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DISSOLUTION RESEARCH- A PREDICTIVE TOOL FOR CONVENTIONAL AND NOVEL DOSAGE FORMS

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ABSTRACT

The dissolution process started to develop about 100 years ago as a field of pharmacy and since then important progress has been made. Interest in drug related dissolution has grown only since the realisation that dissolution is an important factor of drug bioavailability in the 1950s. This review attempts to account the most important developments in the field, from a historical point of view. The purpose of this article is to review USP and non-pharmacopeia dissolution testing methods for conventional and novel pharmaceutical dosage forms and gives an insight to possible alternatives in drug dissolution study design and appropriate choices for dissolution media'. The main aim of this article is to review the scenario of dissolution research development from past to present and the dissolution studies of various pharmaceuticals.

KEY WORDS: Bioavailability, Dissolution, U.S.P Apparatus, Immediate Release Tablets, Suppositories.

INTRODUCTION

Dissolution testing is an official test used by pharmacopeia's for evaluating drug release of solid and semisolid dosage forms dissolution tests were first developed to quantify the amount and extent of drug release from solid oral dosage forms including immediate/sustained release tablets and capsules. More recently, dissolution has become important in testing drug release of dosage forms such as, buccal and sublingual tablets, chewing gums, soft gelatine capsules, suppositories, transdermal patches, aerosols and semisolids the study of the dissolution process has been developing since the end of the 19th century by physical chemists. The goal is to have a fully functional set of USP performance tests for all kinds of dosage forms.

Solid dosage form (tablet and capsule):

I.P. and E.P. :

Apparatus I – paddle apparatus

Apparatus II – basket apparatus

B.P. and U.S.P. :

Apparatus I – basket apparatus

Apparatus II – paddle apparatus

B.P. and E.P. :

Apparatus III – flow through cell apparatus

Conditions (for all):

Temp - 37±0.50C

PH - ±0.05 unit in specified monograph

Capacity – 1000 ml

Distance between inside bottom of vessel and paddle/basket is maintained at 25±2 mm.For enteric coated dosage form it is first dissolved in 0.1 N HCl and then in buffer of pH 6.8 to measure drug release. (Limit – NMT 10% of drug should dissolve in the acid after 2hr.and about 75% of it should dissolve in the buffer after 45 min.

USP apparatus are of 7 types they are as follows

Type 1 USP apparatus: (Basket apparatus)

- Dosage form contained within basket.
- Dissolution should occur within Basket.
- pH change by media exchange.

Useful for:

- Tablets
- Capsules
- Beads
- Floaters

Type 2 USP apparatus: (Paddle apparatus):

- Dosage form should remain at the bottom centre of the vessel
- Sinkers used for floaters
- pH change by media addition

Useful for:

- Tablets
- Capsules

Type 3 USP apparatus: (Reciprocating cylinder):

- Rotations 6-35 rpm

Useful for:

- Tablets**,** Beads**,** controlled release formulations

Type 4 USP apparatus: (Flow through cell apparatus)

Useful for:

- Low solubility drugs
- Rapid degradation
- Media PH change

Type 5 USP apparatus: (paddle over disk)

- Rotations 25-50rpm

Useful for:

- Transdermal patches
- Ointments
- Floaters
- Emulsions
- Bolus

Type 6 USP apparatus: (Cylinder apparatus):

Useful for:

- Transdermal patches

Type 7 USP apparatus: (Reciprocating holder)

- Rotations 30rpm

Useful for:

- Transdermal patches
- Solid dosage forms
- pH profile
- Small volumes.

USP apparatus 4 and apparatus7 and modifications of the official apparatuses have shown great potential and value for *in vitro* release for novel dosage forms. [1,2]

SCENARIO OF DISSOLUTION RESEARCH - PRESENT AND PAST

1) During 1897-1960 (The Foundation for Dissolution Research)

In 1897, Noyes and Whitney conducted the first dissolution experiments and published an article "the rate of solution of solid substances in their own solutions". They studied the dissolution of two sparingly soluble compounds, benzoic acid and lead chloride. The materials were laid around glass cylinders which were submerged into vessels containing water. The cylinders were rotated at constant speed and under constant temperature. the authors noticed that the rate of dissolution is proportional to the difference between the instantaneous concentration,C at time t,and the saturation solubility ,C_S,.This statement can be formulated mathematically as follows;

$d_C /dt = k\ (C_S - C)$ (1)

k is a constant. The experiment configuration ensured that the surface of the materials was kept constant during dissolution as the materials were in excess of the amount needed to saturate the medium.

