recommended to be placed in the oral cavity between the gums and cheek without any additional fluid. The capsule absorbs saliva and softens, flattens with time and the HPMC shell gradually dissolves – slowly releasing the dissolved API. One can use any size of capsule from 5 to 00.

ODTs, OD film/wafers/particles, oral sprays are meant to release the drug very quickly in the mouth cavity. Some researchers also modified conventional hard gelatin capsules to make them fast dissolving for the rapid release of drugs (1). In our concept, the intention is to release the drug slowly so that it can get longer time to get absorbed from the buccal cavity or where required, the drug is available for more time for local action.

Issues in *in vitro* testing of ODCs - The compendial dissolution methods are based mainly for oral systems intended to be swallowed and consider the conditions in the GIT w.r.t. volumes, pH, agitation. On the other hand, the amount of fluid/saliva in the oral cavity is very less compared to the fluid in the Gastro-intestinal (GI) tract. Thus, the USP I method, which uses 900 mL of aqueous fluid, will not mimic *in vivo* conditions in the mouth cavity. Bartlett and Voort Maarschalk compared the oral mucosal absorption to the clinical pharmacokinetic profile of Asenapine (2). Similar to the model presented in their research paper, our model for the absorption of B12 from the capsule can be depicted as shown in **Figure 2**. The sequence of events can be considered to be as follows: released drug from the softened capsule in the oral cavity partitions into the mucosal membrane and reaches equilibrium with the drug in the solution in the oral cavity. The drug is then absorbed in the blood. The drug absorption from the mucosal membrane into the blood stream depends upon the drug properties. Authors reported the Tmax values of several sublingually administered drugs, which ranged from 4.2 minutes for nitroglycerin to 110 minutes for lorazepam (2). The Tmax, as well as its bioavailability, were not found to be dependent on the dose administered (2).

There is no official dissolution method for dosage forms for delivery in the mouth cavity (ODT, ODC, films, lozenges, or oral sprays). Attempts have been made to develop *in vitro* dissolution testing for the delivery in the mouth cavity (3-5). The volume of saliva is very small (about 1-1.5 mL) and the dosage forms are exposed to minimal physiological agitation. One such reported method uses a 0.45-µm nylon filter membrane pre-wetted with 50 µL of distilled water and placed between a 15 mL glass funnel and a fritted glass base, which are clamped and inserted into Büchner flask. The buccal dosage form is placed on the membrane; a disposable plastic collection tube is placed at the outlet tip of the outlet unit to collect the filtrate, which contains the drug released from the dosage form.

Humans swallow saliva continuously as it is formed; hence some drug invariably reaches the stomach and as a result, the buccal or sublingual absorption is reduced. If we desire local absorption through mouth cavity or if we desire a local effect of drug in the oral cavity, the drug must be released slowly allowing it to partition in the mucous membrane.

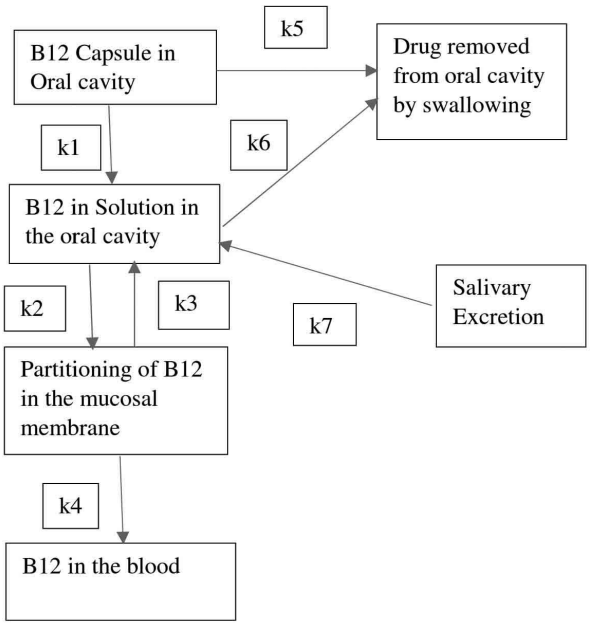

Figure 2: Schematics of Oral mucosal absorption of vitamin B12 from HPMC capsules

Many excipients such as citric acid, phosphate salts can induce salivation, which will reduce the drug concentration in the mouth cavity and produce a short residence time. A formulator must therefore choose excipients very carefully. Another key aspect to be considered in drug delivery in the mouth cavity is the taste of the drug and excipients used. Hence sweeteners, flavours, cooling agents like menthol and mannitol are required. Formulators tend to add a surfactant in the formulations to improve drug solubility. However, the surfactant may produce undesirable taste and foaming in the mouth cavity, which is unpleasant.

The key advantage of absorption through the mouth cavity is obviously the prevention of first pass metabolism. If the drug properties allow enough drug absorption through mouth cavity, we can achieve low Tmax values and an immediate pharmacological effect. For example, Fentanyl is used in treating pain in cancer patients but can also be habituating. For fentanyl lollipops, the patient can suck on the lollipops till he/she achieves adequate pain reduction and then should discard the remaining lollipop. This advantage is not possible for drug products to be administered orally in the GI tract as one would not be able to control the dose of potent drug such as fentanyl.

We are long way from developing IVIVC for drug products to be delivered in the mouth cavity. Developing a biorelevant dissolution medium is easy in this case as we only have to worry about the saliva composition (no food effect). However, as depicted in **Figure 2**, there are several rate-determining steps to be considered in developing the mathematical model.

In another experiment, an orally dissolving capsule containing an ayurvedic formulation with turmeric and filled in HPMC capsule was tested for drug release in the mouth cavity. **Table 2** lists the data for the same. It was clear that the movement of dosage form in the mouth cavity controls the drug release. As observed in any *in vivo* data, intra- and inter-subject variation was evident(6).

Table 2: Inter- and intra-subject variation in the dissolution of orally dissolving capsules of the ayurvedic formulation of turmeric using two methods of administration. Turmeric formulation was filled inside the capsule.

Capsule #	Subject 1		Subject 2		Subject 3	
	Time for the first release of drug	Time to dissolve entire capsule	Time for the first release of drug	Time to dissolve entire capsule	Time for the first release of drug	Time to dissolve entire capsule
Method of administration#1 – The capsule was placed between the gum and the cheek. It was moved in the same space intermittently.						
Capsule 1	4 min 55 sec	12 min 18 sec	2 min 21 sec	8 min 50 sec	3 min 57 sec	12 min 51 sec
Capsule 2	4 min 3 sec	14 min 13 sec	3 min 6 sec	9 min 12 sec	3 min 27 sec	14 min 5 sec
Capsule 3	5 min 53 sec	10 min 27 sec.	3 min 50 sec	8 min 5 sec	4 min 27 sec	14 min 23 sec
Mean±SD (sec)	295±55	739±113	186±44	522±34	237±30	834±54
Grand mean values using Method 1: Time for the first release of drug: 239±62 sec (%RSD – 25.7%) Time for the entire capsule to dissolve: 698±153 sec (%RSD – 21.9%)						
Method of administration #2 – The capsule was placed in the mouth cavity and dissolvedthrough movement within the cavity						
Capsule 1	47 sec	3 min 37 sec	43 sec	3 min 2 sec	55 sec	5 min 10 sec
Capsule 2	42 sec	4 min 1 sec	41 sec	2 min 55 sec	59 sec	4 min 57 sec
Capsule 3	43 sec	2 min 27 sec	45 sec	3 min 22 sec	57 sec	5 min 56 sec
Mean±SD (sec)	44±3	202±49	43±2	186±14	57±2	321±31
Grand mean values using Method 2: Time for the first release of drug – 48±7 sec (%RSD – 14.6%) Time for the entire capsule to dissolve – 236±70 (%RSD – 29.8%)						

Conclusion and Future trends:

The new concept of drug as part of capsule shell, as in the Joshi Capsule, opens up several new possibilities of achieving unique drug combinations, less processing steps. One important application will be the ODC as an alternative to the ODTs and OD films.

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She has filed many patents international/ national, has seven patents granted and five patents licensed. Her research is funded through a number of Grants from the Government and the industry including companies from Japan, Germany and USA. She is also a consultant to the Pharma Industry.

She was Board Member, Member on the Board of Scientific Advisors and Chair of the Young Scientist Mentor Protégé Committee of the Controlled Release Society Inc.,USA, and is currently Chair of the Outstanding Paper Award Committee of the journal Drug Development and Translational Research, of the Controlled Release Society Inc., USA. She is Patron Member of the Controlled Release Society Indian Chapter and Member on the editorial board of the Asian journal of Pharmaceutical sciences an Elsevier publication.

Prof. Devarajan is a gold medalist of Mumbai university at B.Pharm, and currently President of the Alumni Association of UDCT/ICT. She is a nominated Fellow of the Maharashtra Academy of Sciences, a recipient of the American Association of Indian Pharmaceutical Scientists Distinguished Educator and Researcher Award 2011, the VASVIK award for Industrial Research to Women in 2011 and the Association of Pharmaceutical Teachers of India (APTI) Prof. C J Shishoo Award for Research in Pharmaceutical Sciences. Her publication in the International Journal of Pharmaceutics on Gastroretentive drug Delivery, won the prestigious Eudragit Award 2015. She won the Bengalauru Nano Innovation Award for a Nanosystem developed for Veterinary Infection, the IPA-ACG Scitech award for innovation in Solid Dosage form. Her most recent award is the OPPI Sientist Award 2018.

1. How and what prompted you to undertake pharmaceutical research as a career path?

A. As a young aspiring student I was deeply interested in Human Body and Biology. I did not want to be a doctor, however, wanted to be involved with medicines without being a doctor, so chose to be a Doctorate in Pharmaceutical Science and get involved deeply in Research. Teaching has been my passion and integrating it with Research made it a complete wholesome experience, inspiring students continues to give me several 'WOW' moments.

2. How many years have you devoted in research? What have been your career highlights?

   a. I graduated as a Bachelor of Pharmacy in 1980 with honours and post graduated as Masters in Pharmaceutical Sciences from UDCT Mumbai and initiated my independent research in 1987.

   b. My career highlights include the following :

      i. Member of the Board of Governors, ICT Mumbai

      ii. Member on the Board of the Controlled Release Society Inc., USA (2010-2011) and Board of Scientific Advisors of the Controlled Release Society Inc., (2011-2012)

      iii. President of UDCT / ICT Alumni Association (2017-2019)

      iv. Former Head, Department of Pharmaceutical Science and Technology, ICT Mumbai for two terms (2009-2015)

      v. President - ICT Innovation Council

      vi. Coordinator - M.Tech Pharmaceutical Biotechnology

      vii. Chair - Young Scientist Mentor - Protégé Program of the Controlled Release Society Inc., USA (2012-2013)

3. Amongst many of your research endeavours, which one did you find most interesting and why?

A. My current interest lies in finding solutions to acute healthcare needs using Nanotechnology, and focuses on Nanomedicine enabled targeted drug delivery for cancer and infectious diseases. Although it may not be the ambrosia for all kinds of ailments, it can work wonders in niche therapies. Key drivers of my research in this area include identification of relevant therapeutic needs

DR. PADMA DEVARAJAN'S LAB

where the risk benefit ratio of using nanomedicine is high and a major focus on simplifying the manufacturing process to make nanomedicine amenable to scale up and translation, affordable and have great outreach.

