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Effect of Rate of Agitation on Dissolution.

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ABSTRACT:
The main objective of the study was to demonstrate the effect of agitation on dissolution rate. Paracetamol was chosen as model drug. Dissolution of Paracetamol was conducted in 900ml of pH 5.8 phosphate buffer at 37±0.5^{0}C at 50,100 and 150 rpm. Aliquots were withdrawn at regular intervals up to 75 min, equal volume of buffer was replaced to dilute the dissolution medium and maintain sink conditions. It was seen that as rate of agitation increased dissolution rate increased. Percentage cumulative drug release at 150rpm was greater than 100 and 50rpm. Percentage cumulative drug release at 150rpm was 91.43%, 100rpm was 72.04%, and 50rpm was 65.81%. Therefore we can conclude that as the rate of agitation increased dissolution rate increased.

Key words: Dissolution, Agitation, Sink conditions, Percentage cumulative drug release.

I. INTRODUCTION:

Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. In determining the dissolution rate of the drugs from solid dosage forms under standardized conditions, one has to consider several physicochemical processes in addition to the processes involved in dissolution of pure chemical substances. The physical characteristics of the dosage form, the wettability of the dosage unit ,the penetration ability of the dissolution medium ,the swelling process ,the disintegration and degradation of the dosage form are a few of the factors the influences the dissolution characteristics of drugs.[1]

In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, to assess batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development to predict in vivo drug release profiles. In vitro drug dissolution data generated from dissolution testing experiments can be related to in vivo pharmacokinetic data by means of in vitro-in vivo correlations (IVIVC). A well- established predictive in vitro-in vivo correlation model can be very helpful for drug formulation design and post- approval manufacturing changes. [2,3]

Rate of dissolution is the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

Rate of dissolution is directly proportional to concentration gradient

The rate of dissolution is given by Noyes and Whitney

$$\frac{dc}{dt} = k(Cs - Cb)$$

Where,

$\frac{dc}{dt}$ = dissolution rate of the drug

K= dissolution rate constant

Cs= concentration of drug in stagnant layer

Cb=concentration of drug in the bulk of the solution[4]

Factors affecting dissolution rate[5, 6]

Factors related to the physic-chemical properties of the drug[7]

Surface area increases with the decrease in particle size, higher dissolution rates may be achieved through reduction of particle size.

- **Polymorphism**:

The polymorphic forms of drug have shown to influence changes in the solubilizing characteristics and thus the dissolution rate of the drug substance in question.

- **Drug solubility**:

Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems. Studies on several compound of different chemical classes and wide range of solubility revealed that initial dissolution rate of these

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substances is directly proportional to their respective solubility.

- **Salt Formation**:

It is one of the common approaches used to increase drug solubility and dissolution rate. For Weak acids, dissolution rate increases with increase in pH where as for weak bases, dissolution increase with decrease with pH.

- **Anhydrous:**

Anhydrous form of drugs dissolve faster than hydrated form because they are thermodynamically more active than hydrates.

- **Amorphous**:

Amorphous form of drugs tends to dissolve faster than crystalline material.

- **Complexation**:

Complexation with polyvinylpyrrolidine can markedly influence dissolution of drugs. Complexation is employed for enhancing the dissolution characteristics of drug substance e.g.: dissolution is enhanced through formation of a soluble complex of ergotamine tartrate-caffeine complex and hydroquinone-digoxin complex.

- **Surfactants:**

The drugs that are practically insoluble in aqueous medium (<0.001%) are of increasing therapeutic interest, particularly due to the problems associated with their bio availability when administered orally. Drugs with low solubility's when incorporated with surfactants can enhance their dissolution rate.

Factors related to the composition and method of manufacture

Tablets

- **Type of tablets manufacture employed**:

Wet granulation, in general has been shown to improve dissolution rates of poorly soluble drugs by imparting hydrophilic properties to the surface of granules.

- **Granule size:**

The size of granules does not play a role in dissolution behaviour of the dosage form. It is the nature of granule that can influence the dissolution rate of the dosage form.

- **Amount and type of disintegrate**:

Increasing the mixing time of formulations containing 97 to 99% slightly swelling disintegrate resulted in decrease in disintegration time, thereby enhancing dissolution rate.