The next development came from Erich Brunner, and Stanislaus von Tolloczko at Gottingen who published an article in 1900 based on a series of experiments that extended the conditions under which Equation (1) holds and also shows that the rate of dissolution depends on the exposed surface, the rate of stirring, temperature, structure of the surface and the arrangement of the apparatus .The proposed model was derived from Eq. (1) by letting $k = k_1S$:

$d_C / dt = k_1S\ (C_S - C)$ (2)

The main result of two parts publication of Nernst and Brunner in 1904,which was based on the diffusion layer concept and Fick's second law was what is known as the Nernst–Brunner equation, which was derived from Eq. (2) by letting $k_1 = D/ (V_h)$:

$DC/dt = DS/V_h\ (C_S - C)$ (3)

Where D is the diffusion coefficient, h the thickness of the diffusion layer and V is the volume of the dissolution medium.

In 1931 Hixson and Crowell expressed the surface, S of Eq.(2) in respect to the weight,W by letting S to be proportional to $W^{2\backslash3}$, which makes the Eq.(2) applicable to dissolving compact objects. By this consideration ,Eq.(2), when integrated yields an equation which relates tie to the cubic-root of weight and in the case of sink conditions, where small concentrations are considered and the difference (C_s-C) can be considered as constant ,the cubic-root law takes a simple form;

$W_0^{1/3} - w^{1/3} = k_2t$ (4)

Where W_0 is the initial weight and $K2$ a constant . [3-6]

2) During 1950-1980 (The Development of a Relationship between Dissolution and Bioavailability)

The best of authors knowledge, Edwards in 1951 was the first to appreciate that following the oral administration of solid dosage forms, if the absorption process of drug from the gastrointestinal tract is rapid, then the rate of dissolution of that drug can be the step which controls its appearance in the body .In fact he postulated that the dissolution of an aspirin tablet in the stomach and intestine would be the rate of the process of controlling the absorption of aspirin into the blood stream. Two reports were published in 1963 and 1964 drawing attention to the lack of full clinical effect for two brands of tolbutamide marketed in Canada. These tablets show long disintegration time as well as slow dissolution characteristics. Solution profiles of digoxin products and substantiated the view that either lot-to-lot or amongst brands bioequivalence or the above approaches can be categorized as various expressions of the diffusion layer model as a physical explanation for dissolution process,

where the limiting step has been considered to be the diffusion of molecules through a stagnant film of liquid around the solid surface. By the 1950's two more alternative explanations were available. According to this, constantly renewed macroscopic packets of solvent reach the solid surface and absorb molecules of solute, delivering them to the solution. Combinations of these models were also considered. The work of Levich improved the theoretical model of the dissolution experiment using rotating disks, taking into account the centrifugal force on diffusion Many *in vitro* procedures to determine the disintegration time of tablets were suggested, at the time, and some of them were reviewed by Morrison and Campbell. The first official disintegration test for tablets was published in the Pharmacopeia Helvetica in 1934, which used water at 37^0 C as the medium and periodical shaking, while in the United States Pharmacopeia the disintegration test was introduced in the 14th edition in 1950. Other methods, developed later, tried to introduce more realistic conditions, using, for example, simulated gastric fluids as media for the disintegration experiments. One of the most sophisticated was Filleborn's method which was published in 1948 and introduced an artificial stomach with simulated *in vivo* conditions, including pH level, peristalsis and the presence of food. In the early 1950's it became clear that disintegration alone could not account for the physiological Originates from differences in dissolution rates.

Phenytoin toxicity occurred in a large number of patients when the manufacturer replaced the excipient calcium sulphate with lactose in immediate release phenytoin tablets. Initially, the lower extent of absorption of phenytion in the presence of calcium sulphate was ascribed to the formation of insoluble calcium – phenytoin salt. With and after a single dose of 300mg of phenytoin .These results indicated that the higher hydrophilicity of lactose compared to calcium sulphate, promoted the dissolution rate of phenytoin resulting in higher bioavailability and consequently higher concentrations of phenytoin in plasma, exceeding its narrow therapeutic range of 10-20 µg/ml. A decade later, loss of seizure control occurred in a patient on phenytoin was related to altered dissolution characteristics caused by the physical changes of phenytoin capsules. [7-13]

