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Der Pharma Chemica, 2010, 2(6):394-399
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Development Of Discriminating Dissolution Procedure for Artemether and Lumefantrine Tablets

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ABSTRACT

In the Pharmaceutical Industry, Regulatory agencies often insist on discriminating dissolution methods. As a product development continues to multiply at increasingly faster rates , dissolution method development must be able to keep pace with increased number of products and dissolution scientists has a great challenge to develop the discriminating dissolution method especially for combination drug product. Dissolution methods developed using the slowest paddle speed (50 rpm) represent the most appropriate operating condition as they normally produce the steepest drug release profiles. Normally a steep drug release profile is assumed to provide optimum discriminating power to distinguish small variations in the tablet manufacturing process or to detect stability changes on storage. In actual practice many a times , for certain tablet formulations it has been observed that drug release profiles established at slower speed that is at 50 rpm can be steeper reflecting a system defect than a discriminatory tool. Higher paddle speeds that is 75 or 100 rpm which result in flatter drug release profiles can, in some cases ,more accurately reflect true formulation changes or manufacturing changes or process. This point is emphasized in the description of the development of a dissolution method for a compressed tablet containing two active pharmaceutical ingredients (Artemether and Lumefantrine).The selection of dissolution medium for a tablet with Artemether and Lumefantrine having very different solubility properties is detailed. The effects of paddle speed, selection of medium on system performance and method discriminating power are thoroughly evaluated.

Key Words: Discriminating dissolution , Combination drug product, Solubility.

INTRODUCTION

Dissolution testing is a required test currently used to demonstrate the performance of all solid oral dosage forms in which absorption of the drug is necessary for the product to exert a therapeutic effect. It provides measurements of the bioavailability of a drug as well as

demonstrating bioequivalence from batch It is the challenge for scientists working in a research and development environment to develop a procedure that can not only guide the formulation development process but can also be used as a regulatory test to detect manufacturing deviations and to ensure product consistency at release and over the product's shelf life. The test must be rugged and reproducible and highlight only significant changes in product performance. The_robustness of the procedure is particularly important since calibrated dissolution baths are allowed a variation of ± 2 rpm in the rotational speed of the apparatus. If a formulation is sensitive to small changes in rotational speed, then observed changes in the dissolution profile may simply reflect allowable instrument variation. The development of a dissolution procedure involves selecting the dissolution media, apparatus and agitation rate appropriate to the product. The solubility of the active ingredient(s) is one of the key aspects in the screening of possible dissolution media. USP favors medium related to physiological conditions, for example buffer solutions or diluted HCl (0.01 N) (2). The dissolution characteristics of the formulation are to be evaluated over the physiologic pH range of 1.2 to 7.5 (1). The Drugs that are practically insoluble in aqueous medium (≤ 0.01%) are of increasing therapeutic interest, particularly due to the problems association with their bioavailability when administered orally. It has often been suggested that drugs with low solubilities when incorporated with surfactants can enhance their dissolution rate. For water-insoluble and sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulfate, Tween –80, benzylkonium chloride (BKC), cetrimide etc. are recommended. To ensure good mixing of the drug and excipients in the dissolution vessel, a suitable apparatus and rotational speed should be selected. The basket method (Apparatus 1) is routinely used for capsule formulations at agitation speeds of 75 and 100 rpm, while the paddle method (Apparatus 2) is used mostly for tablets dosage forms at 50 and 75 rpm. In short conditions should be chosen in a such a way that will allow maximum discriminatory power, or steepest dissolution profile during dissolution testing. In most cases, the dissolution apparatus tends to become less discriminating when operated at faster speeds that result in a flatter drug release profile. However, for certain tablet formulations, the increased paddle speed results in a method with a higher discriminating power by reducing the variability of the data. Use of a low rotation speed could result in a variation in the data due to poor hydrodynamics in the dissolution vessel and can become more a reflection of system design such as coning rather than true formulation changes. Visual observations such as incomplete dosage form disintegration , erosion or pellicle formation are especially useful during method development to understand the behavior of the tablet in the dissolution vessel. The agitation speed providing optimum hydrodynamics in the vessel can be determined by comparison of the dissolution profiles obtained by making small variations in paddle speed (robustness experiments) as well as by challenging the testing procedure through the use of mismanufactured tablets (discriminatory power experiments). The final dissolution procedure should be robust and should be able to distinguish small but real changes in the product formulation.

MATERIALS AND METHODS

Experimental

Reagents

All preparations (dissolution media and mobile phase) were carried out using the following reagents:Milli-Q grade water, Hexane-1-Sulfonic Acid Sodium Salt, Sodium Dihydrogen Phosphate Monohydrate, Acetonitrile HPLC Grade Concentrated hydrochloric acid (HCl), Orthophosphoric Acid 88% GR, Triethylamine, Benzalkonium chloride 50%.

