Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 11, 2014

Original Article

IN-VITRO DISSOLUTION STUDY OF MELOXICAM IMMEDIATE RELEASE PRODUCTS USING FLOW THROUGH CELL (USP APPARATUS 4) UNDER DIFFERENT OPERATIONAL CONDITIONS

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Received: 17 Sep 2014 Revised and Accepted: 16 Oct 2014

ABSTRACT

Objective: To evaluate and compare the *in-vitro* dissolution profiles of five generic immediate release (IR) products of Meloxicam (MX) available in Egyptian market with the innovator reference product (Mobic®, R) using different operational conditions of the flow through dissolution cell (FTC, USP Apparatus 4), in phosphate buffer (pH=7.5).

Methods: The comparative *in-vitro* dissolution studies were performed under different FTC operational conditions such as cell size, tablet position within the cell, open and closed loops setup and type of flow (laminar and turbulent) on MX dissolution rate from different IR products.

Results: The study showed that two generic products, out of five, gave similar dissolution profiles with R using a specified well controlled condition of FTC. A selected generic product (Mobitil, G1) was tested versus R under different operational conditions of the FTC such as cell size, type of flow, tablet position and open & closed loops setup. The dissolution profile of MX from R was highly affected by changing the tablet position, slightly affected by the open & closed loops setup and not affected by cell size and type of flow. On the other hand, the dissolution profile of MX from G1 was affected by all the previous operational conditions. Comparing f_2 values between G1 against R among the different operational conditions proposed, only one *in-vitro* dissolution test showed similar dissolution profile of G1 with respect to R.

Conclusion: Three generic products of MX might not be interchangeable with the innovator product (Mobic®).

Keywords: Flow through cell apparatus, Meloxicam, dissolution, Immediate release, Turbulent flow, Laminar flow, USP Apparatus 4.

INTRODUCTION

Sensitive and reproducible dissolution data derived from physicochemically and hydrodynamically defined conditions are necessary in order to compare variability and reproducibility in *in-vitro* dissolution data and to be able to use such results as a surrogate for possible *in-vivo* bioavailability, bioequivalelence testing and *in-vitro* / *in-vivo* correlations (IVIVC) [1-3]. With respect to the IVIVC concept, *in-vitro* (mainly dissolution) tests are applied as a tool to predict drug product performance *in-vivo* [1,4].

The dissolution test is an empirical *in-vitro* test used to quantify the dissolution rate of an active pharmaceutical ingredient (API) from a dosage form into solution. Dissolution testing is used throughout the life cycle of pharmaceutical dosage forms, from feasibility studies in formulation development to quality control in manufacturing [5,6].

After the development of a generic product, a pivotal bioequivalence study should be carried out according to reference guidelines (FDA, EMEA, and WHO). The *in-vitro* dissolution study data of the bio batch will be the measure of product performance. Acceptable products are bioequivalent, whereas unacceptable products might be bio-in-equivalent. To achieve an IVIVC, at least three batches, that are differ in both *in-vivo* and *in-vitro* performance, should be available. If batches show differences in bioavailability, then the *in-vitro* test conditions can be modified to achieve the required IVIVC.

The *in-vitro* dissolution curve is usually determined by a suitable dissolution test, and the *in-vivo* absorption curve is frequently determined by deconvolution using model-dependent (e. g., Wagner-Nelson or Loo-Riegelman) [7] or direct mathematical deconvolution [8]. Developing an *in-vitro* dissolution test that gives a 1:1 IVIVC for a particular drug product is an important objective to facilitate product development and serves as a quality control procedure during product manufacture. Drug manufacturers typically use such tests to assess lot-to-lot variability and product shelf life and to predict *in-vivo* performance (i. e., bioavailability) with reasonable assurance after conducting minor formulation and process changes [9]. In the absence of a suitable *in-vitro* test that can be interpolated to changes in drug plasma concentration-time profiles, appropriate testing in humans may have to be carried out, which can add much to the development costs of pharmaceutical formulations [2,10]. Very often, the *in-vitro* dissolution test is found to be more sensitive and discriminating than the *in-vivo* test. From a quality assurance point of view, a more discriminative dissolution method is preferred, because the test will indicate possible changes in the quality of the product before the *in-vivo* performance is affected [11].