2.1. Initiation of the official dissolution during 1970

All of the above bioavailability concerns in the introduction of dissolution requirements in tablet and capsule monographs in pharmacopeia's. Of equal significance was the recognition of the immense value of dissolution testing as a tool for quality control. Equivalence in dissolution was sought in light of both the bioavailability and quality control consideration throughout the last 35 years .A number of studies mainly in the USA during the 20-year period 1950-1970 shed light on the importance of pharmaceutical ingredients and process in regard to the dissolution –bioavailability relationship. As a result of these developments, the basket-flask test (USP apparatus 1) was adopted as an official dissolution test in 6 monographs of the USP and National Formulary in 1970. Remarkable events during this evolution are the adoption of the paddle method (USP apparatus 2) in 1978,the adoption of the reciprocating cylinder (USP apparatus 3) for extended –release products in 1991 and the adoption of the flow-through cell in (USP apparatus 4) for extended –release products in 1995. It should also be noted that the first guidelines for dissolution testing of solid dosage forms were published in 1981 as a joint report of the section for the section for official laboratories and medicines. [14]

2.2. Factors affecting the rate of drug dissolution

During the early stages of drug dissolution research and in particular after dissolution was established to be an important factor in the bioavailability of certain drugs, the detailed study of factors affecting the dissolution rate were studied extensively. Generally higher stirring rates results in higher dissolution rates. This was studied quantitatively as well and several publications appeared that gave experimental evidence of a power law relationship between dissolution rate and stirring rate. Dissolution rate depends also directly on solubility, as the Noyes – Whitney [equation (1)] suggests. This became of particular importance as the influence of solubility on bioavailability was considered to come primarily from its influence on dissolution rather than saturation of GI

fluids. This is so because skin conditions were considered to prevail inside the intestine. It was also realized that solubility can be affected by the presence of solubilising agents in the dissolution medium either by partitioning of the drug into the micelles of a surfactant or complexation of the drug with one or more substances.

Another factor that influences the dissolution rate is the surface exposed in the solvent. This is primarily affected by the particle size. The effect is especially dramatic with poorly soluble compounds for example, digoxin which showed 100% increase in bioavailability when its particle size was reduced from 100 µm to approximately 10µm. The relationship of particle size-surface area-dissolution rate is not always straightforward. If the drug is hydrophobic and the dissolution medium has poor wetting properties, reduction of particle size may lead to a smaller effective surface area and a slower dissolution rate. During this period an important contribution to the mathematical modelling of dissolution curves was published by Langenbucher (1972). He observed that if one plots the quantity –In (1-m) verses time on a log –log plot, where m is the accumulated fraction of dissolved material, the curve looks linear, and one can then perform linear regression. This is equivalent to fitting a Weibull equation to the dissolution data;

$m = 1 - \exp [-(t - T)^{b} / a]$ (5)

Where t is time, T a lag time, a scale constant and b is a shape constant . [15,16]

3) During 1980's (Dissolution comes an essential tool for the development and evaluation of sustained release formulations)

Theeuwes and Bayne were the first to derive 1977 a relationship between t ½, the optimum therapeutic range blood level, C_{max}–C_{min}, and the dosing interval, T, assuming a one –compartment model with repetitive intravenous injections at pseudo-steady state. [17,18]

$T<1.44.t_{1/2} \text{ In } C_{max}/C_{min}$ (6)

3.1. Kinetics of drug release

The kinetics of drug release follows the operative release mechanism of the system, e.g., diffusion through inert matrix, diffusion across membrane or hydrophilic gel, osmosis, ion-exchange, etc .By far, diffusion is the principal release mechanism, since apart from the diffusion-controlled systems, diffusion takes place at varying degrees in both chemically and swelling-controlled systems.

Solute release models proceed the development of drug delivery systems by many years. In fact, the mathematical modelling of drug release from diffusion-controlled systems relies on the Higuchi model published in 1961. He analyzed the kinetics of release from an ointment assuming that the drug is homogeneously dispersed in the planar matrix and the medium into which it is released acts as a perfect sink under pseudo steady-state conditions. Higuchi derived Eq. (7) for the cumulative amount q (t) of drug released at time t:

$q(t)/q\infty = K\sqrt{t}$ (7)

Where $q\infty$ is the cumulative amount of drug released at infinite time and K is a composite constant with dimension time −1/2 related to drug diffusion matrix as well as the design characteristics of the system.

