A Review: Dissolution

***[1]Karabi Kalita, [2]Mrs. Archana Rautela, [3]Dr. Praveen Kumar Ashok, [4]Mrs.Neha Tiwari**

Gyani inder singh institute of professional studies, dehradun, Uttarakhand.

ABSTRACT

Conventional dissolution testing remains critical in drug development. For compounds with poor aqueous solubility, maintaining sink conditions can be problematic rendering complete dissolution characterization a challenging task. To afford sink conditions, several solubility modifiers, such as surfactants, inorganic salts and organic co-solvents, are routinely added to aqueous dissolution media. Moreover, innovative dissolution apparatus such as the flow through apparatus (United States Pharmacopeia, USP, IV) can be utilized. However, the use of these techniques/ additives is accompanied by inherent disadvantages and the search for alternative methods of providing sink conditions remains ongoing. One attractive technique is the use of biphasic dissolution systems, the basis of which is a dissolution medium comprising immiscible aqueous and organic layers. This review aims to highlight the role of the traditional 'dissolution' test and the problems posed to these methodologies by poorly water-soluble materials. An insight into the more traditional techniques used to overcome this issue will then be discussed. A substantial focus will be placed on the potential of a biphasic dissolution system as a future primary method for the dissolution testing of poorly soluble compounds. This work is intended to provide an initial introduction to the topic and provoke debate among analytical and formulation scientists as to the potential long-term development and implementation of a biphasic system in dissolution testing.

KEYWORDS: Aqueous, Biphasic, Dissolution

INTRODUCTION

Most medicinal drugs are formulated into tablets, capsules or other forms of medicine. Formulating a medicine means mixing the medicinal drug with other ingredients (called excipients) according to a prescribed recipe (the formulation). These ingredients have a number of purposes in a tablet, for example, they might help bind the tablet together, control the rate of release of the drug and improve the taste of the tablet. Dissolution of a tablet involves its disintegration into smaller and smaller particles from which the medicinal drug is released more and more rapidly. The speed at which a medicinal drug is released from a tablet or capsule and dissolves in solutions that mimic fluids in the GI tract is an increasingly important measurement. Knowledge of this rate of dissolution contributes to the formulation, development and regulatory approval of medicines. 1 It is also important for quality control, checking that the tablets from a production run have the required characteristics. The process of dissolution followed by absorption determines, in part, the bioavailability of the drug. The rate of dissolution can be determined in vivo by taking samples of a person's plasma or urine and measuring the drug concentration in them. However, this is not appropriate for routine measurements on the vast numbers of compounds investigated during drug discovery and development

Types of apparatus used for dissolution

1. USP Apparatus 1 (Basket apparatus)

The basket method was first described in 1968 by Pernarowski and his co-workers. The most commonly used methods for evaluating dissolution first appeared in the 13th edition of the U.S. Pharmacopeia in early 1970. These methods are known as the USP basket (method I) and paddle (method II) methods and are referred to as "closed-system" methods because a fixed volume of dissolution medium is used. In practice a rotating basket method provides a steady stirring motion in a large vessel with 500ml to 1000 ml of fluid that is immersed in a temperature –controlled water bath. Basket method is very simple, robust, and easily standardized. The USP basket method is the method of choice for dissolution testing of immediate release oral solid dosage forms.

2. USP apparatus 2 (paddle apparatus)

   An apparatus may be considered the forerunner of the beaker method. It consisted of a 400 ml beaker and a three-blade, centrally placed polyethylene stirrer (5 cm diameter) rotated at 59 rpm in 250 ml of dissolution fluid (0.1N HCl). The tablet was placed down the side of the beaker and samples were removed periodically. In the Apparatus 2, (the paddle apparatus method) a paddle replaces the basket as the source of agitation. As with the basket apparatus, the shaft should position no more than 2mm at any point from the vertical axis of the vessel and rotate without significant wobble.

Importance of dissolution 1, 2, 5

- Results from in-vitro dissolution rate experiments can be used to explain the observed differences in in-vivo availability.
- Dissolution testing provides the means to evaluate critical parameters such as adequate bioavailability and provides information necessary to formulator in development of more efficacious and therapeutically optimal dosage forms.
- Most sensitive and reliable predictors of *in-vivo* availability.
- Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.
- It can ensure bioavailability of product between batches that meet dissolution criteria.
- Ensure batch-to-batch quality equivalence both *in-vitro* and *in-vivo*, but also to screen formulations during product development to arrive at optimally effective products.
- Physicochemical properties of model can be understood needed to mimic in-vivo environment.

- Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.
- Serve as quality control procedures, once the form of drug and its formulation have been finalized.

