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Dissolution Test as a Quality Control Tool for Herbal Formulations - A Comprehensive Review

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ABSTRACT

Specific guidelines have not been proposed for the dissolution testing as well as dissolution is not considered as a prerequisite tool of quality control test for herbal medicine. In the quality control test, dissolution tests are performed as an essential evaluation parameter for synthetic medicine and it's not the same case with ayurvedic / herbal medicinal products. Pharmacological activity of drugs can be affected by the extent of drug release which in turn depends on the absorption and bioavailability of drugs. Dissolution of medicament in the biological fluids is required for the absorption and if any variation is observed, it may alter its therapeutic efficacy. Thus dissolution studies have to be considered as a vital evaluation parameter for herbal products. In this review importance of dissolution profiling, challenges associated in the development of dissolution medium and past research works carried out so far on herbal medicines have been discussed.

Keywords: Quality control, Standardization, Surfactants, Polyherbal formulation, Sink condition.

INTRODUCTION

According to WHO, more than 60% of world population still rely on herbals and herbal originated medicaments for treating short and chronic ailments. The herbals and related products are well spread available even at interiors of many rural areas. Due to wide-spread usage of herbals, many domestic and multinational pharmaceutical companies are inducted in production of various herbal formulations. The acceptability of herbal formulations by public is increasing now a day due to their affordability, effectiveness and less toxicity. The effectiveness and therapeutic efficacies are major concerns for any type of formulations. Particularly herbal formulations, in addition to above concerns, built-in quality and product standards are also key concerns for herbal formulations. To impart quality in herbal products with standards, the WHO is trying to establish and implement certain GMP guidelines in association with some government agencies. Another big concern of herbal formulations is their marketing. The major hurdle in the marketing of herbal products is the standardization of raw material / extract and quality control tests. (Capasso *et al.*, 2000; Ong 2004; Liu & Wang, 2008; Alvarenga *et al.*, 2009; Bueno *et al.*, 2009; Valente *et al.*,

2009). To enhance the marketing chances and to surmount the challenges innate to herbal products, novel technologies and methodologies that are implemented in pharmaceuticals have to be extended for herbal medicine (Vasconcelos *et al.*, 2005; Yadav and Dixit, 2008). Thus the safety and efficacy of herbal formulations can be assured (Alves, 2005).

The active moieties of herbal medicine are the secondary metabolites of botanical plants. Without extensive studies on effectiveness and possible risk, consistency of usage is not possible due to quality aspects (World Health Organization, 1998; EMEA, 2003). The quality assessment of synthetic drugs is comparatively easy compared to polyherbal formulations that possess several herbal extracts with numerous chemical constituents. Among them, the prime chemical moiety which is responsible for the pharmacological action is difficult to assess. One cannot evaluate all the chemical moieties despite of their effectiveness. This poses a difficulty in the development of dissolution medium for herbal formulations with complex chemical nature.

Nutraceuticals and herbal products standardization in terms of compendial requirements are still in its early days. Only four herbal products (Ginger, Garlic Delayed Release, Milk Thistle, and Ginkgo) have their monographs in United States Pharmacopeia with well defined dissolution testing procedure and parameters (USP 30-NF 25, 2007). British, European, Indian and

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Japanese pharmacopeias do not present a single monograph with dissolution specifications for herbal formulations. However, in 2007, the Food Drug Administration passed final decision that specific dissolution or disintegration test is not required in current good manufacturing practices for herbal dietary supplements (USP 32/NF 27, 2010).

Till date research work on the development of dissolution medium for polyherbal formulations is very meager. Polyherbal formulations available in the market exhibit a diverse quality parameter which suggests a variant therapeutic efficacy during clinic trials. However, the underlined concept of herbal medicine is utilization of wide variety of chemical constituents (Gao, 2008). Thus it became a challenge to maintain quality standards in the production of herbal formulation (USFDA, 2004; EMEA, 2001).