B. The excitement in my research is the less trodden path I have chosen, namely Interventions for Veterinary Healthcare. This area is comprehensively addressed through preventive therapies, therapeutic interventions and diagnostic kits. A spontaneous plug forming teat dip to cover the milking teats of cattle developed for mastitis has now found application for dry cow therapy is licensed out and already launched in India and will soon be launched globally. A simple urine based Point of Care pregnancy detection kit based on visual detection with proof of concept established, is being evaluated by an industry partner for possible commercialisation. Similar kits based on visual detection for calcium and Phosphorus are under evaluation. The most exciting development however is BU'ANTRAP- *In situ* Solid Lipid Nanoparticles (SLN) of Buparvaquone developed to target buparvaquone to macrophages to treat a veterinary infection, theileriosis. This is based on an unbelievable simple yet revolutionary technology wherein the drug entrapped SLN are prepared on site just prior to injection by dilution with a sterile clear solution of buparvaquone with commercial Dextrose injection to generate a ready to inject SLN dispersion with over 95% drug entrapped. This product which is licensed and expected to be commercialised by end of 2019 won the Bengaluru Nano Innovation Award 2017.

Other innovative developments include expanding the *in situ* nanotechnology application to practical nanoformulations for cancer, HIV, malaria and other maladies for human healthcare. Our group was the first to report shape directed targeted delivery to the spleen and a publication on this study was cited **in the US magazine "The Scientist" as cutting edge research in nanoparticle design.**

My guiding mantra is 'Simple innovative and affordable technology with great outreach"

4. You have been actively associated with SPDS as a member and Chair Scientific Programmes. What are your views on this dissolution society? What efforts can be taken to improve the proceedings and activities of SPDS?

A. I consider SPDS as an exclusive society for one reason - that it is dealing with a niche area of formulation development, namely dissolution and related aspects. It enjoys the patronage of globally accomplished scientists, academicians and stalwarts form industry who form the core working team. This provides a strong foundation to the society. This young society is growing in strength and has set a benchmark for other societies in India to emulate, by recently forming the SPDS USA Chapter. Within a span of about 6 years SPDS has organised DISSO INDIA annually since 2013, DISSO ASIA, DISSO EUROPE and is targeting DISSO AFRICA and even DISSO USA in the coming years. This speaks volumes for a young organisation which is gradually acquiring a strong global presence. The series of certificate courses conducted, the desk book on Dissolution Science and the gamut of eminent speakers from across the globe representing both industry and academia is a unique formula that is proving highly successful in establishing SPDS with a strong footing.

The programme content which focussed extensively on Dissolution, Bioavailability, Biowaivers and related regulatory aspects is slowly expanding to include aspects of formulation development and their importance in dissolution and bioavailability to expand the participant base and strengthen to achieve the objectives of SPDS, which strongly believes in providing scientific value to researchers and students from academia and industry alike. This reflects open mindedness and an inclusive approach, signs of a progressive organization.

5. What technologies and new skill sets should we be inspired from the western world for bettering our research output?

A. One could certainly be inspired by the sophistication and quality scientific output of the western world. Nevertheless, Indian scientists today are not far behind. Nonetheless, technologies and skill sets that would cater to the Indian healthcare scenario which are affordable and can be made available across various socioeconomic strata should be looked at more aggressively.

More than technologies, I believe we should have the right mind-set to start with research

Research involves a multitude of capabilities starting with discipline, patience, curiosity and diligence. These coupled with passion and commitment, and a desire to be creative would be important attributes that could lead to productive research output, be it great science or technologies which can be commercialized.

6. How do you see your overall Pharmaceutical research progressing in next few years?

A. Indian pharmaceutical Industry continues to be among the leading global generic players, despite temporary hiccups. A change in mindset from generics to innovation is integral for India to attain global leadership in pharma. The communication revolution and easy access to world wide literature is enabling the Indian academia to rapidly keep pace with the dynamic changing environment. Hand shake between academia and Industry in India, would provide the stepping stone and enable India to spiral out as a global leader in research.

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Methods in Drug Release Testing - Issues and Updates

Abstract: This review provides an update on drug release testing methods reported in literature, which attempt to tackle some of the issues in the conventional dissolution testing approaches. The review describes two important novel approaches, viz. Teflon flow through device which helps to detect and monitor changes in crystalline nature of drug particles during the dissolution process and Microfluidic approach, which is a flow through cell inbuilt on a microfluidic chip, which is suitable for micro - and nanoparticulate systems, and further these can be connected to a microscopic slide for actual visualization of the particles undergoing dissolution.

Key words: *Teflon flow through device, microfluidic flow through cell, polymorphic changes during drug release.*

The field of drug delivery is vast and mainly comprises of measures to deliver different therapeutic agents showing versatile physicochemical attributes via different routes using patient-friendly dosage regimens. An important characterisation is assessment of drug release profile from the designed delivery system. Determination of the concentration of drug released over a definite period of time can help in designing a time based drug release profile for the specific system.

The basic scheme of drug release testing as given in compendia includes one of the following types:

- A compartment/reservoir containing the dosage form in a suitable medium mimicking the *in vivo* environment at the site of drug release.

- A cell containing the dosage form through which the medium is pumped at a definite flow rate.

In either case, the drug dissolved in the medium is periodically determined by a suitable analytical technique, mostly UV spectroscopy or HPLC.[1]

Some novel approaches in dissolution testing:

a) Teflon Flow through devices

The solubility of a drug and hence its behaviour in dissolution medium is influenced by its crystalline structure; hence drugs exhibiting different polymorphic forms can exhibit differences in dissolution behaviour. [2] A possibility does exist in some cases that the exposure of the dissolution medium and varying dissolution conditions may induce polymorphic changes in the drug during the dissolution studies, causing changes in the drug release profile. Frequent transformations from anhydrous to hydrate forms have been observed for Naproxen sodium drug, thus altering the dissolution results. [3] In such cases, determination of the drug concentration alone does not help in determining the overall effect of such drug changes. There arises a need to establish analytical methods to identify such in process changes during conduct of dissolution studies. The Teflon Flow Through Devices aid to measure the drug concentration from the drug delivery system as well as visually observe the system changes with the support of Ultraviolet spectroscopy, Fourier Transform Infrared Spectroscopy or Raman Scattering techniques. [4, 5]

However, one major limitation observed in use of these systems is that only compact large dosage forms like tablets, capsules may be studied using these advanced systems. Study of drug release behaviour of multiparticulate systems and nanoparticulate systems is difficult using these analytical devices.

b) A Microfluidic Approach

The need for determination of drug levels as well as visual observation of sample changes during drug release studies for multiparticulate systems can be addressed using a Microfluidic approach. [6] The analytical system mainly comprises of a compact assembly in which a flow through cell is inbuilt on a microfluidic chip. The chip contains a hollow chamber in which the sample multiparticulate system is held by barriers to retain the non-aggregated state of the systems. A suitable drug release medium is pumped through the chamber at a fixed flow rate using polyethylene tubings. The chip assembly is built from Polydimethylsiloxane fixed to a glass slide which acts as the main viewing element for behavioural changes in the sample during the in process release studies. To facilitate mimicking of body conditions i.e. the maintenance of sink conditions, a high flow rate of the medium is maintained in the compartment. A larger volume of medium may be pumped to control the saturation levels of drug. (Fig 1)

The drug release behaviour is affected by the geometry of the compartment. An oval shaped compartment is the best suited to ensure uniform drug release. Straight channel shape and rectangular shapes of chip are avoided to prevent deviation from mimicking of body conditions and to prevent the accumulation of drug at the edges respectively. To maintain constant contact between multiparticulate systems and the release medium, the sample systems can be immobilized in the chamber using supports. Variations in the compartment structure can be included like designing of inlets and outlets to generate different flow conditions of the medium.

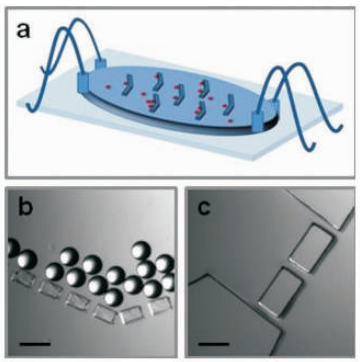

Fig : 1a) A Microfluidic Drug Dissolution chip-Schematic, b-c) Light microscopy images of the internal configuration of a microfluidic chip

Alteration in the number of inlets and outlets helps to modulate the flow rate through the chip. Drug sample can be injected into the chamber using the inlets. The temperature of the system is controlled by heating the medium to desirable temperature on a heating plate. Drug release studies from different types of multiparticulate drug delivery systems can be conducted using a microfluidic chip by altering the structure and dimensions of the chip. The concentration determination from the medium is conducted by connecting the chip outlet to a UV-Visible spectrophotometer with a flow through cuvette. The visual observation of the sample changes can be made by boarding the chip on a microscopic stage. The chips are fabricated by using Soft lithography on Polydimethylsiloxane. Thus the microfluidic drug dissolution chip aids to be an advanced analytical tool for determination of drug concentrations released as well as visual observation of changes in a specific multiparticulate drug delivery system simultaneously. [7, 8]

Drug release studies of core-shell hydrogel particles using a microfluidic chip have been conducted. The core shell hydrogel particles comprise of a polyacrylamide core; non thermoresponsive in nature with a thermoresponsive shell comprising of poly (N-Isopropylamide). The shell is loaded with Rhodamine B Isothiocyanate dextran, fluorescent in nature. The temperature dependent release of the dextran can be studied real time by assessing the reduction in fluorescence intensity over a period of time using the microfluidic chip. [Fig :2]

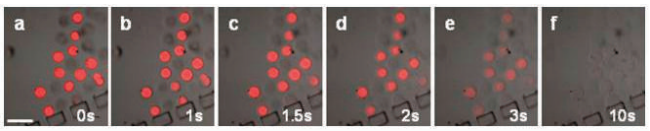

Fig 2: Real time monitoring of temperature dependent dextran release using Microfluidic Chip
(Source: Windbergs M., Weitz DA , 2011)

Future directions: Dissolution testing as a quality control tool is used globally in commercialisation of different pharmaceutical formulations. The applications for approval of new drug and new drug delivery systems require strong supportive data including method establishment and validation protocols. The challenges of data specifications to be complied increase when the data submissions are made by industries globally in regulated and semi-regulated markets. Hence, there arises a need for establishment of analytical tools which enhance speed of data generation and lower analyst-to-analyst variability.

