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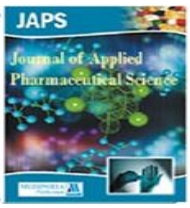

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Invitro studies and evaluation of metformin marketed tablets-Malaysia

Arcot Ravindran Chandrasekaran, Chan Yoke Jia, Choong Sheau Theng, Teeba Muniandy, Selvadurai Muralidharan and Sokkalingam Arumugam Dhanaraj

Arcot Ravindran Chandrasekaran, Chan Yoke Jia, Choong Sheau Theng, Teeba Muniandy, Selvadurai Muralidharan and Sokkalingam Arumugam Dhanaraj
Faculty of Pharmacy, AIMST University, Semeling, Malaysia

***For Correspondence*:**
A.R.Chandrasekaran.
Associate Professor
Faculty of Pharmacy
AIMST University
Kedah- 08100, Malaysia.

ABSTRACT

In this research project, we are assigned a topic to study on the *in vitro* equivalency evaluation of Metformin tablets. The main focus of this research is to conduct dissolution test on the tablets to determine the compliance with a given official monograph. Dissolution testing is a method for evaluating physiological availability that depends upon having the drug in a dissolved state. The release profiles obtained from in vitro dissolution tests can be used for predicting *in vitro in vivo* correlation models. *In vitro* dissolution test is conducted on five different brands of Metformin tablets to evaluate their equivalency. Tablets or capsules taken orally remain one of the most effective means of treatment available. The effectiveness of such dosage forms relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. The rate of dissolution of the tablet or capsule is therefore crucial. In this research, our aim is to develop an *in vitro* test method that fully models the physiological conditions in the GI tract. The dissolution media used closely resembles the GI fluid in the stomach. Simulation of GI pH gradients, peristaltic movement, transit times, biliary and pancreatic secretions and water absorption are examples of features in such dynamic in vitro test model.

Key words: Invitro; Metformin.

INTRODUCTION

Metformin HCl is an oral anti-diabetic drug from the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function. (Lord et al, 2003) Metformin is also being used increasingly in polycystic ovary syndrome (PCOS),(Marchesini et al, 2001) non-alcoholic fatty liver disease (NAFLD) (Ibanez et al, 2006) and premature puberty,(Nair et al, 2007) three other diseases that feature insulin resistance; these indications are still considered experimental. The benefit of Metformin in NAFLD has not been extensively studied and may be only temporary;(8) although some randomized controlled trials have found significant improvement with its use, the evidence is still insufficient.(Socha et al, 2009; John et al, 2006) Polycystic ovary syndrome (PCOS) is a syndrome of ovarian dysfunction and hyperandrogenism. Evidences suggest that insulin resistance and resulting hyper insulinaemia play a central role in the pathogenesis of the syndrome. Metformin, an insulin sensitizer, not only improves hyperandrogenism but also improves ovulation as well as pregnancy rates in patients with PCOS(Ying Lu et al, 2011;Shirzad Azarmi et al, 2006; Giovanna Corti et al, 2006; Vines Pillay et al, 1998;Kyel et al, 2997; Javed ali et al, 2006). Study is carried out to evaluate the *in vitro* equivalency evaluation of Metformin tablets. Five different brands of Metformin tablets were studied for their dissolution (John et al, 2006; Don et al, 1978; yihong Qiu et al, 2009;Alexander et al, 2006; Arthur et al, 2004; Hong wen

et al, 2010; Aminda et al, 1995;), weight variation, disintegration and hardness which are named as product A – E respectively.

Metformin initially sold as Glucophage is an oral anti-diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function (Willima et al, 1991; Pamula et al, ; Block et al, 2008; Prateek et al, 2010; Saptarshi et al, 2010; Flowerlet et al, 2010; Kamlesh et al, 2010; Abul et al, 2008). Evidence is also mounting for its efficacy in gestational diabetes, although safety concerns still preclude its widespread use in this setting. It is also used in the treatment of polycystic ovary syndrome and has been investigated for other diseases where insulin resistance may be an important factor.