Role of dissolution studies in the quality assessment

Dissolution is the process in which a solid medicament dissolves in the precise quantity of the given medium. The dissolution property of a dosage form influences the absorption property. Absorption being the prime step for drugs to exhibit their pharmacological action; it has to be studied extensively. Bioavailability studies that describe the in-vivo performance cannot be carried out each and every time. Thus, in-vitro dissolution testing can be considered as a relevant method to predict the in-vivo performance. In the production and quality control arena of pharmaceuticals, dissolution testing is considered as a prerequisite to perceive the defective product and to maintain content uniformity in batch and reproducibility among the production batches (Schulte-Lobbert, 2003).

Challenges associated in the dissolution studies

The major hurdle in the dissolution studies is the selection of dissolution medium. Selection of the dissolution medium is based on both solubility profiles and dose range of the chemical moiety (FIP guideline 1997; FDA 2000). In order to select the dissolution medium, solubility studies have to be performed over a wide physiological pH range from 1.2 to 7.8 to determine the solubility characteristics of chemical constituents of herbal formulation. This helps to predict the nature of the compound i.e., whether they are acidic, basic or neutral in nature.

For extracts with low solubility, it is quite difficult to pick up the dissolution medium from the aqueous solutions of wide physiological pH range owing to their poor solubility. In such instances, surfactants are added to the aqueous solutions to promote their solubility. The mechanism underlined in the enhancement of dissolution by surfactants is micellar solubilization. Surfactants in aqueous solution result in the formation of colloidal system that helps to solubilise the poorly soluble entity. To predict the required concentration of surfactant, surfactant has to be varied over a wide range. It is essential to maintain sink conditions throughout the study period which can be accomplished by the utilization of surfactants at higher concentrations. Yet

using the surfactants above the limited range may result in the retardation of solubility. It is advisable to use surfactants up to a range of 3%. One may doubt what happens if high surfactants are used despite of gastrointestinal contents. Human gastrointestinal contents do not possess a high surfactant and to our surprise it does not result in the poor correlation with bioavailability.

A biorelevant medium has to be developed that possess similar surface activity as that of bio-fluids. In the study, if surfactants are used, their need and the optimum level of surfactant have to be justified. Generally used surfactants in the development of dissolution medium are sodium lauryl sulfate (SLS), Tween, CTAB, Cremophor, HTAB, Triton, Terigitol, Cyclodextrins and Lecithin. Among these, non ionic surfactant Tween is considered to be biorelevant and is exhaustively used. To every one's surprise 'Tween' is the only surfactant that gets its tribute to be included in Japan Pharmacopeia.

Another assignment is the simulation of biological conditions in dissolution medium. Recent studies are oriented towards the design of artificial media that mimic the physicochemical properties of gastrointestinal contents with respect to osmolarity, pH, buffer capacity, enzymes, bile content, surfactant content etc. Development of biorelevant gastric and intestinal media is the topic of interest. These media have been widely utilized not only in the solubility and dissolution studies but also in the simulation of gastrointestinal stability and to execute permeability studies (Frank, 2012). Biorelevant media can be developed by the addition of bile salts, physiological surfactants, lecithin etc to simulate the gastrointestinal fluid environment. One can achieve best results from poorly aqueous soluble extract by executing the dissolution study in these media.

Biorelevant media viz Fasted State Simulated Gastric Fluid (FaSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF), Fed State Simulated Gastric Fluid (FeSSIF) have been developed to mimic the fasted and fed state of gastric conditions and continuous streamline projects are going on to improve these media (Galia, 1998; Sunesen, 2005; Fujioka, 2007; Jantrid, 2008; Lue, 2008; Ghazal, 2009; Klein, 2010). The major motto for the projects is to development the good correlation between in-vitro and in-vivo performance of herbal drugs.

Dressman et al created dissolution media in which lecithin and taurocholic acid quantity, buffer capacity, osmolality, pH and surface tension values were in sync to physiological values. The composition of bile salts is attuned by the addition of taurocholic acid and phosphatidylcholine from egg. Glycerol monooleate and sodium oleate were commonly used to symbolize triglycerides and fatty acids of gastric contents. Osmolality can be adjusted with sodium chloride (Dressmann, 1998; Dressmann, 2000).

Conventional preparation of these biorelevant media may present several difficulties like time consuming, usage of organic solvents, regular preparation and sometimes end up with unusable medium. To

overcome this, instant preparations are available in the market as 'ready to use' preparations which simplifies the testing procedure (Klofer, 2010).