Use of Fibre Optic Dissolution testing (FODT) has been made to address such challenges. In FODT systems, dissolution methodology followed is as per USP specifications with simultaneous monitoring by Ultraviolet detection and Photo-diode array thus eliminating the step of sample removal for analysis . FODT systems aid to enhance accuracy of measurements alleviating sampling errors. The FODT systems have been demonstrated as desirable analytical tools for formulation samples exhibiting stability issues, needing complex media compositions and for novel nanoparticulate systems which show challenges in filtration. [9,10]

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IN VITRO DRUG RELEASE TESTING METHODS FOR *IN SITU* DEPOT FORMING INJECTABLE FORMULATIONS

ABSTRACT

In situ injectable gel formulations are special type of drug delivery systems that exist in sol state prior to their administration into the body, but once administered, undergo gelation to form a depot at the site of administration. The system is designed to sustain and prolong release of drug for periods ranging from weeks, months to years. *In vitro* drug release test is an important tool in development and routine characterization of these formulations and in evaluating performance and safety. Owing to the existence of gels formed by a variety of mechanisms based on both hydrophilic as well as hydrophobic polymeric depot formers and prolonged duration of drug release, *in vitro* drug release testing from these dosage forms poses special challenges. In the absence of compendial methods, several alternatives have been explored. The objective of this review is to summarize *in vitro* methods employed for drug release studies from *in situ* injectable gels /depots.

Keywords: *In situ* forming injectable depots, drug release testing.

Injectable *in situ* gel forming depots:

Injectable *in situ* gel forming systems are formulated as liquids which undergo solidification or gelation at the site of injection, typically intramuscular, subcutaneous, intraperitoneal, intraarticular or intratumoralsites, post administration. The gels can then perform as sustained release depots and release an entrapped active in a prescribed quantum over a designated duration. These formulations are predominantly designed using polymeric materials or their compositions, and, depending on the nature of the polymer employed, gelation occurs by several mechanisms.

The major mechanisms by means of which the *in situ* depot formation occurs and the corresponding materials employed include:

I) **Solvent diffusion** e.g. based on Poly Lactide-co-Glycolide (PLGA) (Atrigel®) (Graves *et al.,* 2007) sucrose acetate isobutyrate (SABER®) (Dubey *et al.,*2018*),*

ii) **Ion activation or osmotically induced gelation** e.g. based on deacylated gellan gum (Hassan *et al*., 2016),

iii) **pH triggered gelation** eg: based on polyacrylic acid - alginate (Singh *et al.,* 2013*)*

iv) **Temperature triggered gelation** e.g. based on block copolymers of polyoxyethylene- polyoxypropylene (Poloxamers) (Jabarian *et al*., 2013, Yu *et al.,* 2017) and also poly (lactide-coglycolide) - poly (ethylene glycol) (PLGA-PEG-PLGA) (ReGel®) (Qiao et al., 2015)

v) **Crosslinking triggered gelation** e.g. carboxymethylcellulose - hydrazide with dextran-aldehyde (Hudson *et al.,* 2010) and

vi) ***in situ* swelling organogels** e.g. those based on water insoluble amphiphilic lipids, which swell in water and form various types of lyotropic liquid crystals (Couffin-Hoarau *et al.,* 2004, Mei et al., 2018).

In situ gelling systems are promising alternatives for potent drugs requiring chronic administration when compared to other conventional dosage forms due to one or more of the several benefits offered by them. They are amenable to convenient administration using minimally invasive administration techniques when compared to implants, since they are originally injectable. They offer scope for prolonged and controlled delivery of active agents entrapped in them, which in turn leads to reduced dosing frequency, improved patient compliance and comfort and superior therapeutic outcomes. Further, the systems are generally simple to prepare since a majority of the them are simple solutions or suspensions.

A highly preferred attribute for injectable depots would be biodegradability. Although as enlisted above, systems based on several polymers have been investigated, owing to a well-studied and reliable drug release mechanism, safety and biocompatibility and a history of safe use in parenteral depot preparations, formulations based on biodegradable polyesters such as those belonging to the poly lactide-co-glycolide family are the only USFDA approved *in situ* gelling injectable depots (Table I).

Table 1: *In situ* injectable depot formulationsapproved by USFDA(Adapted from Zhong *et al.*,2018)

Drug name	*Active Ingredient*	*Polymer*	*Manufacturer*	*Indication*	*Date of Approval*
Atridox®	Doxycycline hyclate	PLA	Tolmar Inc	Chronic adult periodontitis.	1998
AtrisorbD®FreeFlow	Doxycycline hyclate	PLA	Tolmar Inc	Surgical treatment of periodontal defects in guided tissue regeneration procedures.	2000
Eligard®	Leuprolide acetate	PLGA	Tolmar Inc.	Palliative treatment for advanced prostate cancer	2002
Sublocade®	Buprenorphine	PLGA	Indivior Inc.	Moderate to severe opioid use disorder	2017

The objective of this paper is to summarize various methodologies which have been employed to study *in vitro* drug release from *in situ* gelling injectable formulations.

Drug release from *in situ* gelling depots:

Drug release from the *in situ* formed gels is primarily due to diffusion followed by erosion or in some cases due to a combination of diffusion and erosion of the gel. The hydrophobicity and concentration of the biodegradable carrier, the polar nature/water miscibility of the solvent system used in the product, as well as the aqueous solubility and loading of the drug affect the drug release rate (Shiand Li.,2005). Besides injectable depots, these gelling systems have also been widely investigated for prolonged delivery of actives to, or via eye, nose and vagina. *In situ* gelling systems for application to mucosal surfaces such as ocular, vaginal and nasal membranes are designed to release actives for a few hours. However, injectable systems often serve as depots for prolonged release ranging from days to months. Further, parenteral *in situ* injectable gel formulations contain substantial amounts of potent therapeutic agent, thus running a risk of dose dumping and unanticipated changes of *in vivo* drug release characteristics that may lead to severe side effects. Therefore, it is essential to understand *in vivo* performance and have appropriate *in vitro* release testing methods that can mimic the *in vivo* performance of these systems (Shen and Burgess, 2012).

Drug release testing from *in situ* gelling formulations: special considerations

There is a growing interest in the class of *in situ* gelling injectable formulations as evidenced from several papers exploring existing and novel polymeric systems for the design of this class of depot formulations (Mathew et al., 2018, Khang et al.,2018).

Characterization of the *in vitro* drug release from parenteral *in situ* gelling depots is necessary for several reasons. *In vitro* release serves as an indispensable tool during development of the formulations. It serves to compare between formulations and is a vital parameter for optimizing the desired product having suitable drug release characteristics. It is a major quality control tool which ensures consistent product quality and performance of the pharmaceutical delivery system. *In vitro* dissolution test outcomes should be able to differentiate between acceptable and unacceptable batches, reflect product stability during shelf life and predict the effect of process-parameter and formulation changes. Robust and reliable *in vitro* drug release testing is the key to establishing *in vitro – in vivo* co-relation. Besides, drug release testing plays an important role in evaluation and approval of Scale-Up and Post-Approval Changes (SUPAC), as well as in supporting approval of generic non-oral dosage forms (Anand *et al.,* 2011).

As stated, these systems, in addition to being long acting, exhibit complex formulation designs, have different physicochemical characteristics and vary with respect to their gelling and release mechanisms. Hence, while evaluating methods for drug release studies, a one method suits all approaches may not be appropriate here and a single test system probably cannot be applied to study the drug release properties and mechanisms from various types of gelling systems. Also, there are problems associated with gelling *in vitro* since a suitable depot must be formed in the release medium without emulsification or sample dispersion occurring (Shah *et al.,* 2015). Hence, special methods, procedures, apparatus and techniques may be required to be evolved and employed which is specific for a particular type of gelling system to obtain reliable *in vitro* drug release data.

Dissolution testing methods were first developed for immediate release solid oral dosage forms and then extended to modified release solid oral dosage forms and novel drug delivery systems. With the introduction of more complex delivery systems, methodologies hitherto applied for drug release testing from oral products have been modified and additional methods developed.

While there are no recommended methods for testing of *in vitro* release from *in situ* gelling depots, USFDA approvals for other classes of depots are based on the use of compendial apparatus (e.g. Apparatus 7 for dexamethasone implants, Apparatus 2 for buprenorphine implants) or even on the basis of non-compendial studies (incubated jar method for goserelin implants). In case of the approved products such as the PLGA based *in situ* forming leuprolide acetate depot, the USFDA suggests the development of a dissolution method using USP IV (Flow-Through Cell), and, if applicable, Apparatus II (Paddle) or any other appropriate method, for comparative evaluation by the Agency (FDA Dissolution methods database).

The requirements to be considered while selecting or designing a dissolution testing method in case of *in situ* gelling systems, include ensuring that both, the mechanism by which gelation is attained and mechanism of drug release *in vivo* should be replicated *in vitro*. The method should be discriminatory enough to distinguish between formulation related differences in drug release rates during both, the burst release as well as the subsequent prolonged release phase. The release medium employed should be biorelevant as well as serve as a sink for the drug in question. Finally, the test method may need to mimic several of the post injection intramuscular environmental parameters such as body temperature, target tissue pH, buffer capacity, vascularity, level of exercise and corresponding change in blood flow.

Hence, while selecting and developing the *in vitro* drug release test method and specifications for *in vitro* gelling systems, certain special considerations regarding a number of parameters are due. These are not limited to, but may include:

Method of introduction of sample: The gelled depot may be formed prior to introduction of the formulation into the dissolution medium or, alternatively the depot may be formed on injecting the formulation into the release medium. The advantage of the former method is that it is likely to yield a defined geometry for the depot and a reproducible area of formulation–buffer interface, which in turn, will significantly impact reproducibility of the release pattern. It also allows special measures to be taken to ensure that prior to release, a suitable depot is formed without sample dispersion occurring. Thus, it may be desirable to pre-gel the depot and confine it in a special retainer (Shah *et al.,*2015). However, this fails to mimic the *in vivo* situation and may bring about certain alterations especially with respect to the burst release. If the retainer is used along with an apparatus such as the paddle, where it rests at the bottom, release may also not be in all directions as is likely to occur *in vivo*.

In contrast, forming the depot as a part of the release testing leads to superior mimicking of the *in vivo* environment. However, reproducibility of the extent of burst release as well as the subsequent release may be difficult since the geometry of the gel is variable. Excess variation in release from *in situ* gels reported by some workers (Graves *et al.,*2007) may be a consequence of changes in the shape and therefore gel – medium interface of the gelled drug carrier.

An approach wherein the gelation is carried out into the release medium, while defining the shape and size and allowing for multidirectional release may hold the key to resolving this issue.

***Mechanism of drug release*:** The *in vitro* testing method must provide for ensuring a mechanism of release identical to the *in vivo* situation. The release of the active from the formed depot may be a result of either drug diffusion through the polymer matrix or due to erosion or biodegradation of the polymer or due to concurrent occurrence of these multiple mechanisms.