In 1985, a date which marks the initial rapid phase of growth of delivery systems, Peppas introduced a semi-empirical equation (the so-called power law) to describe drug release from polymeric devices in a generalized way:

$q(t)\ q\infty = K_1\ t^{n}$ (8)

Where K_1 is a constant reflecting the structural and geometric characteristics of the delivery system expressed in time n units and n is a release exponent the value of which is related to the underlying mechanism(s) of drug release. Again, valid estimates for K_1 and n can be derived from the fitting of Eq. (8) to the first 60% of the experimental release data. Detailed discussions of the assumptions of the derivations of Eq. (7) and (8) in relation

to their valid applications to real data can be found in the literature (Siepmann and peppas, 2001; Macheras and Iliadis, 2006). [19,20]

3.2. *In vitro, in vivo* consideration

The major objective in the design of an oral to controlled release formulation is to achieve little or no effect of the gastro intestinal environment upon the rate of drug release a varying milieu: from a pH close to 1 in the fasted stomach through the duodenum (pHs 4-5) and a gradually increasing intestinal pH reaching the alkaline region in the distal section of their intestinal tract. Drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors and physiological variable including regional permeability differences, pH, luminal and mucosal enzymes and intestinal motility among other. Despite this complexity, various qualitative and quantitative approaches have been proposed for the estimation of oral drug absorption

In parallel, these formulations can be dosed either in presence or absence of food and the dramatic physiological changes, e.g., pH, bile and pancreatic secretions can influence the rate of drug release. Overall, this complex-heterogeneous GI environment has a greater impact on drug dissolution for controlled release formulations than that observed with conventional preparations. Based on this realization a separate general chapter, Drug Release 724 was adopted in the USP 21-NF 16 as early as 1985 providing methodology and acceptance criteria for extended-release and delayed-release products.

Dilantin®, an extended-release product of Parke Davis was the first to have an approved dissolution specification attached to it as a condition of lot-to-lot approval by the FDA. Shah et al. (1983) proposed a dissolution window over time to distinguish the two types of Dlantin® formulations (100 and 300 mg) and ensure lot-to-lot bioequivalence. During the same time, two quinidine gluconate formulations, Quinaglute Duratabs® (Innovator brand, Berlex) and an unapproved and marketed product were found to have quite similar dissolution characteristics despite of the fact that they were bio-in equivalent. The similarity of dissolution profiles was justified in 0.1N HCl as well as in 0.1N HCl for the first hour and then in pH 7.4 for seven additional hours. Further dissolution studies in a wide range of pH values (1.0–7.4) revealed significant differences in the dissolution profiles at the intermediate pH values (2.6–5.8) when the percent (dissolved) was plotted as a function of pH and time in a 3D plot (topographical dissolution characterization).

Moller-Petersen, 1984; Hendeles et al., 1985 indicated that food induced changes in theophylline absorption from a number of marketed controlled release formulations. These absorption changes were associated with formulations exhibiting either pH-dependent or pH-independent dissolution characteristics while the fat content of the meal was considered as the major determinant of the so-called “dose dumping”. Since then the term “food effect” was coined and its importance is reflected in the specific requirement for its assessment in the evaluation of bioequivalence of controlled release formulations (FDA, 2002). At that time, a variety of in vitro methodologies based on dissolution tests using media such as oleic acid, sodium deoxycholate and milk were developed for predicting “food effect” under in vitro conditions. [21,22]

4. During 1980-2000 (Emphasis on dissolution as a prognostic tool of oral drug absorption)

Drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors and physiological variable including regional permeability differences, pH, luminal and mucosal enzymes, and intestinal motility among other. Despite this complexity, various qualitative and quantitative approaches have been proposed for the estimation of oral drug absorption.

In 1985, Amidon and co-workers, using a pseudo equilibrium model, made a major step in the theoretical analysis of oral drug absorption when solubility and dose were taken into account for the estimation of the absorption

potential (AP) of a drug, apart from the pH-partition hypothesis parameters (lipophilicity, and degree of ionization) . Four years later a quantitative version of the absorption potential concept was published which enabled the estimation of the fraction of dose absorbed as a function of AP. However, the microscopic model based on mass balance consid- erations and published in 1993 can be considered as a landmark in the history of oral drug absorption since it revealed the three fundamental parameters, namely, dissolution, absorption and dose numbers, which control the extent of oral drug absorption. This work enabled to develop in their seminal paper published in 1995 a Bio pharmaceutics Classification System (BCS). According to BCS a substance is classified on the basis of its aqueous solubility and intestinal permeability, and four drug classes were defined i.e., high solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III), low solubility/low permeability (Class IV). The properties of drug substance were combined with the dissolution characteristics of the drug product, and predictions with regard to the in vitro–in vivo correlations for each of the drug classes were pointed out.

