WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 19, 336-344. Review Article ISSN 2277– 7105

REVIEW ON DISCRIMINATORY DISSOLUTION

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Article Received on
30 Sept. 2018,

Revised on 21 Oct. 2018,
Accepted on 11 Nov. 2018

DOI: 10.20959/wjpr201819-13695

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ABSTRACT

Dissolution is defined as the process by which the solid enters in to the solvent and produces the solvent. Discriminative Dissolution is defined as the method that have ability to detect the change in formulation, raw material characteristic, critical manufacturing variables. The Discriminative Dissolution Method is used for checking the Quality of Product and to detect lot-to-lot variation. Parameters like Saturated Solubility[0.1 N HCl, pH 4.5 Acetate Buffer, pH 6.8 Phoshphate Buffer, Water], Sink Condition, Use of Surfactants [Tween 80 and Sodium lauryl sulphate- SLS], Solution Stability, Apparatus Selection [USP Apparatus I / USP Apparatus I], Agitation Speed [50 rpm/ 75 rpm/ 100 rpm], Dissolution Medium Volume[250 ml/500 ml/ 900 ml] are used for developing Dissolution Media. For Every Dosage form Dissolution Media is Different. With the Selected Media, Check the Discrimination power of media by either change the Quality of Raw material or change the manufacturing variables like Binder, Disintegrant and Processing variables like Hardness. The Discriminatory Developed Dissolution Method is validated by Specificity / Placebo Interference, Linearity and Range, Accuracy / Recovery, Repeatability, Intermediate Precision, Robustness.

KEYWORDS: Dissolution, Discriminatory Dissolution, Dissolution Validation.

INTRODUCTION

Dissolution is the process to check the release of the Drug. The dissolution profile is an Important parameter to Quality Measurement. Dissolution is the process the rate and extend in which amount the drug dissolved over a time period. Dissolution testing is most important stage during the development stage.

In Dissolution, the cumulative percentage of drug dissolved at a number of time points is determined. And plot the graph, % drug dissolved versus sampling times. The resulting graph is referred as a "dissolution profile". If dissolution profile of a test product matches to the dissolution profile of a reference product then the test product behave same as that of a reference in vivo. If dissolution profile of a test product is different to the dissolution profile of a reference product then the test product may be behave different as that of a reference in vivo.

This practice of describing dissolution profile referred as discriminative profile, and the test is referred as discriminatory test. When the same product from the different batch with dissimilarity shows different in dissolution profile than it is called as discriminative. The discriminative word mainly is related to similarity or dissimilarity of in vivo or in vitro results. If the test results shows dissimilarity for dissimilar product, then it is called as Discriminative.

But if different dissolution profiles are obtained for dissimilar products i.e. same formulation or different formulation or contained manufacturing variables but showing same in vivo characteristics, then it is not considered as discriminative, and that procedure is also not considered as discriminative method.

Discriminatory media is that media which is able to distinguish any changes in a formulation, however minor it is. In Official or QC or Release media may show same dissolution profile but when Discriminatory dissolution media is used it will be able to detect the change whether it is minor or not. But If QC media, Bioreleavant, Official media are able to discriminative the good and bad batch, then it is called as Discriminative media.

The Discrimination is depend upon your formulation, you cannot use the same method for different formulation of same drug substance means you have to alter method according to your formulation during formulation development.

METHODOLOGY

Selection of Dissolution Media: Dissolution Media is selected on basis of Saturated Solubility of the Drug.

Solubility: The most important parameter. Solubility of the drug in different pH Media is main parameter for selection of Dissolution media. According to solubility of the drug in

different pH based Dissolution media, the drug is categorized under either highly soluble or poorly soluble drug as per BCS classification. For the poorly soluble drug solubility is critical for dissolution method development. If the highest proposed strength dissolved in 250 ml dissolution media over pH range 1-6.8 as per EMA guideline or pH 1-7.5 as per USFDA guideline, then it is highly soluble drug. For checking of solubility in different pH 1-6.8, check the saturation of drug in different dissolution media. Sometimes more than pH 8 media can be used, but it need justification.

Selection of media is done on the basis of 0.1 N HCl for pH 1.0 - 3.0, glycine for pH 2.0–3.0, citrate for pH 2.5–3.5, acetate for pH 4.0–5.5, and phosphate pH 6.0–8.0. A typical buffer has 0.05 M Buffer is used.

Saturated Solubility is to know the maximum amount of drug dissolved in media. This study helps in deciding the dissolution media's volume and which media to be used. This study is mainly used particularly for poor soluble drugs. By this we can also know about how much drug of maximum strength can release from formulation. Typically used Dissolution media is water(not widely used due to instable pH) There is no such guideline for this purpose. But these study can be carried out by try to dissolving 'x' amount of drug in 'y' ml of solvent by adding drug in small quantities till it dissolved completely. But solubility is also done on the shaker not by sonication because sonication can lead to super saturation.