Dissolution medium: When choosing the medium, the physical and chemical characteristics of the drug and dosage unit must be considered. Evaporative loss of medium should be minimized. Replenishment of evaporated medium may be necessary for tests of long duration. Evaporative losses may be negligible in case of closed systems such as the flow through apparatus.

The composition of the drug-release medium may be adjusted to mimic *in vivo* physiological parameters for pH (pH 7.4) and osmotic pressure (285 mOsm/kg) (Gray et al.,2018). Although surfactants have been included to provide sink conditions (Graves et al, 2007), the use of cosolvents for drug release testing from *in situ* gelling depots is not encountered. For long term release studies, it may be essential to include an antibacterial agent such as sodium azide in the release medium. Besides the nature of the medium, its volume should also be carefully selected. Studies reported have used volumes varying from 900 ml (Ahmed et al., 2016) to 0.3 ml (Zhang et al., 2015).

Sink Conditions: Although non-sink conditions have been occasionally employed, performing the release under sink conditions is preferable (D'Souza *et al.,* 2014). Complete removal of release medium followed by replacement has been employed. Replenishing medium at various stages of the test or changing the medium volume at various stages may also be necessary.

***Agitation method and rate**:* While agitation is necessary to overcome boundary wall effects, the rate and method of agitation require careful consideration since the *in vivo* environment post injection is relatively static. Agitation by means of paddle rotation, magnetic beads, shaker movements and reciprocal movements have all been explored. Static methods have also been employed in the membrane free methods described later.

Sampling Parameters: Sampling time points should be chosen to adequately describe any initial burst release and provide an adequate number of data points for the drug-release profile.

Other variables: Special considerations such as in case of USP apparatus 4 such as flow rate of the medium and considerations of using open or closed loop, inclusion of glass beads etc are required.

Drug release testing from *in situ* gelling formulations: Equipment and Methodology

Compendial methods employed include those based on the USP apparatus 2 or even occasionally USP 3 and less frequently, USP apparatus 4. Non-compendial methods are based on the use of dialysis bags, or the membrane free release tests. In addition, hybrid methods such as using a dialysis set-up along with a dissolution apparatus or with a flow through cell may also been investigated.

Release studies based on Official Apparatus:

USP type 2 apparatus (paddle method):

Several studies have used the USP type II apparatus having the paddle as the stirring element as such or with minor modifications regarding sample placement, volume of medium used etc. Injectable *in situ* gelling system prepared using poly acrylic acid in combination with sodium alginate containing cytarabine (Singhet al.,2013) as well as PLGA based ***in situ*** **gel of atorvastatin** (Ahmed et al, 2016) have been subjected to drug release studies in this apparatus. The duration of the study was 24 h in the first case and 10 days in the second case respectively. The method has been effectively used to adjudge the burst release and optimize the formulation to obtain minimal burst release of the drug in several studies (Hosny and Rizg., 2018, Ahmed et al., 2016).

The variations in protocol observed during drug release study from *in situ* gelling systems using USP Apparatus 2 in reported experiments include:

Sample introduction: The method of introducing the sample into the USP dissolution vessel should be well specified, repeatable, and reproducible (Shah et al.,2015). The dosage form is usually introduced into the medium through syringe and needle, pipets, spatulas, or weighing boats. As discussed earlier, the sample may be placed directly into the bottom of the dissolution vessel or held within a suitable casing (Chaibva and Walker.,2007). Most studies seem to have relied on forming the depot in the release medium. But several papers have failed to include sufficient details on the method of sample introduction.

Agitation: Release studies from *in situ* gels have been reported using paddle rotating speeds as high as 100 rpm (Singh *et al.,*2013) to as low as 25 rpm (Chaibva and Walker, 2007).

Volume of dissolution medium: The use of USP 2 apparatus mandates the use of a minimum volume of about 500 ml to allow complete submergence of the paddle.

The use of USP apparatus 2 is time tested, well established and acceptable to regulatory agencies. It may be more suitable than most other methods to judge the maximum extent of burst that is likely from a formulation, a parameter which greatly dictates the safety of a depot preparation. Nevertheless, the method suffers from a few drawbacks when employed for drug release studies for parenteral depots. Relatively large volumes of dissolution media are used, but there is less amount of fluid available intramuscularly, thus this dissolution method may be less useful in mimicking *in vivo* drug release behaviour. Also, in the absence of a suitable casing to hold the formulation, the geometry of the gelled depot may vary greatly, thereby altering surface area, diffusion path lengths and thus, as a result of which both the initial burst release as well as the subsequent release may be difficult to obtain in a reproducible manner. Further, hydrophilic gels which are amenable to disintegration and/or erosion such as poloxamer based systems may be difficult to be subjected to release studies using this method.

USP type 3 apparatus:

The USP type 3 apparatus, also referred to as the reciprocating cylinder apparatus, is versatile equipment originally developed for the study of drug dissolution from oral dosage forms. However, it has been adapted for release testing from modified dosage forms including *in situ* gelling systems. The main components of the reciprocating cylinder apparatus are internal cylinders closed with screen fitted caps and used to hold the dosage form, external cylinders which serve to hold the release medium, metallic agitation rods and a heating bath. The internal cylinders are coupled to the metallic rods which enable the downward and upward i.e. the immersion and emersion movements (reciprocating action) within the dissolution vessel or the external cylinder.

The apparatus was investigated as a possible alternative for release testing of oxytocin during formulation development studies of a Pluronic® F127 *in situ* gel-forming parenteral dosage form (Chaibva *et al.,* 2007). A dissolution medium volume of 180 mL was used in these studies. A 177-µm pore size screen mesh helped to retain the dosage form in the inner tube, and a 5-dpm dip speed provided agitation. Besides the USP type 3 apparatus, the *in vitro* release tests that were investigated included the use of USP Apparatus 1, 2; a dialysis bag in USP Apparatus 2; and a membrane-less diffusion method. ANOVA and the *f*1 and *f*2 factors were used to assess the discriminatory ability of each of the test methods that were assessed. The study led to the conclusion that the USP Apparatus 3 was the most suitable *in vitro* release test apparatus for studying formulation factors affecting oxytoxin release during the development of a parenteral dosage form prepared using Pluronic® F127.

USP type 4 apparatus (Flow through cell) method:

The flow through cell (USP type 4 apparatus method) is considered most appropriate and reliable for testing of novel systems such as *in situ* gelling depots. The method simulates *in vivo* conditions most closely as sample is being exposed to a constant perfusion by the test medium (Figure 1), thus making it a method with higher biorelevant potential (Brown *et al.,*2011, Shen et al.,2012,Shah *et al.,* 2015, Tomic *et al.,* 2016, Gray *et al.,* 2018).

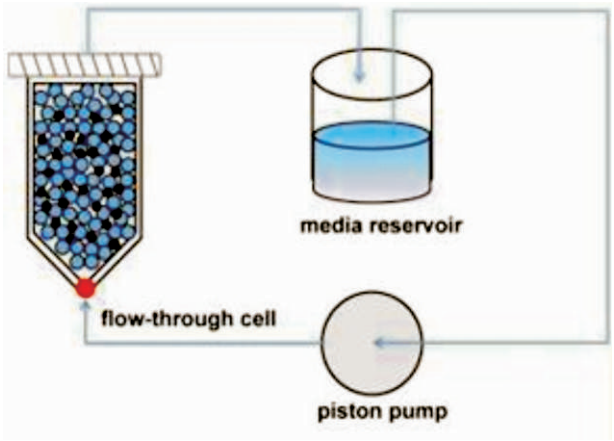

Figure1: Pictorial representation of key concept of the flow through drug release apparatus. (Adapted from Shen et al., 2012).

Here, the sample is held within a cell loaded with glass beads (about 1-mm diameter) which are positioned at the apex to prevent material from descending into the inlet tubing and/or to prevent agglomeration, depending on the type of formulation under test. The dissolution medium is continuously pumped using peristaltic and pulsating piston pumps through the test sample. Usually glass fiber filters are used which are positioned at the inner top of the cell to retain undissolved material. At pre-determined time points, required amounts of filtered samples are withdrawn and analyzed by appropriate method.

Variables which require to be selected/optimized in this case include:

Sample cells: The VDC (Vertical Diffusion Cell) recommended by the USP, is one of the more widely accepted apparatuses for *in vitro* testing. Horizontal cells and cells with various modifications to basic design are accessible for different formulations. Cells with the following diameter, cross-section, volume are available.

Cell diameter	Cross section area	Volume of cone
12mm 22.6mm	4.01cm2 1.13cm2	0.6cm3 4.2cm2

The literature recommends filling of the cone in laminar operation with 0.9 g and 6.4 g of glass beads of approximately 1- mm diameter, in 12 mm and 22.6 mm cells respectively. A 5-mm bead is placed at the cone apex, to prevent materials from descending into the inlet tubing(Brown *et al.,*2005).

Pumps and flow rates: Constant flow of media is achieved by using a peristaltic, syringe, pulsating pump (Fotaki *et al.,* 2011) or high-performance liquid chromatography pump (D'Souza *et al.,*2006). Peristaltic pumps are most commonly used. The release medium may be recirculated (close mode) or fresh buffer may be pumped constantly (open mode) through the system (Figure 2). The open system is used for samples which require high volume of medium (i.e., low solubility compounds), and the closed system is used when a low volume of medium is required (highly soluble compounds) (Fotaki *et al.,*2011).

Selection of a flow rate seems to depend on the type of pump used to study release or vice versa. Flow rates varying from 5 µl/min have been obtained with syringe pumps, 0.4 ml/min with HPLC pumps, and up to 200 l/h with peristaltic pumps (D'Souza *et al.,*2006).

Depending on the flow rate of the medium and the presence and quantum of glass beads, the flow within the cell can be laminar or turbulent. Turbulent conditions exist when the cell is operated without glass beads (open column packing).It is characterized by the rapid movement of fluid particles in all direction within the flow direction (Fotaki *et al.,*2011). Filling the cell cone with 1-mm glass beads (packed column) is reported to produce laminar flow conditions, but does not ensure a fully developed laminar flow profile (Brown *et al.,*2005). A laminar flow is characterized by fluid particles moving in parallel to one other in the flow direction (Fotaki *et al.,*2011).

A lower flow rate will lead to slower hydration of the polymer matrix which in turn results in incomplete drug release. While there are reported findings that changes in flow rate do not significantly impact drug release from microspheres (Rawat et al.,2011), the observation may not be extrapolated to *in situ* gelling systems, considering the semi solid consistency expected from most of these formulations. While a highly turbulent flow may not be desirable for drug release testing from an injectable *in situ* forming depot, the appropriate flow rate needs to be carefully evaluated.