These advances attracted the obvious interest of scientists in the importance of dissolution tests as predictors of oral absorption for Class II drugs. In an attempt to establish correlations between the results of the dissolution tests and the in vivo absorption data, artificial fluids, simulating gastric and small intestinal conditions in the fasted state, were developed. Also, media mimicking the fed state conditions in the human intestinal fluids were proposed. In some cases the in vitro dissolution rate of poorly soluble drugs in simulated media in the fasted state do not always correlate with the dissolution rate in aspirated intestinal fluids. Although all these studies contribute to the proper selection of representative media mimicking gastric and small intestinal conditions, the simulation of the in vivo hydrodynamic conditions remains an insuperable obstacle. This is particularly so since recent studies based on computational fluid dynamics revealed not only the complexity of the fluid flow in the everyday use of basket and paddle methods of dissolution, but also the chaotic aspects of hydrodynamics. These results in conjunction with the complexity of (i) gastrointestinal drug absorption phenomena and (ii) the heterogeneous in vivo conditions indicate that we are far away from the simulation of the in vivo hydrodynamics and the proper design of a really prognostic dissolution test. [23-29]

5. Dissolution in the frame work of BCS from 2000 to present

The FDA guidance on BCS issued in 2000 provides regulatory benefit for highly permeable drugs that are formulated rapidly dissolving solid immediate release formulations. The guidance classifies a substance to be highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH ranges 1-7.5, while a drug product is defined as rapidly dissolving when no less than 85% of the dose dissolves in 30 min using USP apparatus I at 100 rpm in a volume of 900 mL in 0.1N HCl, as well as IN pH 4.5 and 6.8 buffers. Thus petitioners may request bio waivers for high solubility-high permeability substances formulated in immediate release dosage forms that exhibit rapid *in vitro* dissolution.

The reference of the FDA guidance exclusively to “the highest dose strength” for the definition of highly soluble drugs implies that a drug is always classified in only one class regardless the possible different performance in respect to solubility of smaller doses used in actual practice. However, this is not in accord with the dose dependency (non-Michaelian type) of oral drug absorption, which consistently has been demonstrated in the early and recent studies. Moreover, the dissolution criteria of the FDA guidance have been characterized as conservative and suggestions for broadening them have been pointed out. In a similar vein, the high solubility definition of the FDA guidance on BCS has been criticized by Yazdanian et al. (2004) as too strict for acidic drugs and they also quote “an inherent limitation of the solubility classification is that it relies n equilibrium solubility determination,

which is static and does not take into account the dynamic nature of absorption". Their remarks were based on the fact that several non-steroidal anti-inflammatory drugs exhibit extensive absorption despite their classification in Class II of the BCS. These experimental observations were explained by Rinaki et al. (2004) utilizing simulations for the in vivo drug dissolution and wall permeation. However, two recent studies provide results of provisional classification of the drugs contained on the WHO Essential Drugs List and the top 200 drugs lists from the US,GB, ES, JP and suggest that for more than 60% of oral immediate release drug products on the market today, bioequivalence may be regulated based on dissolution testing.

It should be noted that dissolution specifications of the FDA guidance are not correlated with the drug's solubility/dose ratio, which has been shown to control the rate of drug dissolution. It was Lansky and Weiss (1999) who raised a question on this issue for the first time in 1999, and soon after dose was incorporated explicitly into the fundamental relationships used routinely in dissolution. These advances are important for the quantitative aspects of biopharmaceutics drug classification as well as the in vivo dissolution modelling approaches used to interpret the extensive absorption of Class II drugs. In addition, the extent of drug dissolution is either directly or indirectly associated to the solubility/dose ratio assuming the diffusion layer model . These findings have both theoretical and practical interest since they indicate that dissolution data contain explicit information regarding the solubility of drug and therefore can be in principle used as sole indicators for biopharmaceutical drug classification. [30-35]

DISSOLUTION STUDIES OF VARIOUS DOSAGE FORMS

Immediate releases tablet

Immediate release dosage forms are intended for rapid delivery of a drug into the blood circulation. However, drug absorption into systemic circulation may be limited by the dissolution rate. Studies of dissolution in immediate release drugs are typically done with USP apparatuses 1-4, those being the rotating basket, paddle, reciprocating cylinder and flow-through cell, respectively. Examples of using apparatus (1) in the USP are aspirin, brompheniramine maleate and ethambutol hydrochloride tablets. Bethanecol chloride, betaxolol and cefadroxil tablets are examples of using apparatus (2) for USP dissolution test. Demonstrated how the application of a dynamic dissolution protocol can be used to simulate the *in vivo* dissolution of glyburide, a biopharmaceutical classification System (BCS) class II drug. In this study SIF and bio relevant dissolution media were used in apparatus (2) to investigate the dissolution of different immediate release glyburide tablets. The pH of the dissolution medium was changed from pH 6.5 glyburide to pH 7.5 and back to pH 5.0 these changes simulate the physiological pH change in the small and large intestine. [36]