One of the technique used for Saturated solubility is 'Shake and Flask Method'.

Shake and Flask Method: In this method, the specific amount of drug is added in specific mL of dissolution media. Then put it on shaker for 24 hours to maintain the constant temperature at 25 ºC. After the 24 hours, If the drug is fully dissolved, then add more quantity of drug in dissolutions media until the dissolution media is fully saturate with drug. Then compare the solubility with freshly fully prepared solution in which the solute is completely dissolved.

From the solubility data, we can find either the drug meet the sink condition or not. Sink condition is defined by having a volume of medium at least three times the volume required to form a saturated solution of drug substance.

When the sink conditions are met, there is more likely that the dissolution results more likely to reflect the condition of dosage form. But for the poorly soluble drug, when the drug's

solubility does not meet the sink condition, then sink condition is achieved by addition of surfactatant. Most widely used surfactatnt is Sodium Lauryl Sulphte i.e. also known as Sodium Deodecyl Sulphate because it is easily available from vendor, available in mostly pure form and also give accurate preparation. But if the media contained pH 2.0 then Sodium Lauryl Sulphate gets degrade in media.

The use of surfactant should be under justification. The normal USFDA range for use of surfactant is 0.1- 3%. Above this range, use of surfactant need justification. Sometimes the above level of surfactant may cause formation of micelle. It may sometime cause instead of increase solubility, decrease the solubility of drug. The need of the surfactatnt and its concentration must have to justified by the checking of dissolution profile of drug at different surfctants concentration.

Solution Stability: While selection of dissolution media, solution stability of the drug is most important factor. Drug should be stable in selected dissolution media at least 48-72 hours at 37°C. Stability should allow for sufficient time to complete or repeat the analytical procedure.

METHODOLOGY

To check the stability of drug, first of all make the drug's saturated solution by same as Shake flask method. Then check the solution stability by finding area at interval 8 hrs, 12 hrs, 48 hrs, 72 hrs.

The % Deviation should be less than 2. The more the deviation is occurred if the drug is degrade in the media, which cause the reduction of area over a time period.

Optimization of Dissolution parameters

Selection of Apparatus

Selection of Apparatus is based on design of Formulation. But most commonly used apparatus are USP Apparatus I (Basket) and USP Apparatus II (Paddle).If dosage form is floated on the dissolution media, then it may require sinkers. Sinkers mostly related with Capsule dosage form. But when sinkers are needed there is need to check which size and which construction material should be used. Selection of Apparatus is also based on dissolution profile graph i.e. Cumulative % drug release Vs time points. Sometime Dosage form in Basket shows good dissolution profile as compare to Dosage form in sinker.

Selection of Agitation speed

Agitation speed is also an important factor for the dissolution method development. For capsule (both soft gel and hard gel) dosage form formulations, USP Apparatus I (baskets) at 50 to 75 rpm or For tablets, USP Apparatus 2 (paddles) at 50 to 75 rpm are most commonly used. Other agitation speed can be used but it need proper justification. Because of inappropriate of the inconsistency of hydrodynamics lower and higher rpm are usually unaccepted. Coning or mounding problems can be reduced by increasing the rpm of paddle. Decreasing or increasing the apparatus rotation speed may be justified if the profiles better reflect in vivo performance and/or the method results in better discrimination without adversely affecting method reproducibility.

Filter Compatibility

Filter compatibility is used to check the absorbance of the drug in filter material. The filter selection is based on material of filter and porosity of filter material. Adsorption of drug may deviate the result. Sometimes the material used in the filter composition may be interact with dissolution media or drug. Different filters have different binding properties. Even different concentration of the drug may also show different percentage of drug loss. The filter should be try to saturate with different amount of initial discarding through filter. The filter is either leachable or not, it also must necessary to check. Filter compatibility is checked at the end time point of dissolution. Approx amount of filtered is compared with unfiltered amount i.e. centrifuged supernatant layer. Check the % deviation. The deviation should be less than 2.

Sampling time point and Q - point Selection

Dissolution testing is mostly depend on the time points means the amount of drug that released at specific time point. Time point selection is based on the dosage form selection. For Immediate release dosage form, it is selected from 5 min to 60 min based on dissolution profile. For Extended release dosage form, it is selected up to 24 hours. Quantity 'Q' is the amount of dissolved active ingredient specified in the monograph. Required to be released in the stated time, expressed as a percentage of labelled strength, then the batch of the tablet or capsules is acceptable, if each unit is not less than Q + 5%. For IR release, the time point at which the drug shows 80 - 85% drug release. For example if it is found that if the drug shows more than 85% drug release at 15 min, then 15 min select as Q - Point.