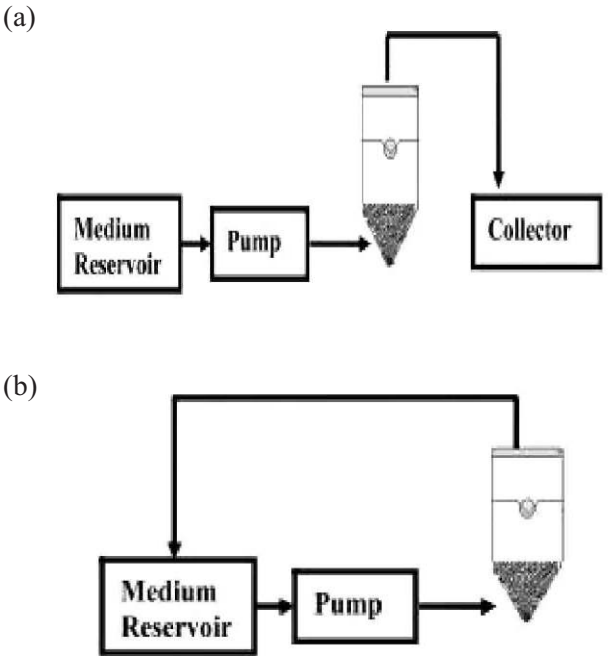

Figure2: Open (a) and closed (b) modes for operation of a flow through cell (Fotaki *et al.,*2011).

Volume of medium: The volume of medium used in a open setting is simply dictated by the flow rate and duration of release studies since fresh medium is continuously introduced into the sample. In a closed-loop configuration, the volume used can vary from as low as 20 ml to several liters. When operating the system in a closed-loop setting, the volume of the medium should be selected with consideration of the solubility of the API and sink condition (Shah *et al.,* 2015).

***Filter Material*:** The filter head for the flow-through cell should be fitted with an appropriate filter material (Shah *et al.,* 2015). The filter material should be durable enough so as not to physically degrade over the duration of the test. Typical filter materials such as glass fiber filters, polyvinylidene fluoride, polytetrafluoroethylene, and regenerated cellulose are considered. Small filter pore size is unacceptable as it results in back-pressure in the system (Tomic *et al.,* 2016).

The USP 4 apparatus has been discussed as the most appropriate for drug release studies from depot formulations, as it shows several advantages over other techniques, such as the possibility to use large as well as small volumes without violating sink conditions, superior simulation of *in vivo* environment and the amenability to changing medium and its flow rate within a single run. Also, determination of carry-over effects during the experiment, and testing of formulation robustness is feasible (Fotaki *et al.,* 2011) and release from dosage forms over extended periods can be studied without the evaporation issue that can be observed with other apparatuses (Fotaki *et al.,* 2011).

The limitations during use of the flow through cell for long term release studies stem from issues such as blocking and clogging of filter may occur which affect the maintenance of desired flow rates and create back up pressure (Fotaki *et al.,* 2011). Another limitation is the lack of availability of the equipment due to its high cost which is possibly the reason for lack of drug release studies from *in situ* gelling depots based on the flow through cell.

Non-compendial methods

Dialysis method:

In vitro drug release studies in several research papers is based on the use of dialysis bag for holding the drug containing system in case of *in situ* injectable gels (Graves *et al.,* 2007, Brown *et al.,* 2011, D'Souza *et al.,* 2014).

The method involves placing the formulation into a dialysis sac or tube. This dialysis sac is then placed into release medium (receiver chamber) maintained at 37 ± 2 °C. The receiving chamber is stirred to ensure mixing of the released drug. The drug released from the formulation diffuses through the dialysis sac membrane, and the drug concentration is determined by taking samples from the release medium at appropriate time intervals and replenishing them with fresh medium to achieve sink conditions.

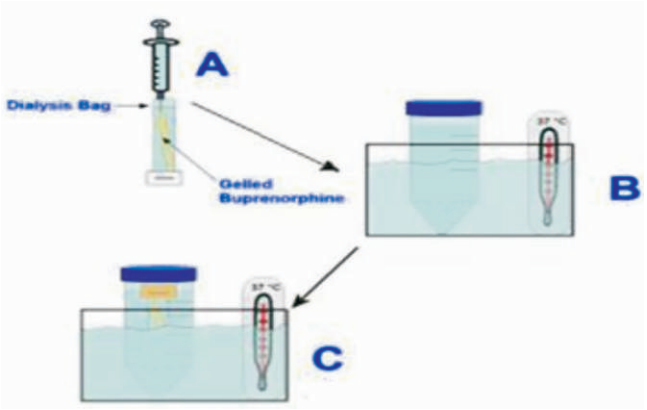

Figure 3: Pictorial representation of the use of dialysis bag for study of drug release from *in situ* forming PLGA based gel (Graves *et al.,*2007).

The dialysis sac method is advantageous because the medium and the sample are already physically separated by a membrane, and there is no need for extra separation before the sample measurement as well as for the retention of specimen in the system. This is particularly useful for *in situ* gelling systems prepared using hydrophilic polymers wherein parts of the gel may separate from the depot during the testing period due to continuous residence in the turgid release environment.

The method has been used for *in vitro* drug release testing of buprenorphine from an *in situ* forming PLGA based gel which showed controlled release of drug for 55 days (Figure 3) (Graves *et al.,* 2007).

The use of the method involves selection and standardization of a number of variables including:

Dialysis membranes: Ester, regenerated cellulose, and polyvinylidene difluoride are the most commonly used membranes for the dialysis sac. These are commercially available from several sources. The membrane should have appropriate molecular weight cut-off so that drug diffusion through the membrane is not a rate-limiting step. Also, it must be ensured that the drug does not bind to the membrane.

Sample Introduction: The formulation can be introduced to the dialysis sac using fine-tip pipet or syringe and placed in the dialysis sac containing a small volume of release medium (Shah *et al.,*2015). Volume of medium inside the dialysis membrane containing the *in situ* gel should be at least 6- to 10-fold less than that of the outer bulk, providing a driving force for drug transport to the outside. (D'Souza *et al.,* 2006). Ensuring a reproducible geometry for the gel within the dialysis sac is extremely challenging and has not been addressed in the reports so far.

Agitation: Drug diffusion from the dialysis bag into the outer sink may be increased by agitating the vessel contents, thereby minimizing unstirred water layer effects. Common modes of agitation include a horizontal shaker or using the

USP paddle apparatus under agitation or a magnetic stirrer (Shah *et al.,*2015). Literature on dialysis method for drug release from *in situ* gelling depots include the use of both static (Graves *et al.,*2007) as well as agitated (Hassan et al, 2015) media.

Although convenient to use and widely used for *in situ* gelling depots, the dialysis bag method for drug release studies is generally associated with a few limitations. This technique is not applicable if the drug binds to dialysis membrane. The method being non-compendial, different laboratories use different setups which can result in unreliable release profiles (Shen et al., 2012). Also, a serious drawback is that a limited volume of release medium is present within the sac and there is complete absence of any agitation within the sac. When drug release is rapid, it may be impossible to maintain sink conditions within the dialysis sac, and as a result, the dialysis sac becomes a rate limiting membrane (Shah *et al.,* 2015). The burst release may not be suitable reflected by the dialysis bag method.

As a means of overcoming some of these drawbacks, adaptations such as the rotating dialysis cell model and a Float-A-Lyzer® method have been used in *in vitro* release testing for extended release parenteral dosage form (Figure 4). The Float-A-Lyzer is an example of a group of ready-to-use commercially available dialysis devices. The cylindrical tubing geometry provides open access for total volume retrieval by pipette. These are prepared using proprietary dialysis membranes and are available in various precise Molecular Weight Cut Off's (MWCOs) and in a range of sizes for dialyzing volumes from 500µl to 10 ml. The rotating dialysis cell comprises of a modification of the Type I USP dissolution apparatus wherein the basket is placed horizontally and is encased in a dialysis membrane with the drug releasing system within. Another modification, also based on the USP dissolution apparatus I, is the glass basket dialysis method, wherein the conventional basket was replaced with glass cylinders closed at the lower end by dialysis membrane (Abdel-Mottaleb *et al.,* 2010). The authors found the method to be more discriminating than the conventional dialysis bag when evaluated for drug release from various nanosystems. However, none of these, although promising, have been explored for release testing from *in situ* gelling depots.

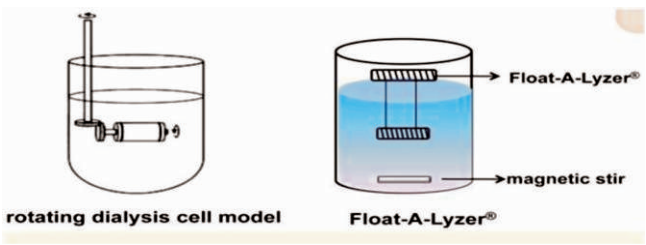

Figure4.Pictorial representation of rotating dialysis cell and float-A-lyzer (Shen et al.,2012).

Another means suggested to overcome some of the problems with conventional dialysis methods is the use of a reverse dialysis sac method which involves placing the formulation directly into an appropriate volume of release medium in a suitable chamber, with suitable agitation, has also been proposed. Here, two or more dialysis sacs are placed in the release medium and at appropriate time intervals, one dialysis sac is removed, and the drug concentration is analyzed to calculate the percentage of release. Although this approach helps to maintain sink conditions since the formulation is diluted in the large volume of release medium outside the dialysis sacs, it may be less suited for release testing from *in situ* gelling systems due to the changes such as erosion which may be associated with the gel while resting in a larger volume of release medium.

Membrane-less methods:

The membrane less model uses the layering of a very small volume of release medium over a preformed gel in a container such as a test tube. At each sampling point, the entire medium is withdrawn and replaced. The method has been reported by several authors for a variety of actives undergoing release from various *in situ* gelling depots. In case of gels which may be susceptible to gradual erosion into the release medium, such as poloxamer based thermoreversible gels, most studies have relied on a gravimetric method, i.e. weighing of the gel at each time point, to quantify the erosion process. A study on PEGylated octreotide thermoresponsive *in situ* gel uses such a non-compendial membrane less dissolution model for *in vitro* dissolution testing at 37°C (Jabarian *et al.,* 2013). The *in vitro* release rates of astragalus polysaccharide (ASP) injectable thermoresponsive *in situ* gel (Yu *et al.,* 2017) was measured using a test tube / membrane less method which showed sustained release profile for about 132 hr with a low initial burst .

The method is advantageous for its simplicity and typically uses very limited, as little as 0.3ml (Mei *et al.,* 2018) release medium, and may therefore mimic turgidity in the intramuscular tissue. However, it also suffers from significant drawbacks including absence of sink conditions (unless the drug is potent with very high aqueous solubility), unidirectional release, static test condition and loss of gel due to erosion in certain cases.

Hybrid Methods:

Methods fusing these approaches such as the use of the flow through cell with a dialysis adapter as well as use of the USP apparatus 1 with the dialysis bag in various configurations are also reported.