Dosage forms for the oral cavity

Dosage forms for the oral such as sublingual tablets, buccal tablets, chewing gums and chewable tablets are solid dosage forms that are placed in the mouth, allowing the active ingredient to dissolve in the saliva & then absorb either via the oral route or by the buccal/sublingual mucosa within the mouth. However, there are challenges regarding the extent of drug delivery in the mouth as opposed to the oral route ,namely due to a short residence time in the mouth, and the small volume of liquid available to dissolved the medication. As a result modification in the standard USP test apparatus (as well as the development of novel apparatuses) is required in order to mimic *in vivo* conditions for accurate analysis of these dosage forms. [37]

Chewable tablets

Rapidly disintegrating chewable tablets are used primarily for the oral route of administration, and are designed to increase compliance among individuals who are unable to swallow traditional tablets. But the extent to which each tablet will be chewed may vary from individual to individual, ranging from being completely chewed to swallowing the tablet in chunks. The USP has stated the need to use apparatus 2 for chewable tablets, the same as for traditional tablets with the exception of ampicillin chewable tablets, here the USP 29 requires use of apparatus 1, and carbamazepine chewable tablets, the USP 29, uses apparatuses 2 and 3 as two different tests. Furthermore, has recommended the use of USP apparatus 3, a reciprocating cylinder, along with glass beads in order to create a large amount of agitation within the dissolution medium. They also recommend mechanical breakage of the tablet. [38]

Buccal / Sublingual tablets

Rapid orally disintegrating tablets may be used to achieve a fast onset of action. Alternatively, the buccal/sublingual route is also suitable for medications that cannot or shall not be taken by the oral route due to instability of drug at the low pH of the stomach, or their susceptibility to the hepatic first pass effect. Much like the previous dosage form, these tablets are also advantageous for patients who are unable to swallow whole tablets. USP 29 states the use of disintegration test for ergoloid mesylate and ergotamine tartarate sublingual tablets and apparatus 2 with water as dissolution medium for isosorbide dinitrate sublingual tablet. Which has been introduced recently, comprises a single stirred continuous flow-through filtration cell with a dip tube to remove finely divided solid. An alternative method is used to study the release of nicotine from buccal tablets. They used modified Franz diffusion cell for this purpose. The dissolution medium was 22 ml phosphate buffer saline (PBS) (pH7.4) at 37^0 C. uniform mixing of the medium was provided by magnetic stirring at 300 rpm. Provided unidirectional release, each bio-adhesive tablet was embedded into paraffin wax which was placed on top of a bovine buccal mucosa as membrane **Fig-1** shows a schematic drawing of the dissolution apparatus for buccal/sublingual tablets.**Fig-2** shows the schematic drawing of the dissolution apparatus used for studying the dissolution of buccal tablets used by Mumtaz and Ch ng (1995) . [39]

Chewing Gums

The USP has not yet created an apparatus test the release of medication. Today drugs are more and more delivered by convenient dosage forms like gums or lately by strips. The European Pharmacopoeia has developed a 3- piston apparatus, which in essence “chews” the gum at a rate of 60 cycles/min in a test medium with pH of 6.0 at 37^0C. The medicated gum for a specific period of time (i.e.10, 20, 30, or 40 min); followed by analyzing the residual quantity for the amount of active ingredient remaining in the gum. This method definitely warrants some scrutiny in methodology but is a prime example, which demonstrates the need of developing an appropriate *in vitro* test apparatus to analyze the release of medication from chewing gums. [40]

Soft gelatine capsules

Soft gelatine capsules can be composed of either hydrophilic or hydrophobic components. In the case of hydrophilic capsules dissolution tests can be performed quite easily using USP apparatus 2 but this becomes more difficult for hydrophobic medication. However, it is speculated that exposure of the gelatine shell to such media may induce physical and/ or chemical changes of the drug, arising either through complex formation or cross-linking reactions. The official methods have the serious disadvantage that the dissolution condition for lipophilic floating materials is poorly. It is not suitable for lipid filled soft gelatine capsules, because after capsule rupture, the oil phase is quickly drawn into the filter on the top of the cell, which can clog the filter, or the oil is forced through the filter. Introduced a new flow through cell for lipid filled soft gelatine capsules. **Fig- 3 and Fig- 4** shows the schematic view of this device. The rises up due to its lower density. When the lipid phase reaches the triangular area top of the left side cell, it stays there. Thus the dissolution medium continuously extracts the drug

from the lipid layer as it flows through the cell. The dissolved drug can now be determined using a conventional fraction collector and be analyzed in the medium. The results of their study showed that, after 6 h of dissolution, most of the viscous oily vehicle still remained entrapped within the basket; hence failure to release drug into the aqueous phase. It appears that the standard dissolution basket pores (40 meshes) and lack of appropriate hydrodynamic conditions within the basket had a significant limiting effect on drug release from the oleaginous formulation. The study showed that the most reproducible results can be obtained when the paddle is positioned in aqueous medium and the capsule is below the mesh assembly . [41]