- **Compressional force and speed of compression:**[8, 9]

The influence of the compression force employed in the tableting process on the apparent density, porosity, hardness, disintegration time and average particle size of compressed tablet. Bonding of particles and crushing of particles are common effects observed on increasing force of compression. At low pressures tablets were easily penetrated by the dissolution media, but the tablet didn't breakup extensively, during the dissolution test and dissolution rate was slow. At relatively higher pressure, penetration still occur quickly, loss of small air bubbles caused much more disruption.

Environmental factors involved with dosage forms

- **Humidity:**

In relation to the dissolution rate of the drug substance, humidity is usually associated with storage effects. Moisture has been shown to influence the dissolution of many drugs from solid dosage forms.

- **Age of dosage forms:**

It might be expected that the effect of aging of tablets should always result in decrease in dissolution rate. In many cases, however, there is no effect at all

Factors related to drug product formulation

- **Binders:**

The hydrophilic binders increase dissolution rate of poorly wettable drug. Large amount of binder increases hardness and decrease disintegration rate of tablet.

- **Effect of lubricants:**

Lubricants are hydrophobic in nature and prolong the tablet disintegration time by forming water repellent coat around individual granules. This retarding the rate of dissolution of solid dosage forms.

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Coating polymers:

Tablets with MC coating were found to exhibit lower dissolution profiles than those coated with HPMC at 37℃.

Enteric coating > Sugar coating >Non – enteric film coat.

Processing factors[10]

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 granules.

- **Drug excipient interaction**:

These interactions occur during any unit operation such as mixing, milling, blending, drying, and granulating results change in dissolution.

Factors related to dissolution apparatus[11]

Agitation:

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 relatively low rate.

Basket method – 100 rpm

Paddle method- 50-75 rpm

The rate of dissolution of a pure drug substance is determined by rate at which solvent-solute forces of attraction overcome the cohesive forces present in the solid. This process is rate-limiting when the release of solute in to solution is slow and the transport in to bulk solution is fast. In this case dissolution is set to be interfacially controlled. Dissolution may also be diffusion-controlled, where the solute-solvent interaction is fast compared to transport of solute in to the bulk solution

It can be stated with a significant amount of certainty that the degree of agitation, or the stirring conditions, is one of the most important variables to consider in dissolution. Given the background on the various theories of dissolution, it is apparent that agitation conditions can markedly affect diffusion-controlled dissolution, because the thickness of the diffusion layer is inversely proportional to agitation speed. Wurster and Taylor39 employed the empirical relationship.

$K=a(N)^b$

Where N is the agitation rate, K the reaction (dissolution) rate, anda and b are constants. For diffusion-controlled processes, b =I. Dissolution that is interfacial-reaction-rate-controlled will be independent of agitation intensity and thus b=0.

Dissolution rate often increased with increasing agitation speeds but didn't necessarily proportionally increase with the vibration level.

PURPOSES OF AGITATION

• Suspending solid particles
• Blending miscible liquids
• Dispersing a gas through the liquid
• Dispersing a second liquid to form an emulsion or suspension
• Promoting heat transfer

POWER CONSUMPTION OF AGITATORS it is a function of the volumetric flow rate and the kinetic energy.

VIBRATION

The speed of the rotational device selected by official compendium is 100 rpm. Other speeds are specified for certain drugs. Precise speed control is best obtained with a synchronous motor that locks into line frequency. Such motors are not only more rugged but are far from reliable. Periodic variations in rpm might result in possible disturbance in rotational acceleration. This phenomenon, present in almost all rotational devices, is commonly referred to as torsional vibration, such vibration indicates a variation in the velocity of rotation for short periods of time. There average velocity was well within ±4% of the specified rate. Vibration is a common variable introduced into a dissolution system due to various causes. It can effect change in the flow patterns of the dissolution medium. Additionally, it can introduce unwanted energy to the dynamic system. Both effects may result in significant changes in dissolution rate.

ECCENTRICITY OF AGITATING (Stirring) ELEMENT

- The current official compendium specifies that the stirring shaft must rotate smoothly without significant wobble.. Additionally, USP XX/NF XV states that the axis of rotation of the stirring shaft must not deviate > 2 mm from the axis of the stirring vessel. This implies that this specification permits eccentricity up to ±2 nun but that such eccentricity must not significantly affect the dissolution rate. This is certainly an excessive amount.

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- **Sampling probe position**:

Sampling probe can affect hydrodynamics of the system. Sampling should be removed at approximately half the distance from the upper surface of basket or paddle and surface of dissolution medium and not closer than1cm to side of the flask.