Dissolution Methodology

Experiments were carried out using a manual Electrolab Dissolution System equipped with paddles (USP Apparatus II) and transparent dissolution vessels. A dissolution volume of 1000 mL was used at a temperature of 37 ± 0.5^{o} C. The procedure used paddles at 100 ± 2 rpm Samples were taken at 15, 30, 45, 60 and 75 minutes. A minimum of 6 vessels were sampled for each analysis.

HPLC Methodology

Quantization was performed with a Waters series (Auto sampler: Waters 2695, Detector: Waters 2487 (Dual λ Absorbance Detector), Pump: Waters 2695, Software: Empower) High Performance Liquid Chromatograph (HPLC). The method utilizes a Waters symmetry C18, 15 cm x 3.9-mm internal diameter, 5-micron particle size HPLC column with a mobile phase composed of 25% buffer (5.65gm of Hexane-1-Sulfonic Acid Sodium Salt & 2.75gm of Sodium Dihydrogen Phosphate Monohydrate in 800ml of water +5ml triethylamine. Adjusted pH to 2.3 with orthophosphoric acid and diluted to 1000 ml with water), 75% acetonitrile for lumefantrine estimation. Mixture of 40% buffer and 60% acetonitrile for artemether estimation, a flow rate of 1.0 mL/min (run time of 15 minutes), a column temperature of ambient and an injection volume of 100 µL for artemether and 10µL for lumefantrine. Detection of both actives was by UV detector at a wavelength of 210nm for Artemether and 380nm for Lumefantrine.

RESULTS AND DISCUSSION

Medium Selection

Artemether and Lumefantrine has low solubility and low permeability, so they are placed in class IV as per BCS classification.

Dissolution depends on physicochemical properties viz. nature : crystalline, amorphous, solubility, particle size etc., there are two properties on which dissolution of any drug product depends on those are disintegration of drug product and intrinsic solubility of drug substance. For both these are rate limiting steps of dissolution. When intrinsic dissolution of Artemether and Lumefantrine carried out, we observed no dissolution of actives, shows solubility is a critical and rate limiting step. When solubility of both, drug substances is carried out as per BCS, solubility is the highest dose of drug substance in 250ml of the medium. Clear solution indicates that the substances is soluble in that particular medium. 20mg is the highest dose of Artemether and 120mg is the highest dose of Lumefantrine. It is observed that both are not soluble in any of the medium pH ranging from 1-7.5 and water. Further dissolution is carried out in the following physiological pH i.e. SGF pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The release of both the drug substances in innovator as well as in test product is 2-4%. The visual observation shows the tablet disintegrate within few seconds, but particles settles down immediately at the bottom of the flask indicting poor solubility of the drug substance, limiting rate of dissolution. To improve the solubility of the active 0.5% sodium lauryl sulfate (SLS) in sodium dihydrogen phosphate buffer pH 7.2 is used as medium and solublility of the drug substance studied in 20mg active is found to be soluble in 300ml of the medium but Lumefantrine is not soluble in the same medium. Even with increased concentration of SLS to 1.0% the solubility of Artemether remains unchanged and Lumefantrine still remains insoluble. Then tween 80 is added in different concentration in the sodium phosphate buffer pH 7.2 but artemether and lumefantrine were practically insoluble, hence not selected as dissolution medium. Further 1% Benzylkonium hydrochloride in 0.1N HCl is tried as a medium where in solubility of the artemether and

lumefantrine is carried out. Artemether is found to be practically insoluble whereas lumefantrine found to be sparingly soluble.

After several trials of different medium it is concluded that addition of surfactant is needed for both the drugs. As solubility of both drugs differ drastically it is very difficult to carried out dissolution in a single medium, hence it is decided to use two different dissolution medium for each of artemether and lumefantrine. Medium 0.5% SLS in sodium phosphate buffer pH adjusted 7.2 is chosen for artemether and 1% BKC in 0.1N HCl is chosen for lumefantrine. Both the drug substances require approximately 300-325ml of the medium to dissolves 20mg & 120mg in respective medium. To achieve sink condition minimum 3 times of volume required than what is required to soluble maximum dose hence volume 1000ml is decided per jar. This selection was found to be ok for lower strength of lumefantrine but at higher strength, results of lumefantrine were found to be poor (up to 40% at a decided time). In an attempt to understand the origin of the method variability at, a visual observation of the tablet behavior in the dissolution vessel was performed. The results found showed that after a certain point precipitation was found to occur and it was increasing with time. According to definition of saturation, up to a certain point the solubility increases and after that point precipitation forms and goes on increasing. To increase the solubility one available option was to increase the volume of dissolution media i.e. from 1000 ml to 2000 ml or increase the surfactant quantity or increase the time. Increasing volume to 2000ml was having practical problem of dissolution apparatus. Hence, 2% BKC was used instead of 1% BKC which showed adequate results for all strengths. Then dissolution profile was carried out having 15 minutes interval up to 2 hours. The results showed that up to a certain point, the dissolution increases, after which it showed drastic drop it is because of precipitation of lumefantrin due to super saturation. Therefore the time selected is time at which absorption was found to be maximum was selected .