Suppositories

Similar to lipid-filled soft gelatine capsules, it is challenging to find a standard method to test *in vitro* drug release from lipophilic suppositories. This is due to the medium and deformation of the suppository in the dissolution medium and deformation of the suppository in the dissolution medium UPS 29 states apparatus 2 for conducting dissolution tests of indomethacin suppositories. Lipophilic suppositories release the drug after melting in the rectal cavity. Therefore rectal temperature greatly affects drug release. In the rectum, the drug partitions between the lipophilic base and the present fluid. Distribution equilibrium between the base and fluid can occur rather than complete dissolution. For *in vitro* release testing, one requires knowledge of the melting point range of the suppository base, and testing temperature should be similar with physiological conditions. [38]

Transdermal patches

For transdermal delivery system, many variables may alter the release of the drug into the skin .Large changes in the rate and extent of drug delivery may occur caused by the slightest change of the formulation .The USP has published three different *in vitro* drug release tests for dissolution testing of patches .These include paddle over disk, cylinder method and reciprocating disk method, apparatuses 5,6,7.respectively(USP29).The paddle over disk method is the most widely used method because it is simple and easy to reproduce. The testing conditions should be ideally adjusted to pH 5-6 reflecting physiological skin condition. The temperature may increase when it is covered by the transdermal delivery system. The agitation speed rate should be set at 100 rpm. Nicotine transdermal patch is an official monograph in the USP. They used phosphate buffered saline (PBS) pH4.5 containing 20% PEG 400, water, PBG 400, water, PBS at pH 7.4 and PBS at 5.4 as the dissolution medium in the receiver chamber respectively. [42]

Semisolid dosage forms

Semisolid dosage forms include creams, ointments and gels. Currently no monograph exists in the USP with used dissolution testing of semisolid bases. In research the drug release test is normally performed using the Franz cell diffusion system. A schematic picture of Franz diffusion cell is shown in **Fig. 5.** Critical components of the *in vitro* release test for semisolid products include selection of an assay method, diffusion cell volume, selection of an appropriate membrane, nature of receiving medium, equipment related parameters, e.g. stirring speed and temperature and validation of the method. The membrane must be an inert material that does not interact chemically or physically with the drug .The membrane should not contain leachable that may interfere with the assay. Common membranes are Tuffryn®, Supor®, Cellulosic, Acetate Plus®, Nylon, Teflon, and polycarbonate. The receiving medium must be similar to physiological conditions of the skin.Thakker Kailas and Chern Wendy (2003) assert that no more than 30% of the total amount of the dose applied should be released into the medium at the end of experiment. [43-45]

CONCLUSION

During the past 35 years dissolution studies have become an essential part of drug applications .In this regard dissolution tests are used in the pharmaceutical industry for quality control and to assist with the determination of bioequivalence. The dissolution studies provide useful information at several stages of drug development. The

experience gained so far indicate that the design of a dissolution test to be used reliably as a prognostic tool for oral drug absorption. There are different dissolution media and apparatuses for dissolution testing of both conventional and novel dosage forms. However some of these methods and dissolution media which are reviewed in this article are intended to be used in research and development only and might not be suitable for routine quality control.

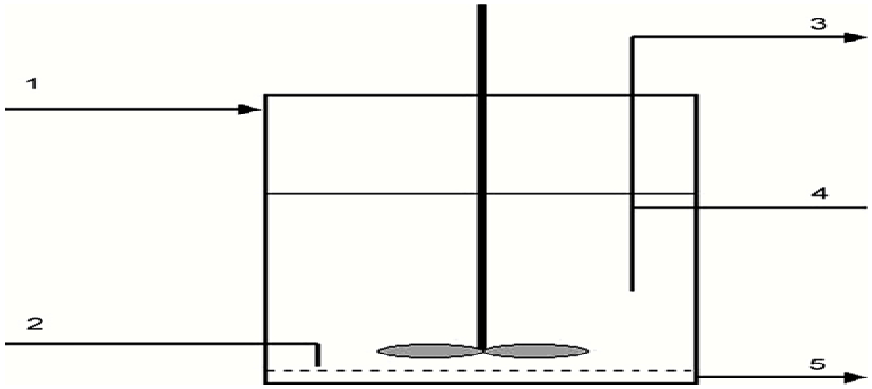

Fig.1.Schematic of dissolution apparatus for buccal /sublingual tablets; (1) inlet, (2) filter membrane, (3) outlet, (4) dip tube, (5) outlet to flow through UV cell (adapted from Hughes, 2003).