Factor affecting dissolution rate

1. Physicochemical Properties of Drug
2. Drug Product Formulation Factors
3. Processing Factors
4. Factors Relating Dissolution Apparatus
5. Factors Relating Dissolution Test Parameters

1. PHYSICOCHEMICAL PROPERTIES OF DRUG 2,8,9

1.1. Drug solubility

Solubility of drug plays a prime role in controlling its dissolution from dosage form. Aqueous solubility of drug is a major factor that determines its dissolution rate. Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems. Studies of 45 compound of different chemical classes and a wide range of solubility revealed that initial dissolution rate of these substances is directly proportional to their respective solubility. 2

1.2. Salt formation

It is one of the common approaches used to increase drug solubility and dissolution rate. It has always been assumed that sodium salts dissolve faster than their corresponding insoluble acids. Eg. sodium and potassium salts of Penicillin G, sulfa drugs, Phenytoin, barbiturates etc. While in case of Phenobarbital dissolution of sodium salt was slower than that of weak acid. Same is the case for weak base drug, strong acid salts, such as hydrochlorides and sulphates of weak bases such as epinephrine, tetracycline are commonly used due to high solubility. However, free bases of chlortetracycline, methacycline were more soluble than corresponding hydrochloride salt at gastric pH values, due to common ion suppression.

1.3. Particle size

There is a direct relationship between surface area of drug and its dissolution rate. Since, surface area increases with decrease in particle size, higher dissolution rates may be achieved through reduction of particle size. Micronization of sparingly soluble drug to reduce particle size is by no means a guarantee of better dissolution and bioavailability. Micronization of hydrophobic powders can lead to aggregation and floatation when powder is dispersed into dissolution medium. So, mere increase in S.A. of drug does not always guarantee an equivalent increase in dissolution rate. Rather, it is increase in the “effective” S.A., or area exposed to dissolution medium and not the absolute S.A. that is directly proportional to

dissolution rate. Hydrophobic drugs like phenacetin, aspirin shows decrease in dissolution rate as they tend to adsorb air at the surface and inhibit their wettability. Problem eliminated by evacuating surface from adsorbed air or by use of surfactants. So these drugs in-vivo exhibit excellent wetting due to presence of natural surfactants such as bile salts. 1,2, 8

1.4. Solid state characteristics

Solid phase characteristics of drug, such as amorphicity, crystallinity, state of hydration and polymorphic structures have significant influence on dissolution rate. Anhydrous forms dissolve faster than hydrated form because they are thermodynamically more active than hydrates. Eg. Ampicillin anhydrate has faster dissolution rate than trihydrate. Amorphous forms of drug tend to dissolve faster than crystalline materials. E.g. Novobiocin suspension, Griseofulvin.9,10

1.5. Co-precipitation

Dissolution rate of sulfathiazole could be significantly increased by co-precipitating the drug with povidone. 8

2. DRUG PRODUCT FORMULATION

Factors Dissolution rate of pure drug can be altered significantly when mixed with various adjuncts during manufacturing process such as diluents, dyes, binders, granulating agents, disintegrants and lubricants. Generically identical tablet or capsules exhibited differences in their dissolution rates of their active ingredients.5,10

2.1. Diluents

Diluents in capsule & tablet influence the dissolution rate of drug. Studies of starch on dissolution rate of salicylic acid tablet by dry double compression process shows three times increase in dissolution rate when the starch content increases from the 5 – 20 %. Here starch particles form a layer on the outer surface of hydrophobic drug particles resulting in imparting hydrophilic character to granules & thus increase in effective surface area & rate of dissolution. Different types of dissolution apparatus utilized affect ranking of different varieties of starch. With stirring type of agitation, order was potato starch > cornstarch > arrowroot starch > rice starch. With oscillating type, a different order observed. Corn > rice > arrowroot > potato. The dissolution rate is not only affected by nature of the diluent but also affected by excipient dilution 2

2.2. Disintegrants

Disintegrating agent added before & after the granulation affects the dissolution rate. Studies of various disintegrating agents on Phenobarbital tablet showed that when copagel (low viscosity grade of Na CMC) added before granulation decreased dissolution rate but if added after did not had any effect on dissolution rate. Microcrystalline cellulose is a very Zishan Journal of Drug Delivery & Therapeutics. 2017; 7(3):19-27 ISSN: 2250-1177 [22] CODEN (USA): JDDTAO good disintegrating agent but at high compression force, it may retard drug dissolution. Starch is not only an excellent diluent but also superior disintegrant due to its hydrophilicity and swelling property. Disintegration and dissolution rate of disintegrants with moderate swelling capacity depend to a large extent on mixing time of drug/excipient preblende, with lubricant. On other hand, disintegrants with strong swelling capacity such as sodium starch glycolate were hardly affected by mixing time with lubricant. 2,10, 11, 12, 13

2.3. Binders and Granulating agents

The hydrophilic binder increase dissolution rate of poorly wettable drug. Large amount of binder increase hardness & decrease disintegration /dissolution rate of tablet. Non aqueous binders such as ethyl cellulose also retard the drug dissolution Phenobarbital tablet granulated with gelatin solution provide a faster dissolution rate in human gastric juice than those prepared using NaCMC or polyethylene glycol 6000 as binder. Gelatin imparted hydrophilic character to hydrophobic drug surface whereas PEG 6000 formed a poorly soluble complex while NA-CMC was converted to its less soluble acid form at the low pH of gastric fluid. 2,8 4.