Similarly, agitation by the paddle has been replaced by a gentle movement within an orbital shaker. Release of

tramadol hydrochloride from a pluronic gel was followed into a medium agitated at 30 rpm for 5 days. The speed was kept slow enough to avoid the breaking of gelled formulation and to simulate the mild agitation expected under physiological conditions (Mirajkar et al., 2018).

Accelerated testing methods:

As reported in case of the polyester microsphere based injectable depots, it would be beneficial to identify accelerated methods for the study of drug release from *in situ* gelling depots. While real-time *in vitro* release testing is necessary to gain a mechanistic understanding of drug release and to develop a good *in vitro-in vivo* correlation, accelerated release testing for extended release parenteral dosage forms is essential for quality control purposes as well as to assist in formulation development (Shen and Burgess., 2012). The accelerated test should be able to discriminate between batches with respect to manufacturing variables that can impact on bioavailability.

Accelerated test should maintain the bio relevant aspect of *in vitro* method, i.e. mechanism of release should not change under accelerated test conditions. It is also important that the accelerated test should mimic the physiological conditions at the site of administration to the extent possible (Tomic *et al.,* 2016, Shen et al., 2012). Especially, such a release method should be able to identify burst release from the formulation and also supply information about the duration of this phase for controlling the efficacy and safety of the product. In general, an *in vitro* release of over 80% is considered desirable (Brown et al., 2011). Studies show that, by altering the temperature, the pH or the composition of the release medium, it is possible to achieve a significant acceleration of the drug release from PLGA-based microspheres. In case of the *in situ* gelling depots, in addition to methods such as variation in medium pH, temperature, addition of enzymes or surfactants, change in agitation rate etc, a controlled increase in the surface area of the *in situ* formed depot can be investigated as means of accelerating drug release in certain cases.

Conclusion:

A brief review of the literature sharply points towards the absence of standardized methods for drug release studies from *in situ* gelling depots. Although methods based on the use of compendial apparatuses, especially apparatus 2 are widely reported, non-compendial tests using membrane-less release or dialysis bags are more common. Information on the use of the flow through cell in literature for drug release from *in situ* gelling depots is limited. There is also scope to identify accelerated methods for testing the *in situ* gelling injectable depots in a rapid, albeit reliable manner.

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FOOD DRUG INTERACTIONS: Factors affecting and *in vitro* methods to study the interactions.

Abstract: This article attempts to give an overview of a common issue in drug bioavailability, viz. drug-food interactions. Factors governing such interactions and in designing *in vitro* studies to predict food-drug interactions are discussed. Further some example drugs and two case studies have been included from literature.

INTRODUCTION:

What you eat and drink can affect the way of your medicines work. When the way of a medicine works is affected by food and drinks this is called a "food-drug interaction."Commonly, food contains protein, carbohydrates, fats, and amino acids. Food intake may bring about physiological changes in the pH and viscosity of the gastrointestinal lumen, which could affect the oral absorption of drugs. Food may have negative, positive or no effect on drug absorption. Negative food effect is of concern for active pharmaceutical ingredients (API) with narrow and therapeutic index, where impaired drug absorption may lead to a risk of treatment failure; whereas, positive food effect may increase the risk of drug toxicity (Fleisher et al., 1999).The negative food effect on the drug absorption can be mediated through several mechanisms, including: Postprandial changes in the GI physiology (pH, motility, transient times, and viscosity), complexation interactions of the API with food components, reduced drug diffusivity and solubility, delayed dosage form disintegration and drug release under fed conditions (Abrahamsson et al., 2004, Kalantzi et al., 2005, Radwan et al., 2012).

FOOD-DRUG INTERACTIONS:

Many drugs have a low degree of oral bioavailability, because of food-drug interactions (negative food effects). Major effects include alteration in absorption of drugs by fatty, high protein and fiber diets (Ayo J.A. et al., 2005).

Food intake exercises a multifaceted influence on the bioavailability of drugs. It may affect tablet disintegration, drug dissolution, drug transit through the gastrointestinal tract, as well as the metabolic transformation of drugs in the gastrointestinal wall and in the liver. However, enteric-coated tablets that start to disintegrate when they reach the middle-to lower region of the small intestine could reduce negative food effects. Thus, food and its components and contaminants may have both short- and long-term effects on both the absorptive and dissolution processes influencing systemic availability of drugs.

FACTORS AFFECTING FOOD-DRUG INTERACTIONS:

Composition of the GI fluids: Usually, food containing green vegetables contain metal ions, protein, carbohydrates, fats, and amino acids. A number of studies give evidence that drugs forming slightly soluble complex with metal ions of food show reduced bioavailability. Co-administration of acetaminophen with pectin delays its absorption and onset. Casein and calcium present in milk decrease the absorption of ciprofloxacin (Papai K, et. al., 2010). Azithromycin absorption is decreased when taken with food, resulting in a 43% reduction in bioavailability (Stormer F.C, et. al. 1993). Tetracycline should be taken one to two hours after meals, and not taken with milk because it binds calcium and iron, forming insoluble chelates, which influences its bioavailability (Gurley B. J., et. al., 2003). Fatty foods stimulate the secretion of bile flow; bile salts are surface active and can increase the dissolution of poorly soluble drugs, and hence promote absorption (Gibaldi M. et. al., 1970). However, bile salts also have been shown to impede absorption of some compounds because they form insoluble complexes (Bates T. R. et. al.1970). Theophylline serum concentrations tended to be higher when the drug was taken with a protein rich meal or with water than when taken with meals rich in fat or carbohydrates (Welling P.G. et.al., 1975).

Food and antacids can also be implicated in affecting the bioavailability of tetracyclines. Thus, the absorption of first generation tetracyclines such as oxytetracycline or tetracycline can be drastically reduced by concomitant intake of antacids, or of calcium-containing food items, such as milk and cheese (Kirby et al., 1961; Neuvonen 1976; Hurwitz 1977). Iron preparations also have a marked inhibitory effect on absorption of tetracycline. It seems well established that non-absorbable chelates are formed between the metals (Al, Mg, Ca, and Fe) and the tetracyclines (Turakka, 1974; Neuvonen. 1976). The effect of interaction of five fruit juices on the dissolution and absorption profiles of ciprofloxacin tablets was determined. It was found that the absorption of ciprofloxacin (500 mg) tablets can be reduced by concomitant ingestion of grape fruit juice. Therefore, to avoid drug therapeutic failures and subsequent bacterial resistance as a result of sub-therapeutic level of the drug in the systemic circulation, ingestion of the juice with ciprofloxacin should be avoided. (Akinleye M.O. et. al.,2007).

Viscosity: Ingestion of foodstuffs containing water soluble fibres has been demonstrated to elevate the luminal viscosity by several orders of magnitude (Blackburn N.A, et. al., 1981 and Dikeman CL et. al.,2006). Food viscosity is one of the physiological parameters that can affect oral drug absorption. Most of the studies that addressed the influence of viscosity on drug absorption demonstrate a reciprocal relationship between drug absorption and gastric viscosity (Eshra AG, et. al., 1988). Ingestion of food leads to an elevation in the digesta viscosity, which was reported to be in the range of 300–4000 mPa·s (Marciani et al., 2001). The viscosity of gastric aspirates from healthy volunteers was reported to range from 200–2000 mPa.s immediately after food ingestion (Marciani L., et. al.2001). The average intestinal content viscosity values of rats fed with an oat based meal was found to lie in the range of 199–370 mPa.s (Gallaher D. D et. al.1999). The viscosity of the gastric juice in the fasted state lies in the range 0.01–2 mPa·s. The *in vivo* flow patterns within the GI tract are laminar and very low. The average gastric flow velocity was estimated to be 3 mm/s with the Reynold's numbers in the range of 0.01 to 30. Different theories have been proposed to explain the mechanisms behind this food viscosity effect: (i) an inhibition of gastric emptying and/or modification of intestinal transit time (ii) a slower diffusion of drug molecules in the viscous lumen towards the intestinal membrane; (iii) a reduction in the disintegration rate of the drug formulation under viscous conditions; reduction in drug dissolution rate (Reppas C. et al.,1998). An increase in viscosity of the dissolution fluid will in particular affect the absorption of BCS type III compounds with preferential absorption in the upper small intestine if the API release is delayed from the dosage form. Media viscosity was identified as one of the key parameters affecting drug release (Radwan et al., 2012).

Eshra et al., (1998) explained the reduction in ketoprofen absorption in humans by a retarding effect of food on the dissolution and diffusion rates of the dissolved drug. Khoury et al., (1991) reported reduced dissolution kinetics of hydrocortisone acetate in dilute polymeric HPMC solutions, which act as a diffusion barrier. Yet, there are also data showing that tablet disintegration, for example in canine stomach in the fed state, can be influenced by a viscosity-independent mechanism, i.e. a formation of a film coat around the dosage form. Anwar et al. (2005) state that the viscosity plays an important role in delayed tablet disintegration in milk. Parojcic et al. (2008) have reported reduced disintegration and dissolution rates of paracetamol tablets in viscous solutions of HPMC K4M. This was attributed to the poorer wetting of the tablet surface and reduced hydrodynamic shear stress.

Food composition and viscosity plays an important role in the dissolution process of BCS class III drugs. Changes in disintegration times may be responsible for the different dissolution profiles observed in these different media. Changes in media viscosity can significantly influence the disintegration times of tablets through changes in liquid penetration rates (Radwan et al., 2012).

pH: The pH raising by influence of food and antacids is important, as the solubility of many drugs is reduced with increasing pH. Barr W.H., et. al., (1971) have reported any substance which significantly increases the intra gastric pH may result in a decreased fraction of tetracycline in solution available for absorption by a mechanism which is independent of the ability of the substance to chelate with tetracycline. Physiologic or pathologic conditions which increase gastric pH, such as achlorhydria might also result in a decreased absorption of tetracycline. Although it is commonly stated that antacids containing divalent or trivalent metals should be withheld from patients receiving tetracycline therapy, this caution should also be extended to include any antacid or substance capable of raising intra gastric pH.

The decreased absorption of a solid dosage form, but not a solution, of tetracycline in the presence of bicarbonate indicates that the dissolution step must be involved and can be explained by the importance of a low gastric pH to effect dissolution of solid tetracycline prior to absorption. The aqueous solubility of tetracycline at pH 1 to 3 is 100 times greater than that at pH 5 to 6. The rate of dissolution is markedly reduced at the higher pH values (Barr W.H., et. al., 1970). A 2gm dose of sodium bicarbonate will increase the intra gastric pH above 4, which is unfavourable for dissolution, for a period of 20 to 30 minutes. This period of time is sufficient for 20 to 50 per cent of the undissolved drug particles to be emptied into the duodenum (Harvey R. et. al.,1970), where the pH (5 to 6) is also unfavourable for dissolution. Thus, if the drug is not dissolved in gastric fluids before gastric emptying into the more alkaline pH of the intestinal fluids, dissolution may not be complete and the fraction of total drug absorbed will be decreased (Barr W.H., et. al., 1971). Thus, the concurrent intake of tetracyclines and antacids and/ or food containing iron should be avoided, and, if possible, tetracyclines should be taken in the fasting state (Neuvonen P.J. et. al.,1976).