Research is going towards the replacement of FaSSIF with surfactant media. The major concern in the utilization of surfactants is the possibility of drug surfactant interaction. Extensive studies have to be carried out to determine the permissible levels with respect to drug excipient interactions thus promoting the potential to substitute FaSSIF by simple, economical conventional surfactant media (Zoeler, 2007). So far simulated fluids have been used limitedly in the dissolution medium development for herbal formulations. Milk can also be used to mimic the postprandial stomach conditions as it has protein, fat, carbohydrate ratio similar to western diet. The proposed mechanisms for the solubility enhancement by milk are solubilization of active principle in the fatty portion and caseine micelles; high pH favors the solubilization of weakly acidic constituents. Filtration and separation of drug from this media is difficult presenting its unsuitability for regular quality control.

Apart from these, formulational factors like raw material processing, particle size of extract powder, moisture content, compressional forces in tableting, excipient interaction, extraction process etc may also lead to alteration / diversified drug release (Bempong & Houghton, 1992; Taglioli *et al.*, 2001; Kressmann *et al.*, 2002; Westerhoff *et al.*, 2002; Kratz *et al.*, 2008). For instance, excipients in the formulation that influences solubility and wettability of the matrix was investigated by de Souza. Maytenus ilicifolia tablets containing lactose and cellulose as excipients showed faster release in lactose based formulations owing to the variation in their solubility, water uptake capacity and hardness of tablet (de Souza, 2001).

The dissolution test developed to predict the biopharmaceutical performance must closely simulate the gastrointestinal environment as well as maintain the sink conditions for proper release. Thus it may not be possible always to develop single dissolution test or select single dissolution medium which assures batch-to-batch consistency. So, selection of the most relevant medium for regular analysis should be done on the basis of their discriminatory capacity, ruggedness, stability of the chemical compound in the test medium and its relevance to in vivo performance wherever applicable.

With this context, a brief review on the dissolution studies and dissolution medium development for herbal products carried out so far have been discussed.

Andrographolide

Dissolution method for a polyherbal formulation containing four standardized herbal extracts namely *A. paniculata* (10% andrographolide), *Boerhaavia diffusa* (0.25% Boeravinone B and E), *Phyllanthus amarus* (0.5% of Phyllanthin and Hypophyllanthin) and *Picrorrhiza kurroa* (4% Kutkoside and Picroside-I) was investigated by Vivek *et al* in 2012. The aqueous solubility of the andrographolide was evaluated 0.1%,

0.5%, 1% w/v of sodium lauryl sulphate, 0.1M and 1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The solubility studies were carried out for andrographolide in order to establish an aqueous dissolution medium that ensures sink conditions during dissolution testing.

Andrographolide has limited aqueous solubility which necessitates the change in dissolution volume, addition of anionic or nonionic surfactants or change in the pH to enhance the solubility. Pure water is not well thought-out as an "ideal" dissolution medium, owing to its exceptionally low solubility capacity at different pH ranges during the dissolution tests. Due to its poor aqueous solubility, sodium lauryl sulphate (SLS) was added to water to enhance its dissolution. Dissolution studies were carried out in 0.1 M HCl, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) which present simulated gastric fluid, simulated duodenal and simulated intestinal pH conditions respectively.

Different factors like type of apparatus, volume of dissolution medium, stirring rate were evaluated. Paddle and basket type apparatus were used and it was found that the dissolution rate was faster when paddle was used compared to basket. Increasing the media volume from 500 ml to 900 ml significantly improved the dissolution rate in a given span of time. A 75 rpm was found to be optimum after dissolution profiling at 50, 75 and 100 rpm. Thus, dissolution parameters developed to estimate the release of andrographolide from polyherbal formulation are Phosphate buffer pH 6.8 of 900 ml, carried out in paddle type apparatus at 75 rpm and 37 °C (Vivek, 2012).