- **Temperature:**

Drug solubility is temperature dependent, therefore careful temperature control during dissolution process is extremely important.
Generally, a temperature of 37℃ ± 0.5 is maintained during dissolution determination of oral dosage forms and suppositories.

- **Vessel design and construction:**

Plastic vessels provide more hemisphere than glass vessels.

- **pH of dissolution medium:**

Weak acids, dissolution rate increases with increase in pH where as for weak bases, dissolution increases with decrease in pH.

II. MATERIALS AND METHODOLOGY:

Materials: Paracetamol API was obtained from Akshaya Associates, Hyderabad, Telangana. Paracetamol tablets were procured from local Pharmacy. Mono basic potassium phosphate, sodium hydroxide pellets and methanol were procured from S D Fine Chem Limited, Mumbai.

METHOD:

Determination of absorption maxima (ƛ max)

10 ml solution of Paracetamol in pH 5.8 phosphate buffer was scanned in UV visible spectrophotometerfrom 200-400nm. Paracetamol shows maximum absorbance at 244 nm .

Preparation of Standard graph of Paracetamol

The Standard stock solution of Paracetamol in the range of concentration 2 µg/ml to 12 µg/ml were prepared using pH 5.8 phosphate buffer and absorbance were measured at 244nm using pH 5.8 phosphate buffer as blank . Standard graph was plotted with absorbance on Y-axis and concentration in µg/ml on X-axis.

In-vitro dissolution

In-vitro dissolution studies were conducted using dissolution USP Type II apparatus. A dissolution medium consisting of 900ml of phosphate buffer (pH 5.8) was utilized and maintained at a temperature of 37 ± 0.5 °C. Three different rotation speeds, namely 50, 100, and 150 RPM, were employed. At predetermined intervals, 5 ml of dissolution samples were extracted and replaced with an equal volume of dissolution medium. The collected dissolution samples were then analysed using a UV-VIS spectrophotometer at a wavelength of 244 nm to determine the concentration of Paracetamol released, with a blank used for comparison.

In-vitro dissolution conditions

- Apparatus-dissolution apparatus type 2
- Medium- pH 5.8 phosphate buffer(900ml)
- Sampling interval-15 min, 30 min,45 min,60 min and 75 mins
- RPM-50,100,and 150
- Temperature-37^{o}C ± 0.5

III. RESULTS AND DISCUSSION:

Construction of Standard graphs of Paracetamol

Suitable dilutions of Paracetamol were made with pH 5.8 phosphate buffer and the absorbance was determined in UVVisible Spectrophotometer as shown in table1

Table-1:Standard graph of Paracetamol

S.no	Concentration(µg/ml)	Absorbance
1	2	0.168
2	4	0.299
3	6	0.476
4	8	0.581
5	10	0.718
6	12	0.818

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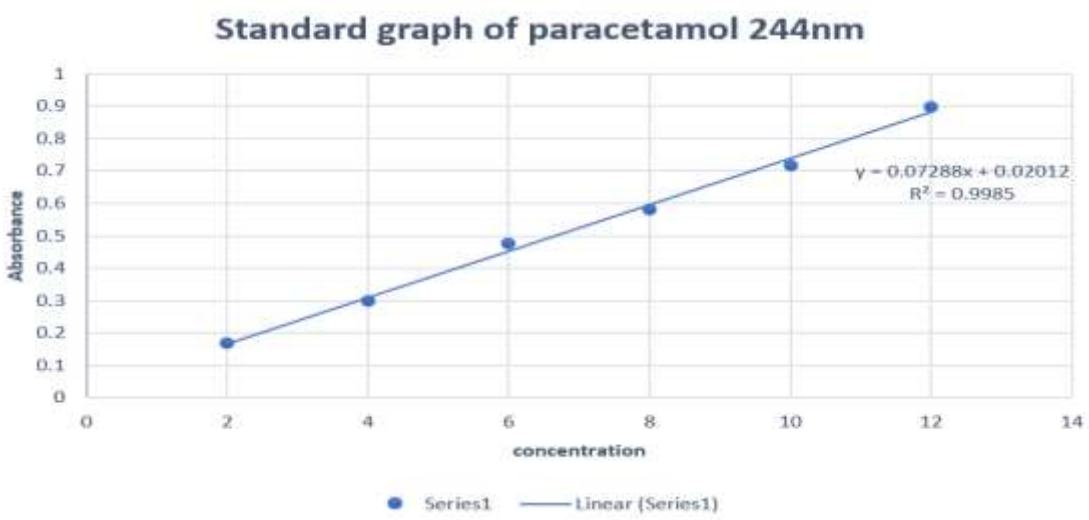