Quality control procedures, which are useful tools for batch-to-batch consistency in manufacturing, should be performed for every drug product. Drug having more than three generic products require analysis for their biopharmaceutical and chemical equivalency. These methods ensure that any of the generic products can be used interchangeably.

The prediction of the in vivo bioavailability of most oral drugs depends on the in vitro dissolution studies because in vitro disintegration tests do not always give good correlation. Dissolution testing of drug products plays an important role as a quality control tool to monitor batch -to- batch consistency of drug release from a dosage form.

There are many apparatus for dissolution test have been developed over the years. Paddle, rotating basket and flow – through cell method are the mainly three types that have been retained in official compendia. In this paper we discussed about In vitro equivalence evaluation of Metformin tablets.

MATERIALS AND METHODS

Chemicals

Potassium dihydrogen phosphate, sodium dihydrogen procured from AR, unilab chemical

Instrumentation

UV-du600-Decman coulter

Preparation of standard solutions

A stock solution is prepared using an analytical balance (1 mg/ml) that is 100 mg of pure Metformin is dissolved in 1000ml of phosphate buffer pH 6.8. Different working standard namely 5µg/ml , 10 µg/ml, 15 µg/ml, 20µg/ml and 25µg/ml was prepared by appropriate dilutions.Absorbance of those solutions at the λ max 233 nm is measured.

Calibration Curve

For the calibration curve, accurately weighed of metformin was transferred to a 100 ml volumetric flask and dissolved in a mixture of buffer. From this solution, other solutions with concentrations of different µg ml were obtained by diluting adequate amounts in triplicate.

In vitro release studies

The *in vitro* dissolution studies of the marketed conventional IR tablets and the developed SR tablets were carried out using USP type II apparatus (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of distilled water maintained at 37 ± 0.5°C. The drug release at different time intervals was measured using an UV visible spectrophotometer. It was made clear that none of the ingredients used in the matrix formulations interfered with the absorbance of the drug. The release studies were conducted for three tablets in a batch and the mean values were plotted against time.

Dissolution test by USP paddle apparatus. The *in vitro* dissolution study is carried out using apparatus II (paddle). The dissolution jars are cleaned with a mild detergent and then rinsed with distilled water and dry to room temperature. 900 mL of dissolution medium is transferred into the dissolution jars and are placed in the test assembly which is maintained at 37 degree Celsius which is given an allowance of 0.5 degrees Celsius. The medium is allowed to attain the set temperature. The rpm is set to 100. The test sample is introduced inside the dissolution jar and the test assembly is brought down to the Static position and the medium is stirred at 100rpm. 10 mL of the samples are withdrawn at various time intervals such as 0 minutes, 10 minutes, 20 minutes, 30 minutes, 45 minutes, and 60 minutes using a graduated pipette and transfer it immediately to clean, dried and labeled test tubes. The equal volume of fresh dissolution medium is replaced after each sampling and maintained at the correct temperature. The sample withdrawn is diluted 10 by 10 times and the absorbance is measured at 233nm. 10 mL of sample is withdrawn at the end of 30 minutes from each of the test jar, using a graduated pipette and it is filtered if necessary. It is then transferred to a cleaned, dried and labeled test tube. The sample is diluted by 10 times and the absorbance is measured at 233nm. The cumulative percentage of released is calculated using the given formula.

Formula for determination of percentage of release of drug Metformin from *in vitro* dissolution testing

Concentration of drug (µg/ml)= (slope × absorbance) ± intercept

$$\text{Amount of drug released mg/ml} = \frac{\text{Concentration} \times \text{Dissolution bath volume} \times \text{dilution factor}}{1000}$$

$$\text{Cumulative percentage release (\%)} = \frac{\text{Volume of sample withdrawn (ml)}}{\text{Bath volume (v)}} \times P(t-1) + Pt$$

Where Pt = Percentage release at time t

Where P (t – 1) = Percentage release previous to‘t’

RESULT AND DISCUSSION

Linearity

Five point’s calibration graphs were constructed covering a concentration range 5–25 mcg/ml. Three independent determinations were performed at each concentration. Linear relationships between the absorbance versus the corresponding drug concentration were observed, as shown by the results presented in Table 1. The standard deviations of the slope and

intercept were low. The determination coefficient (r^2) exceeded 0.99 (Fig. 1).