Hyperoside

Dissolution studies have been conducted using USP Dissolution test apparatus II (paddle method) with 750ml of 2% SDS solution as medium at 50 rpm and 37 °C to determine the drug release pattern of hyperoside from the coated tablets of dry hawthorn extract (Aggrey MO, 2012)

Curcumin

The dissolution has been carried out in phosphate buffer pH 4.0 and 0.05 M hydrochloric acid with sodium lauryl sulphate in different concentrations of 0.2%, 0.3%, 0.4%, 0.6% and 0.8%. After a detailed experimentation, the proposed dissolution test for turmeric capsules containing curcumin was the basket device at 100 rpm with a release of 75% in 60 minutes. Thus the proposed dissolution medium is composed of 0.05 M hydrochloric acid with sodium lauryl sulfate at 0.8% w/v (Nantana, 2007).

Researchers observed variability in the results owing to the coning effect due to dense materials in the product. They found that the basket type apparatus was not adequately efficient to stir the bottom contents. Then they aimed to develop an alternative system to overcome these limitations. They carried out the dissolution testing using the paddle device (with helix) at 75 rpm. Helix acts as a sinker and averts the capsule from hovering on medium surface providing an additional agitation ahead

of the predictable stirring rate of paddle. Sodium lauryl sulfate (SLS), was used to enhance the dissolution of curcumin. The dissolution medium designed further was 0.6% w/v SLS in 0.05 M HCl and the test was carried out in paddle type apparatus set at 75 rpm (Sirichai, 2010).

Ashwaganda capsules

The dissolution test was performed for ashwaganda capsule in basket type USP dissolution apparatus. Dissolution medium of dilute HCl (900 ml) warmed to 36.5-37.5°C was used to maintain the sink conditions. The rotating speed of basket was maintained at 50 rpm throughout the study (Soni Hardik, 2010).

Passiflora species with flavanoids

Paddle type dissolution apparatus with 500 ml of 0.1 M HCl as dissolution medium was utilized to detect the release pattern of total flavanoids from passiflora species containing formulations. The experiment was carried out at a stirring speed of 50 rpm and a temperature of 37±0.5 °C (Ane RT Costa, 2011).

African potato products with hypoxide and β-sitosterol

Dissolution tests were performed using the USP-2 (Paddle) apparatus for tablet formulations and USP-1 (Basket) apparatus for capsules. Volume of dissolution medium was 900 ml and the experiment was carried out at 100 rpm maintaining the temperature at 37 ± 0.5° C. Dissolution medium differs for hypoxide estimation and β-sitosterol quantification. Dissolution media of 100 mM hydrochloric acid of pH 1.2 was used for hypoxide release determination. Biorelevant dissolution media viz. FaSSiF and FeSSiF with lecithin as emulsifier and bile salts as solubilizer were utilized to monitor the release of β-sitosterol from African Potato products. The internal

standards used in the analysis of hypoxoside and β-sitosterol was Sulphamerazine (10 µg/ml) cholesterol (50 µg/ml) respectively (Vipin Devi Prasad Nair, 2008).

Parthenolide present in feverfew products

Dissolution testing was conducted using USP Method I (basket) maintain the hydrodynamic conditions such as temperature set at 37 ± 0.5 °C, basket rotation speed of 100 rpm and 500 mL of 0.5% sodium dodecyl sulfate (SDS) in water as dissolution medium (Ping Jin, 2007).

Theophylline, caffeine, catechin and epicatechin from guaraná

In order to determine the release of theophylline, caffeine, catechin and epicatechin, dissolution studies were carried out using USP apparatus 2 (paddle) of 900 ml of 0.1 M HCl, pH 1.2 at 37.5 ± 0.5 °C temperature and a stirring speed of 75 rpm (Sandra Alves de Sousa, 2011).

CONCLUSION

Dissolution testing provides a major pathway to produce high quality generics thus consistently minimizing the regulatory burden. This has to be adopted in herbal quality control too. The principle active moiety has to be determined priorly in case of Polyherbal formulations and then dissolution method can be developed. The developed dissolution method should be well validated and possess the characteristics of accuracy, precision, ruggedness and reproducibility. It should be able to discriminate the minute changes in the test that could influence the in-vivo performance of the product. Extensive brainstorming research has to be carried out in the development of discriminating dissolution medium for herbal formulations to ensure their quality.

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