The FTC was developed to answer some deficiencies perceived in other compendial techniques and offers a viable option for carrying out dissolution of various dosage forms such as tablets, powders, suppositories, hard gelatin capsules, implants, semisolids, and drug eluting stents [12-15]. This method has distinct advantages compared with the USP paddle and basket methods, especially for drugs with poor solubility and wettability [11,16], Powders with very low solubility and wettability present unique problems that necessitate optimized methods of sample loading into the FTC in order to achieve acceptable results [15]. The FTC dissolution apparatus is specially designed to have a small holdup volume compared with other USP dissolution apparatuses, which helps to minimize spreading of drug particles to undefined sites of the apparatus [15,17]. Moreover, FTC has several characteristics that can offer important information for the study of compounds and dosage forms including [18,19] (1) a built-in filtration system; (2) use as either an open-or closed-loop setup; (3) a high degree of automation; (4) sink condition can be maintained, due to the continuous flow of fresh medium and this feature is important for the study of poorly soluble drugs [15,19]; (5) ideal and controlled hydrodynamic conditions pumped either laminar (packed column) or turbulent flow mode for mild agitation, homogeneity, and definable flow. The hydrodynamics inside the FTC are not affected by media change and sampling, as can occur in traditional closed systems (i. e., rotating paddle apparatus, rotating basket apparatus) [15,16,19]; (6) dissolution medium and/or flow rate can be changed within a single run in order to mimic pH changes along GIT [20]; (7)

the possibility of changing the pH during the experiment, could be an alternative method for enteric coated dosage forms [21]; (8) the system can be used for the characterization of apparent dissolution, as samples (powder) can be placed in the cell without application of mechanical forces (i. e., compression) [17,19]; (9) development of IVIVC can be easier [22]; (10) several cell types are available for evaluation of different sample types and dosage forms, and (11) release from dosage forms over extended periods can be studied, as FTC eliminates the evaporation issue that can be observed with other apparatus [15,19].

Few literature [11,15,17,23-29], discussed the optimization of the operational conditions of FTC affecting the release of drugs e. g. flow rate, the type of flow [laminar flow (packed column) or turbulent flow], cell size, gradient change of pH of the dissolution medium, operation of the FTC as a closed or open loop setup and the position of the dosage form in the dissolution cell.

For IR formulations [23,30], many studies have shown that compendial *in-vitro* dissolution tests with Apparatus 2 make it difficult to show the differences among them. This is mainly related to the higher agitation level that causes the rapid disintegration of the tablet. The objective of this study is to evaluate the dissolution profiles of MX (practically water insoluble drug) from IR products available in the Egyptian market (7.5 mg/ product) using FTC (USP Apparatus 4) under variable operational conditions such as: cell size, type of flow, position of tablets within the FTC, different operational mode. Therefore, an optimum FTC design was proposed to predict MX dissolution from different pharmaceutical products.

MATERIALS AND METHODS

Materials

Pure Meloxicam (MX) was kindly donated from Delta Pharma, Cairo, Egypt. All products used in this study were immediate release MX available in an Egyptian market, each contain 7.5 mg MX / products and all tests were performed within product expiration dates. Innovator reference product R was Mobic® tablets, obtained from Boehringer Ingelheim, Germany (batch number 905340).

Generic product G1 was Mobitil® tablets, MUP, Egypt (batch number 92054); G2 was Mexicam® tablets, Delta Pharma, Egypt (batch number 80815); G3 was Melocam® tablets, Amoun Pharmaceutical Co., Egypt (batch number 90434); G4 was Moxen® tablets, EGPI, Egypt (batch number 90034); G5 was Anti-CoxII® capsules, Adwia Co., Egypt (batch number 81051). Sodium hydroxide pellets and Potassium dihydrogen orthophosphate were purchased from Laboratory Rasayan, India. Methanol (HPLC grade, Prolabo, France) was used for stock solution preparation. Milli-Q purified water (Millipore Corp., Billerica, MA, USA) was used to prepare the dissolution medium.