Motility of GI: Gastric emptying may also be delayed by ingestion of hot meals (Davenport H. W.,1961), by solutions of high viscosity (Levy G. et. al.,1965), by fat, and to a lesser extent by protein and carbohydrate (Bachrach W. H et. al.,1959). Solid diets have been shown to almost double stomach emptying time compared to liquid meals in rats (Marcus C. S. et. al., 1962). Although passage of a drug from the stomach into the intestine is thus likely to be mechanically inhibited by the presence of food, prolonged residence in the stomach may have varying effects on drug absorption depending on the drug's solubility and stability in the acidic gastric juices and the lipophilic character of the dissolved molecule. Once food has passed from the stomach into the upper small intestine, it has a stimulatory effect on intestinal

motility, and this increased motility may accelerate dissolution of solid particles and also decrease the diffusion path of drug molecules to the intestinal mucosa. On the other hand, increased intestinal motility also may increase the rate of transit of compounds through the intestine.

SOME EXAMPLES OF FOOD-DRUG INTERACTIONS:

Antibiotics:

Antibiotics are widely prescribed in medical practice. Many of them induce or are subject to interactions that may diminish their anti-infectious efficiency or elicit toxic effects. (Hodel M. et.al., 2009). Avoid coadministration of antibiotics with milk products and food which are rich sources of divalent ions, such as calcium and magnesium that complex with many antibiotics and prevent their absorption. The intake of dairy products, however, needs to be monitored and encouraged with appropriate consideration of specific antibiotics involved (McCabe B. J, et. al.,2003). Several studies give evidence that fluoroquinolones forming slightly soluble complex with metal ions of food show reduced bioavailability. Casein and calcium present in milk decrease the absorption of ciprofloxacin. (Papai K, et. al.,2010) Ciprofloxacin with fruit juice, tetracyclines interaction with dairy products and Ca are all examples of food -drug interactions which are reported by several researchers (Akinleye M.O.; Stormer F.C, et. al. 1993; Kirby et al., 1961; Neuvonen, 1976; Hurwitz, 1977; Neuvonen and Turakka, 1974; Neuvonen 1976; Barr et al., 1971;Neuvonen, 1976).

Warfarin:

Warfarin is commonly used to treat or prevent thromboembolic events. If warfarin sodium is ingested with leafy green vegetables, the hypoprothrombinemic effect of warfarin may be decreased and thromboembolic complications may develop (Walker S.E. et.al.,1996).

Patients taking warfarin are at particular risk of interactions with dietary supplements, yet approximately 30% use herbal or natural product supplements on a regular basis (Harris J.E.et. al.,1995).

Analgesics and Antipyretics:

Analgesics and antipyretics are used to treat mild to moderate pain and fever. For rapid relief, acetaminophen should be taken on an empty stomach because food may slow the body absorption of acetaminophen. NSAIDs like ibuprofen, naproxen, ketoprofen and others can cause stomach irritation and thus they should be taken with food or milk. The daily dosage and frequency of ibuprofen must be reduced when administered with Coca-Cola (Kondal A, et. al., 2003). Food intake did not appear to affect the extent of absorption (ie, total exposure) of oral Diclofenac potassium soft gelatin capsule doses (Scallion R, et. al., 2009).

Bronchodilators:

Bronchodilators like theophylline, albuterol, and epinephrine possess different effects with food. The effect of food on theophylline medications can vary widely. High-fat meals may increase the amount of theophylline in the body, while high carbohydrate meals may decrease it. Avoid alcohol if taking theophylline medications because it can increase the risk of side effects such as nausea, vomiting, headache and irritability. Avoid eating or drinking large amounts of foods and beverages that contain caffeine (e.g., chocolate, colas, coffee, and tea) since theophylline is a xanthine derivative and these substances also contain xanthine. Hence consuming large amounts of these substances while taking theophylline, increases the risk of drug toxicity (Stormer F.C. et. al.,1993).

Antihistamines:

Fexofenadine, loratadine, rupatadine, cimetidine cetirizine, are all antihistamines. It is best to take prescription antihistamines on an empty stomach to increase their effectiveness. Rupatadine is commonly used for the management of diseases with allergic inflammatory conditions. A study indicates that concomitant intake of food with a single 20 mg oral dose of rupatadine exhibits a significant increase in rupatadine bioavailability (Solans A, et. al. 2007). Cimetidine is given with food to assist the maintenance of a therapeutic blood concentration (Roe DA. Et al., 1991).

Antitubercular Drugs:

Rifampicin is a antituberculosis agent that is usually given once daily. Absorption of this drug is also reduced when it is taken together with food (Acocela G. et al., 1978; Fiegler et al., 1974). Rifampicin should be given on an empty stomach and it appears to be a common routine to administer this drug in the morning, in due time (say 1 hour) before breakfast. Anti-tubercular drugs like isoniazid have been associated with tyramine and histamine interactions. Inhibition of monoamine oxidase and histaminase by isoniazid can cause significant drugfood interactions. Food greatly decreases isoniazid bioavailability (Self T.H, et. al.,1999). High fat meals decrease the serum concentration of cycloserine, a bacteriostatic anti-tubercular drug and results in incomplete eradication of bacteria (Zhu M, t. al.,2001).

Antitumor Drugs:

Mercaptopurine is a purine analog used for acute lymphoblastic leukemia and chronic myelogenous leukemias. Since it is inactivated by xanthine oxidase (XO), concurrent intake ofsubstances containing XO may potentially reduce bioavailability of mercaptopurine. Cow's milk is known to contain a high level of XO. This interaction may be clinically significant. Therefore, most patients should try to separate the timing of taking mercaptopurine and drinking milk (Lemos M.L. et. al., 2007).

Some literature examples given in Table 1.

Drugs	Food	Drug-Food Interaction
Warfarin	High-protein	Raise serum albumin levels
	Vegetables containing vitamin k	Interferes with the effectiveness and safety of warfarin therapy.
	Charbroiled	Decrease warfarin activity
	Cooked onions	Increase warfarin activity
	Leafy green vegetables	Thromboembolic complications may develop
Theophyline	High-fat meal and grape fruit juice	Increase bioavailability
	Caffeine	Increases the risk of drug toxicity
Esomeprazole	High-fat meal	Bioavailability was reduced
Cimetidine, Rupatadine	With food (any type)	Increase bioavailability
Cycloserine	High fat meals	Decrease in serum concentration
Esomeprazole	High-fat meal	Bioavailability was reduced
Cycloserine	High fat meals	Decrease the serum concentration
Glimepiride	With breakfast	Absolute bioavailability
Acarbose	at start of each meal	Maximum effectiveness
Mercaptopurine	Cow's milk	Reduce bioavailability
ACEs inhibitors	Empty stomach	absorption is increased
NSAIDs	Alcohol	Can increase risk of liver damage or stomach bleeding
Levothyroxine	Grapefruit juice	Delay the absorption

IN VITRO METHODS TO STUDY THE FOOD DRUG INTERACTIONS:

Drugs present in the gastric fluids are exposed to mixtures of foodstuffs made up of protein, carbohydrates, fats and amino acids and dissolution in the intra-gastric fluid is essential for the subsequent absorption of basic lipophilic drugs, in particular. Different food components have different effects on drug dissolution. Effect of food increases dissolution of many drugs such as Propranolol, Hydrochlorothiazide, Nitrofurantoin, dicoumarol, phenytoin and carbamazepine but reduces that of drugs such as isoniazid, rifampicin, tetracycline, penicillin and ampicillin, while having no consistent effect on the dissolution of metronidazole, oxazepam, melperone, propylthiouracil, sulphasomidine and sulphonylureas.

Dissolution testing is a potential predictive tool to give an idea of oral absorption of drugs but, to achieve this, test conditions need to simulate the physiological conditions prevailing in the intraluminal environment. Tablet disintegration and drug dissolution are critical steps in the process of drug absorption, any delay in one of these steps will affect the overall release of the active ingredient.

The most important interactions are those associated with a high risk of treatment failure arising from a significantly reduced bioavailability in the fed state. Such interactions are frequently caused by interruption or poor dissolution in presence of food content, chelation with components in food. *In vitro* dissolution and disintegration tests are recognized as valuable means for predicting drug bioperformance under fast and fed conditions.

To understand and predict food drug interactions by *in vitro* testing, media composition and viscosity should be considered for adequate prediction of food effect on drug release. Biorelevant media based on food constituents are recommended for the prediction of the behavior of the drugs in the gastro intestinal tract as they appear as more realistically representative of the intraluminal fluids than the simple compendial dissolution media. Biorelevant media are virtually the same as intestinal juices. They contain key natural surfactants (bile salts, phospholipids) present in

intestinal juices, and can provide a much more accurate picture of how drugs and their formulations are likely to dissolve *in vivo*. Biorelevant media include Fasting state and Fed state simulated Gastro Intestinal fluids. The composition of the gastric fluid in post-prandial conditionsis variable according to the type of the administered meal (Koziolek M, et. al., 2013). Therefore, to tackle the problem of variability in gastric fluid composition, biorelevant dissolution media were suggested to standardize the composition of simulated gastric fluids at fedstate. Milk was utilized as it is a nutrient that contains the three basic components of fat, protein and carbohydrates in a ratio resembling a typical diet (Galia E, et al.,1998). In 2008, Jantratid et al. recommended the use of a mixture of milk and acetate buffer and subsequently a formulation of milk digested with pepsin and lipase was proposed to represent the changes in intra-gastric composition according to the digestion stage (Diakidou A. et. al.,2009). Artificial liquid meals, such as Ensure™ and Intralipid™ were recommended as they are specifically designed to reflect the composition of a standard meal and can be well standardized (Buckton G et. al.,1989). The use of Ensure Plus™ containing a viscosity enhancer, 0.45% pectin (Klein S.et al.2004) or medium containing 1.4% HPMC in acetate buffer (Radwan A. et. al., 2012) were suggested as an alternative media to the homogenized standard breakfast. A medium containing two types of vegetable oils, sucrose and surfactants was used to mimic fed gastric conditions (Muschert S. et. al., 2010). Media based on mono-components of proteins, carbohydrates or amino acids were utilized as simple dissolution media that allowed the investigation of the effect of these individual components on the dissolution of drugs (Macheras P. et al., 1987).