Evaluation of Discrimination power of Dissolution Media

Batches prepared from variants of target commercial formulation or processing parameters

are used to check the discriminatory power of the dissolution method. The variable may be include formulation variables i.e. different concentration of binder and disintegrant and processing variable i.e. hardness.

Validation of Dissolution Method Specificity / Placebo Interference

In the case of dissolution, demonstration of specificity is required to show that the results are unaffected by placebo constituents, other active drugs, or degradants. Placebo consists of all excipients and coating, with inks and capsule shells included. Placebo interference can be evaluated by using a spiked placebo that is prepared by weighing of the placebo blend, dissolving or dispensing them in dissolution, medium at concentration that would be encountered during testing, and adding a known amount of drug in solution. Check the interference from Dissolution media (Blank) and Placebo.

Acceptance Criteria: The Interference should not exceed 2%.

Linearity and Range

The linearity of an Analytical procedure is the ability to check the obtained results is directly proportional to concentration. Linearity and range are generally established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during release. A minimum of five concentration is normally used. Typically, solution are made from the common stock. Also can use the organic solvent for dilution. But not more than 5%.

The Range of the procedure is the interval between the upper and lower concentration of the drug substance.

Acceptance Criteria: A square of the correlation coefficient r2 0.98 demonstrate linearity. The y- intercept must not be importantly different from zero.

Accuracy / Recovery

Accuracy / Recovery is established by preparing multiple samples containing the drug substance and any other constituents present in the dosage form (e. g; excipients, coating materials, capsule shell) ranging in concentration from below the lowest expected concentration to above the highest concentration during release.

For poor drug solubility, it may be appropriate to prepare a stock solution by dissolving the drug substance in a small amount of organic solvent (typically not exceeding 5%) and final concentration of the solution should be diluted with dissolution medium.

ICH guidelines recommend a minimum of nine determinations over a minimum of three concentrations e.g. three concentrations, three replicates each. Instead of adding the drug powder directly in to the vessel, an amount of stock solution equivalent to the target label claim used is more appropriate. Similarly, for very low strengths, it may be more appropriate to prepare a stock solution than to attempt to weigh very small amounts.

Acceptance Criteria: The measured recovery is typically found to be within 95% to 105%.

Precision

The Precision can be done over Repeatability and Intermediate Precision.

Repeatability is determined by replicate measurements of standard and/or sample solutions. The repeatability should be assessed using a minimum of nine determination covering the specified range for the procedure i.e. three concentrations and three replicates of each concentration or using a minimum of six determination at 100% of the test concentration. It can be measured by calculating the RSD of the multiple HPLC injections (peak area and retention time) or spectrophotometric readings for each standard solution. Repeatability can also be measured from the same samples used in the accuracy, recovery and linearity experiments.

Acceptance Criteria: The acceptance criteria is an RSD of < 2%.

Intermediate Precision To demonstrate the reproducibility of test results obtained by this Method for the variabilities namely Instrument to Instrument, Column to Column, Analyst to Analyst, and Day to Day. Prove ruggedness of test method for the variabilities like Two Instrument, Two Different days, Two Analyst. Dissolution to be perform seperately at different time points (i.e. 15 min, 30 min,45 min) on six units on 2 different Dissolution Instrument. Intermediate precision may be evaluated to determine the effects of random events on the precision of the analytical procedure. This evaluation is typically done later in the development of the drug product.

The dissolution profiles on the same sample may be run by at least two different analysts, each analyst preparing the standard solutions and the medium. This procedure may not need to be performed for every strength; instead, bracketing with high and low strengths may be acceptable.

Acceptance Criteria: Difference in mean dissolution result from first instrument to second instrument does not exceed an absolute 10% at time points with < 85% Drug release and does not exceed an absolute 5% at time points with above 85% Drug release.

Robustness

The robustness of an analytical procedure is a measure of how to remain unaffected by small, but deliberate changes in method parameters. For dissolution testing, parameters to be varied include medium composition (e.g., buffer pH or surfactant concentration), pH, volume, agitation rate, and temperature. These parameters should also checked for instrumental parameters for either spectrophotometric or HPLC which ever used for Analysis.

CONCLUSION

This article give the idea about the development of discriminatory dissolution method for checking the quality control of drug product. For each drug and dosage form, the different dissolution method should be developed. Dissolution method should be developed by different apparatus, different agitation speed, dissolution media. The discrimination of dissolution media is checked by formulation variables / processing variables.

Conflict of interest

The authors declare that there is no conflict of interest.

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