2.4. Lubricants

Lubricants are hydrophobic in nature (metallic stearate) and prolong tablet disintegration time by forming water repellant coat around individual granules. This retarding effect is most imp factor in influencing rate of dissolution of solid dosage forms. Both amount and method of addition affect the property. It should be added in small amount (1% or less) and should be tumbled or mixed gently for only very short time. However, if an enhancing effect in dissolution of hydrophobic granules is desired, water soluble lubricant such as SLS or carbowaxes may be used. 8 4.

2.5. Surfactants

They enhance the dissolution rate of poorly soluble drug. This is due to lowering of interfacial tension, increasing effective surface area, which in turn results in faster dissolution rate. E.g Non-ionic surfactant Polysorbate 80 increase dissolution rate of phenacetin granules. The increase was more pronounced when the surfactant was sprayed on granules than when it was dissolved in granulating agent. 4.

2.6. Water-soluble dyes

Dissolution rate of single crystal of sulphathiazole was found to decrease significantly in presence of FD&C Blue No.1. The inhibiting effect was related to preferential adsorption of dye molecules on primary dissolution sources of crystal surfaces. They inhibit the micellar solubilization effect of bile salts on drug. Cationic dyes are more reactive in lower conc. than are anionic dyes. 3 4.

2.7 Coating polymers

Tablets with MC coating were found to exhibit lower dissolution profiles than those coated with HPMC at 37ºC. The differences are attributed to thermal gelation of MC at temp near 37º, which creates a barrier to dissolution process & essentially changes the dissolution medium. This mechanism is substantiated by the fact that at temp below the gel point & at increased agitation, the effect disappears. 10 4

3. PROCESSING FACTORS

3.1 Method of Granulation

Wet granulation has been shown to improve the dissolution rate of poorly soluble drugs by imparting hydrophilic properties to the surface of granule.

3.2 Compression Force

The compression process influence density, porosity, hardness, disintegration time and dissolution of tablet.

3.3 Drug excipient interaction

These interaction occur during any unit operation such as mixing, milling, blending, drying or granulating result change in dissolution. Polysorbate-80 used in capsules causes formation of formaldehyde by autoxidation which causes film formation by denaturing the inner surface of capsule.

4. FACTORS RELATING DISSOLUTION APPARATUS 4

4.1 Agitation

Relationship between intensity of agitation and rate of dissolution varies considerably acc. to type of agitation used, the degree of laminar and turbulent flow in system, the shape and design of stirrer and physicochemical properties of solid. Speed of agitation generates a flow that continuously changes the liquid/solid interface between solvent and drug. In order to prevent turbulence and sustain a reproducible laminar flow, which is essential for obtaining reliable results, agitation should be maintained at a relatively low rate. Thus, in general relatively low agitation should be applied 13 I. Basket method - 100 rpm II. Paddle method- 50-75 rpm

5. FACTORS RELATING DISSOLUTION TEST PARAMETERS

5.1 Temperature

Drug solubility is temperature dependent, therefore careful temperature control during dissolution process is extremely important. Generally, a temp of 37º ± 0.5 is maintained during dissolution determination of oral dosage forms and suppositories. However, for topical preparations temp as low as 30º and 25º have been used 2,8,

5.2 pH of dissolution medium

For weak acids, dissolution rate increases with increase in pH. Where as for weak bases, dissolution rate increases with decrease in pH.

5.3 Vibration

The excessive vibration of dissolution apparatus increases dissolution rates.

Conclusion

The dissolution test procedure is well established, reliable, and reproducible, and it is a valuable tool for characterizing a drug product at different stages in its lifecycle. A thorough understanding of all sources of variability within dissolution laboratory systems will minimize uncertainty when examining or acting on results. Qualification of the dissolution system should include verification of the dimensions and tolerances of the apparatus. Critical test parameters such as rotation speed, media temperature, and volume need to be monitored periodically during use. Overall system performance can be monitored by running a performance verification test by testing a well characterized dosage form, such as USP performance verification tablets or an in house product, with sufficient knowledge of the mean, variability, and stability. As a standard practice, laboratory scientists are encouraged to critically evaluate dissolution data variability within and between laboratories to determine if the variability is product-related Vs laboratory system related.

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