Table 1 Linearity study.

No.	Concentration of Metformin Hydrochloride in Phosphate Buffer pH 5.8 (µg/ml)	UV Absorbance at 233nm
1	0	0
2	5	0.5234
3	10	0.8737
4	15	1.2484
5	20	1.6191
6	25	1.8933

Table 2 Mean Cumulative Percentage Drug Release.

Time interval(min)	A	B	C	D	E
10	77.0770	67.5039	65.6680	69.8669	67.6244
20	81.1203	79.5405	75.6360	78.8712	85.5911
30	81.9900	84.7769	77.9005	79.8186	87.3809
45	83.1873	89.8424	78.3755	79.1659	89.1998
60	83.5297	96.6195	78.0405	79.4642	75.8797

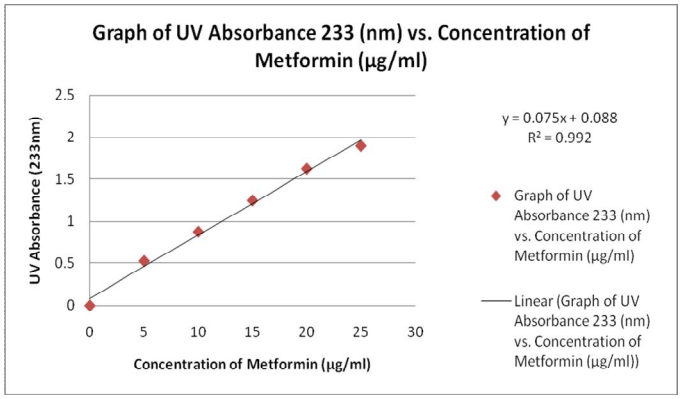

Fig. 1 Linearity graph.

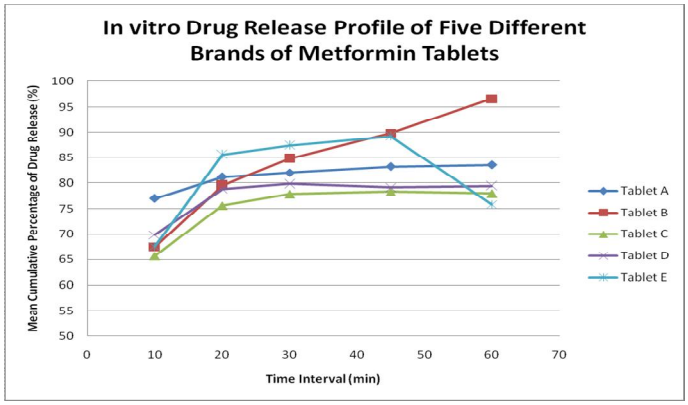

Fig. 2 Metformin mean curve.

Invitro studies

The *in vitro* drug release characteristics of the developed marketed tablets were studied. Dissolution data for all the experiments were highly reproducible and hence only the average values were plotted. The dissolution of the marketed tablets indicated that more than 80% of the drug is released within 1 h, which complies with the pharmacopoeial specifications. In all the batches, we observed that as the polymer concentration increases, the drug release rate decreases.

CONCLUSION

In vitro dissolution methods are developed to evaluate the potential in vivo performance of a solid oral dosage form, and as quality control tests demonstrating the appropriate performance of drugs products. In recent years, the convergence of the increased understanding of the physiological environment and processes of absorption, critical deconstruction of the mechanisms of release from formulations, and improved computational tools has led to a more sophisticated discussion of the role of dissolution testing in drug product design and control. It is clear that meaningful results and interpretation of dissolution data can be achieved only when the biopharmaceutical and physical properties of the drug products are well understood, and that test methods are properly established through studies during formulation and manufacturing process design and clinical development.

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