Apparatus and Paddle Speed Selection

The apparatus and rotational speed selected must provide adequate mixing to disperse the drug product in the media and to provide a homogeneous mixture for sampling, while maintaining the discriminatory power of the dissolution procedure.

USP Apparatus II was chosen due to its acceptance as a standard procedure for tablet formulations. Paddle speeds of 50, 75 & 100 rpm were evaluated with samples taken after 15, 30, 45, 60, 90 and 120 minutes of paddle rotation. In order to demonstrate method robustness, dissolutions were performed using paddle speeds of 50 ± 2 rpm, 75± 2rpm and 100± 2rpm. Dissolution methods developed using the slowest paddle speed (50 rpm) represent the most appropriate operating condition as they normally produce the steepest drug release profiles. Normally a steep drug release profile is assumed to provide optimum discriminating power to distinguish small variations in the tablet manufacturing process or to detect stability changes on storage. In actual practice for the selected combination formulations it has been observed that drug release profiles established at slower speed that is at 50 or 75 rpm can be steeper reflecting a system defect than a discriminatory tool as due to low solubility lumefantrine and artemether both precipitates in the dissolution flask. Higher paddle speeds that is 100 rpm which result in flatter drug release profiles can, in some cases ,more accurately reflect true formulation changes or manufacturing changes or process. With 50/75rpm particles of drug substances remains floating in the jar whereas with 100rpm particles dissolves and no settling is observed hence though100rpm is harsh, and low dissolution values with 50/75 rpm becomes more of method limiting rather with than product quality hence 100rpm is selected as best rpm.

Discriminating dissolution method

Method is challenged by carrying out dissolution with two different particle size drug substances. Use of micronised Lumefantrine and non micronised Lumefantrine, the dissolution method differentiate the two formulations proving discriminating nature of the method. Results described in table 1 and table 2 proves that the method is discriminatory.

Table 1: Dissoluiton results of Lumefantrine

B.no.	Lumefantrine Lot A- particle size of d(0.1) - Less than 5% d(0.5) -Less than 50 microns d(0.9) – Less than 90 microns	B.No.	Lumefantrine particle size of B.no. PP5002 LURI d(0.5) - Not more than 100 µ d(0.9) – Not more than 250 µ
R & D –A/05	73.0% 80.9% 62.7% 63.2% 58.5% 62.7%	R &D –B/05	101.91% 89.90% 92.33% 92.19% 91.26% 94.50%
Observation	Shows saturation and reprecipitation that is particles start settling down immediately.	Observation	Uniform dispersion is observed.

Table 2: Dissoluiton results of Artemether

B.no.	Artemether particle size of Lot-A d(0.9) – 330 microns	B.No.	Artemether particle size of lot-B d(0.9) – 37 microns
R & D –A/05	74.1% 79.2% 74.2% 74.1% 78.6% 74.1%	R & D –A/05	91.1% 94.8% 101.4% 101.8% 99.8% 100.0%
Observation	Shows particles floating and settling down.	Observation	Uniform dispersion is observed.

Conclusions

In general, use of the slowest calibrated paddle speed (50 rpm) results in a method with a steeper drug release profile, typically leading to a higher discriminating power. However, for this formulation the use of a slower rotation speed resulted in a lack of robustness and the dissolution became more a reflection of system artifacts, such as precipitation of actives and variable dissolution results than true formulation changes. Visual observations were especially useful during method development, when understanding the physical behavior of the tablets in the dissolution vessel was necessary. The agitation speed providing optimum hydrodynamics in the vessel was determined through comparison of the dissolution profiles obtained from small variations in paddle speed as well as by challenging the testing procedure with the use of mis-manufactured tablets. Although the method using a paddle speed of 50 rpm produced a more “classic” dissolution profile, its ability to discriminate between manufacturing changes was overwhelmed by lack of method robustness. A paddle speed of 100 rpm not only produced an expected increase in robustness but also provided a

procedure with superior discriminatory power. The final dissolution procedure selected is robust and able to distinguish small changes in the product formulation.

Acknowledgement
The authors are thankful to all the members of the management of Laboratories Limited, Mumbai , for providing all facilities to conduct this experimental work.

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