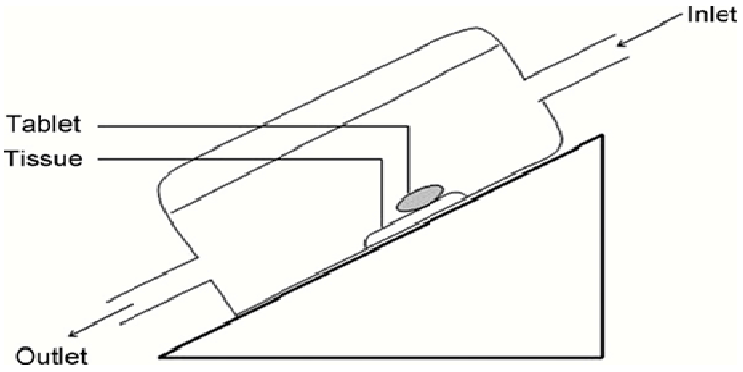

Fig.2. Schematic drawing of the dissolution used by Mumtaz and Cn ng (1995) studying the dissolution of buccal.

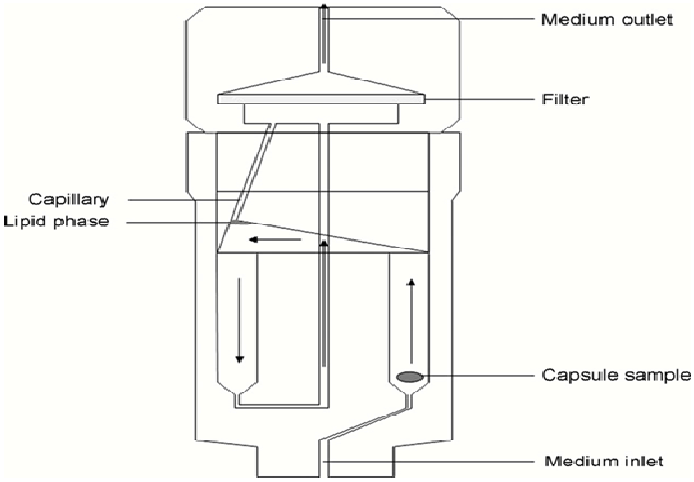

Fig.3.Schematic view of flow-through cell designed for lipid-filled soft gelatine capsules.

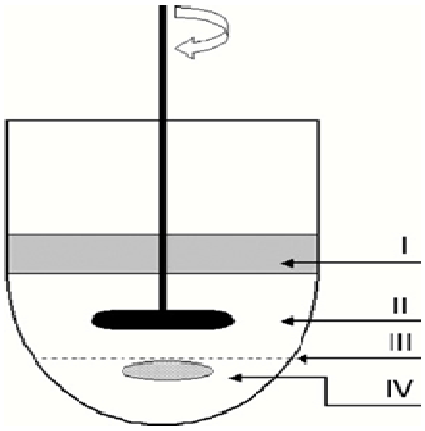

Fig.4. Schematic illustration of apparatus for the dissolution testing of lipid filled soft gelatine capsules.1=organic phase, i.e., 100m 2=aqueous phase, 3=ring\mesh assemble and 4=position of capsule.

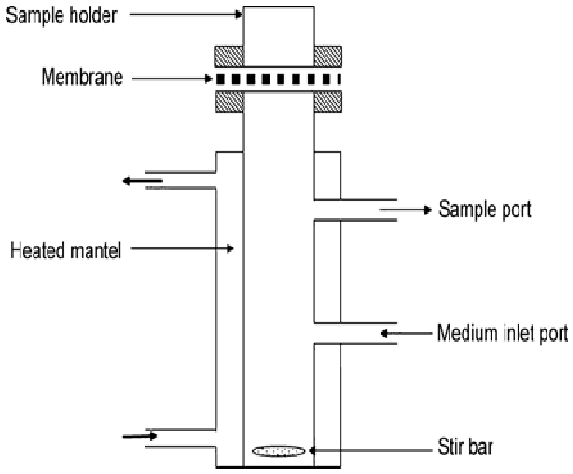

Fig.5. Schematic picture of Franz diffusion cell.

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