SOME CASE STUDIES FROM LITERATURE:

Isoniazid:

Isoniazid taken together with the standardised breakfast [the breakfast consisted of 150ml low fat milk, 100ml orange juice, 1 egg, 2 pieces of crisp bread, 5g margarine, 20g orange marmalade, 20g cheese and 100ml non-sweetened black coffee or tea, yielding a total energy of I 840kJ (= 440kcal), as 20g (20%) protein, 17g (35%) fat, and 50g (45%) carbohydrates], the bioavailability of the antituberculosis agent isoniazid was markedly reduced; both the peak concentration and the area under the serum concentration time curve was decreased by about 50% (fig. 1; Melander et al., I 976). It cannot be stated whether the reduced bioavailability in the therapeutic situation would be so extensive that the clinical effect of conventional isoniazid doses would be jeopardised. This is not unlikely, however, as the reduction of the peak concentration was very large in some subjects and the peak concentration is of great importance for the antituberculosis effect of isoniazid (Mitchison, et. al., 1973). Since the drug is administered only once daily, oreven less frequently, it may be given routinely in the fasting state without any difficulty.

As for the mechanism responsible for the inhibitory effect of food on the bioavailability of isoniazid, it seems probable that food intake alters the absorption of isoniazid by effects on gastric emptying and gastrointestinal pH (Melander et al., 1976). This hypothesis is supported by the findings of a study in which antacids were found to have an inhibitory effect onthe bioavailability of isoniazid (Hurwitz and Schlozman. 1974); in the case of aluminium hydroxide gel the effect was due to delayed gastric emptying (Hurwitz et al.,1977).

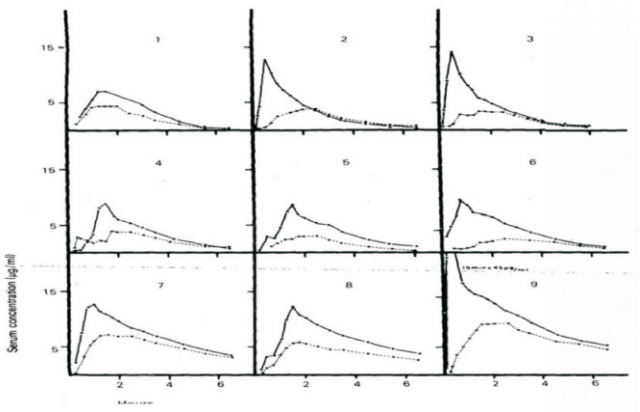


***Fig.* 1.** Serum concentrations of isoniazid in 9 healthy volunteers ingesting a single dose of the drug (10mg/kg) both on anempty stomach (---) and together with a standardised breakfast (- - -) The mean reduction in AUC values was about 50%(after Melander et al., 1976).

Ciprofloxacin HCl:

The study demonstrated the significance of luminal pH and viscosity on the dissolution and disintegration of solid formulations, wherein *in vitro* dissolution data of ciprofloxacin in Jute soup [The fresh leaves of *C. olitorius* were cut and mixed thoroughly with 1 L media (SIF or 0.1N HCl)] was used to predict the negative food effect encountered following oral administration of solid dosage form of this compound with this type of food. The magnitude of the reduction in the *in vitro* drug release in the viscous Jute soup may be indicative of the degree of decrease in the *in vivo* release profiles. The predicted negative effect of Jute soup on the rate of ciprofloxacin absorption can be ascribed to the elevation in the gastric viscosity, delayed gastric emptying as well as prolonged tablet disintegration (Radwan A. et. al., 2017).

The *in vitro* dissolution of Ciprofloxacin tablet was investigated in different media and the dissolution profiles are shown in Fig. 2. Observations indicate that pH has significant effect on the drug release profiles. In fact, the rate of ciprofloxacin HCl release was higher at gastric compared to luminal conditions. Precisely, in SGF, 90% of the drug was dissolved within 30 min, reflecting the good solubility of the drug substance at low pH. However, the drug release in SIF was reduced to less than 40% within 120min. The addition of *C.olitorius* leaves in the media resulted in a significant reduction in the dissolution of ciprofloxacin in a concentration dependent manner. 35% of drug was released

within 30 min in 2.5% Jute soup compared to 20% in 5.0% soup, while, in 7.5% Jute solution, a marked reduction in the dissolution rate was observed, less than 18% of the drug from formulation dissolved within120 min as reported in Fig. 2. This delay in dissolution rates reflects the slower disintegration of tablets in the soup. Results of similarity were lower than 50 at both dissolution conditions, which indicate that the release of the drug in presence of *C.olitorius* was negatively affected as can be shown in Fig. 2.

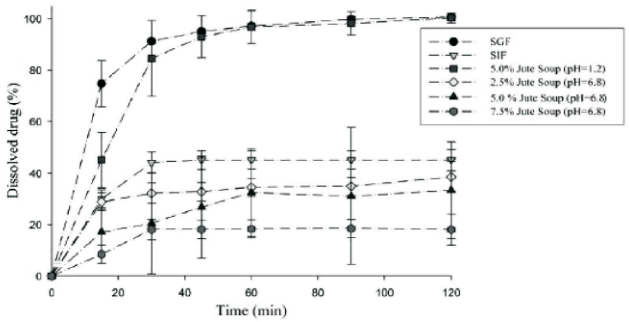
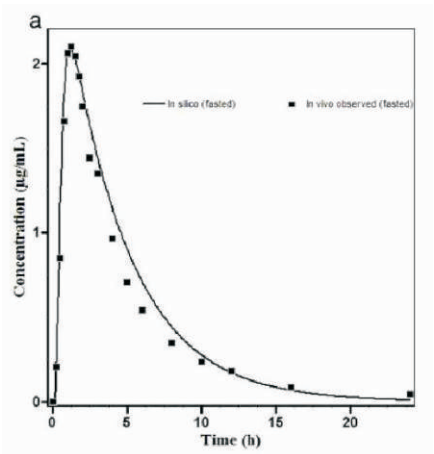


Fig. 2. Dissolution profile of ciprofloxacin at two pHs, with *C.olitaruis* leaves and without soup. (Radwan A. et. al.,2017)

In silico modeling was employed based on in vitro dissolution data to predict the *in vivo* performance of ciprofloxacin under fasted and fed states. The variations in the physiological pH within the GI tact had a pronounced effect on ciprofloxacin release from the formulations (Fig. 3). The acidic conditions of the stomach enhanced the dissolution of ciprofloxacin.

The limited solubility at the intestinal pH can be considered as an explanation for the observed impaired dissolution. Food is known to elevate the gastric pH. Therefore, postprandial elevation in gastric pH would decrease ciprofloxacin solubility and hence its dissolution rate which may limit its absorption. The viscosity of the medium clearly has a significant effect on the dissolution and disintegration rates. The addition of *C.olitorius* leaves in the dissolution media resulted in markedly reduced drug dissolution and prolonged tablet disintegration rates, which can be attributed to the high viscosity of the *C.olitorius* soup. The mucilage content seems to have the crucial role in this study.



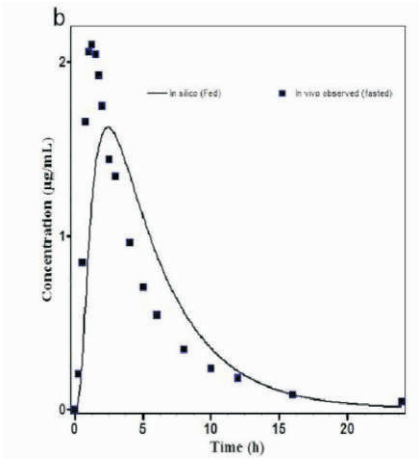


Fig. 3. a) In silico simulated and *In Vivo* observed ciprofloxacin plasma Cp–time profiles following oral administration of 500 ciprofloxacin table under fasted. b) In silico predicted ciprofloxacin plasma Cp–time profiles under fed conditions compared to the *in vivo* observed under fasted state. (Radwan A. et. al.,2017)

CONCLUSION:

The drug-food interactions need to be well identified. It must be taken seriously into account with oral drugs administration in order to minimize variations in systemic drug availability and hence in clinical efficacy and safety. Media composition, viscosity and pH are important parameters affecting drug release. Reduced drug solubility at high pH, prolonged tablet disintegration and precipitation of a food film layer on the surface of the tablet are the postulated mechanisms. Biorelevant media based on food constituents should be used for the prediction of behaviour of the drugs in the gastrointestinal tract as they appear as more realistically representative of the intraluminal fluids than the simple compendial dissolution media.

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Vinod P. Shah Award

Vinod P. Shah, PhD was presented with the **Albert Nelson Marquis Lifetime Achievement Award by Marquis Who's** Who on 6th Aug 2019.

He has been endorsed by Marquis Who's Who as a leader in the pharmaceutical industry.

Dr. Mala Menon Award

"IPA-ACG Scitech Innovation Award 2018 for Promising Innovation in Solid Dosage Form", in recognition of "Dry Powder inhalation (DPI) formulation for alveolar macrophage (AM) targeting to achieve improved therapy of of Tuberculosis (TB)." at IPA Awards' Function, held on 22nd December 2018 at New Delhi

Dr. Mala Menon received the award for "Best Professor in Pharmaceutics" at the **Business School Affaire & Dewang Mehta National Education Awards** on Nov 28th 2018 at Taj Land's End, Bandra, Mumbai

Dr. Padma Devarajan Award

Dr. Padma Devarajan Received the **OPPI SCIENTIST AWARD 2018 for Research contribution in the area of Veterinary and Human healthcare** with focus on innovative drug delivery systems for infectious diseases, by comprehensively addressing diverse needs, identifying lacunae and designing innovative, simple low cost, scalable technological solutions backed by science, to enable translational outreach through affordable excellence for socioeconomic development.

Dr. Arvind Bansal Award

"IPA-ACG Scitech Innovation Award 2018 for Best Innovative Development of Solid Dosage Form", in recognition of NanoCrySP a technology platform for Nano Crystalline Solid Dispersion at IPA Awards' Function, held on 22nd December 2018 at New Delhi

Professor Bhupinder Singh Bhoop _Awards _Last One Year : 2018-2019

Indian Pharmaceutical Association (ÌPA) Fellowship Award 2018 for exemplary attainments towards Pharmaceutical profession. This prestigious award was conferred upon him, along with a citation, robe of honour and a momento by Dr. TV Narayana (President, IPA) and **Dr. B Suresh (President, Pharmacy Council of India)**, accompanied with other eminent stalwarts from the pharma world during the IPA Awards' Function, held on 22nd December 2018 at New Delhi.

Professor DVS Jain Best Researcher Award - on the basis of highest cumulative impact factor of publications authored by him as corresponding author/first author, by Professor Raj Kumar, Vice-Chancellor, Panjab University and Professor A. Raghuram Rao, Director, NIPER, Mohali, on 4th March 2019. Selected under the aegis of "Smt. Prem Lata and Prof. D. V. S. Jain Research Foundation", on the basis of cumulative impact factor of the research publications authored by him during 2017, the Award carried a citation and the total prize money of Rs. 30000/-

Pharmaceutical Quality by design (QbD) Excellence Award: by M/s Shengjie Business Management & Consulting Co. Ltd., Shanghai, during a two-day Pharmaceutical Industry Internationalization Strategy Summit held on 16th-17th May 2019 in Shanghai, for his exemplary and seminal contribution towards steering pharmaceutical industry across the globe on various QbD paradigms.

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