Figure 2

As seen in table 1 and figure 2 the graph was found to be linear in the range of 2 to 12µg/ml. The equation for the graph is y= 0.07288x+0.0201 and R^2 was found to be =0.9985

In-vitro dissolution

Dissolution of Paracetamol tablet was conducted in pH 5.8 phosphate buffer at different rates of agitation mainly 50rpm, 100rpm, 150rpm. Dissolution of Paracetamol at different rpm is seen in figure 3

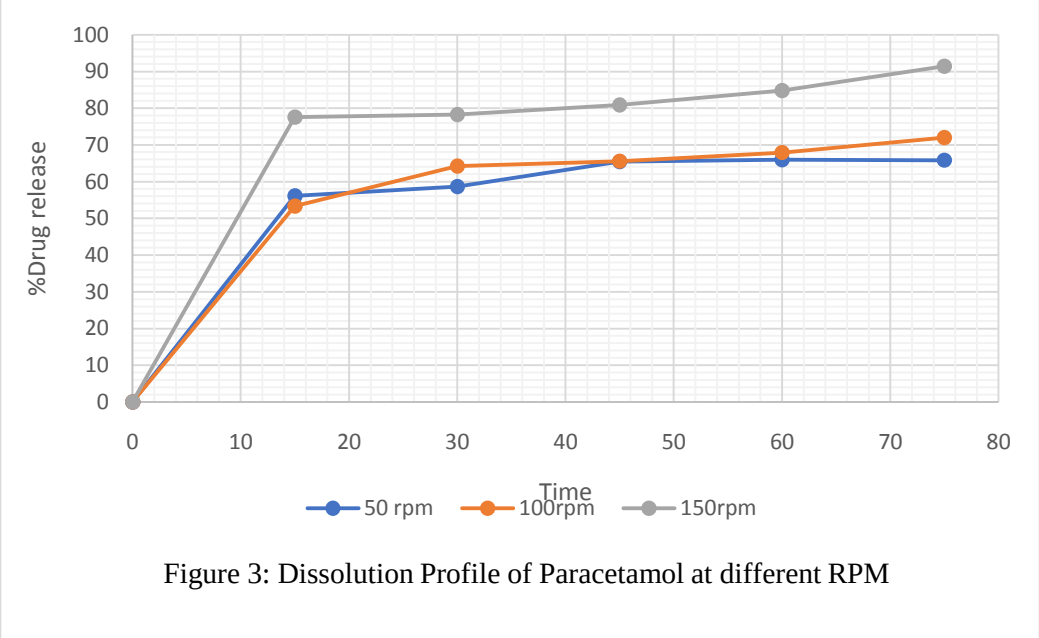

Figure 3: Dissolution Profile of Paracetamol at different RPM

It can beseen from figure 3 that as the rate of agitation increases dissolution rate increases. Percentage cumulative drug release at the end of 75mins is shown in table number 2

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Table no: 2: Percentage Cumulative Drug Release.

S.no	Rpm	%drug release
1	50	65.81
2	100	72.04
3	150	91.43

As seen in table 2, Percentage drug release at 150rpm (91.43) is greater than 100(72.04)and 50 rpm (65.81).

IV. CONCLUSION:

Dissolution test is a well-established, reproducible, reliable and valuable tool for characterizing a drug product at different stages in its lifecycle. The objective of the study was to demonstrate the effect of agitation rate on dissolution of the drug. Paracetamol was chosen as the drug for study.

Dissolution of Paracetamol tablets were conducted at different rates of agitation. It is seen from the results that increase in the rate of agitation increase the rate of dissolution. Percentage drug release at 150 rpm was more compared to 100 rpm and this was higher compared to 50 rpm.

However50 rpm is specified in Pharmacopeia as it is the most discriminatory method of dissolution and provides a laminar flow. In-vitro in-vivo correlation is better at lower rpm. Increase in the rate of agitation increases the rate of dissolution as thickness of diffusion layer decreases.

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