Methods

Analysis of MX

A standard curve ranging from 0.4 to 30 µg/mL in phosphate buffer (pH 7.5) was constructed [31]. A stock solution was prepared by dissolving 5 mg of MX powder in 50 mL methanol to yield a concentration of 100 µg/mL. This solution was serially diluted with phosphate buffer of pH 7.5 to yield the desired concentration range. The absorbance of the prepared solutions was measured spectrophotometrically (DU–650 UV-Vis spectrophotometer, Beckman, USA) at predetermined λ_{max} of 363 nm against the phosphate buffer of pH 7.5 as blank. The absorbance was plotted against the concentration, and the response factor was calculated. Each concentration was analyzed in triplicate, and the mean values were calculated. A linear zero-intercept relationship was established, where the slope and regression coefficient was 0.0589 and 0.9998, respectively. Percent recoveries ranged from 96.32% to 113.75%, and the average response factor was 16.639 ± 1.045.

Comparative *in-vitro* dissolution study of MX products

The comparative *in-vitro* dissolution studies of 6 different IR market products (each contained 7.5 mg MX); one reference product (R) and five generic products (G1-G5) were carried out using the open loop setup of FTC [USP Apparatus 4, a Dissotest CE-6 equipped with a CY 7-50 piston pump (Sotax, Switzerland)]. Each tablet was placed into the large dissolution cell (22.6 mm diameter) according to the cell design shown in fig. 1 Pattern-A. A Built-in filtration system with 0.7-µm What man glass micro-fiber (GF/F and GF/D) and glass wool was used throughout the study. Dissolution medium was filtered degassed phosphate buffer (pH 7.5) maintained at 37.0 ± 0.5 °C, pumped at 8 ± 0.2 mL/min. The dissolution studies were carried-out in triplicate. Sample fractions were collected at the following time intervals 10, 20, 30, 45, 60, 90, 120, 150 and 180 min. and analyzed by UV/spectro photometric method at 363 nm against phosphate buffer pH 7.5 as blank.

The dissolution profiles of the five tested products of MX were compared with the innovator R using similarity factor (f_2) and dissolution efficiency (D. E.).

Similarity Factor

For comparing the dissolution profiles of different MX market products, the similarity factor (f_2) as proposed by Moore and Flanner [32] was calculated from the mean dissolution data and was used to compare between different FTC designs. (f_2) is defined by FDA [5] as

$$f_2 = 50 \times \log \{[1+ (1/n) \Sigma t=1n (Rt - Tt)\ 2]\text{-}0.5 \times 100\}$$

Where n is the number of time points collected during the *in-vitro* release test, R_t and T_t are the cumulative percentages release at the selected (n) time point of the two tested formulae. The (f_2) value is a measure of the similarity between two dissolution profiles and its value ranges from 0 and 100. FDA has set a public standard of **(f_2)** value of 50-100 to indicate similarity between two dissolution profiles [5,32,33].

Dissolution efficiency

This concept was proposed by Khan and Rhodes in 1975 [34] and is defined as follows:

$$\text{D. E.} = 0\int^{t} y \times dt \times 100 \quad y_{100} \times t$$

Dissolution efficiency (D. E.) was calculated from the area under the dissolution curve at time (t), measured using the trapezoidal rule, and expressed as percentage of the area of the rectangle described by 100% dissolution, y_{100}, in the same time [35,36].

Study of different FTC designs on dissolution of MX from IR products:

The dissolution profile of one selected generic product (G1) was compared to the reference product R using different cell designs (fig. 1, Patterns A-D), as follows:

Pattern-A: Large dissolution cell (22.6 mm), laminar flow (packed column, glass beads fill the entry cone), free tablet position.

Pattern-B: Small dissolution cell (12 mm), laminar flow (packed column, glass beads fill the entry cone), free tablet position.

Pattern-C: Small dissolution cell (12 mm), turbulent flow.

Pattern-D: Large dissolution cell (22.6 mm), laminar flow (packed column, glass beads fill the whole cell volume), embedded tablet position.

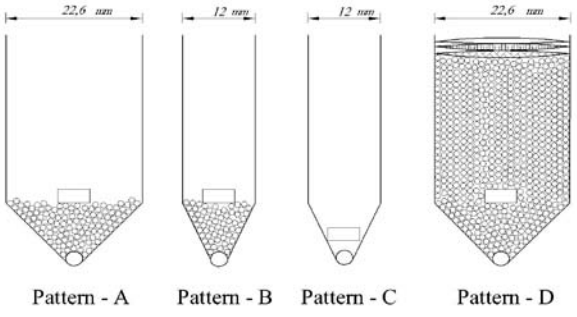

Fig. 1: Schematic diagrams showing the four patterns for MX tablet loaded into the FTC

Study of the open and closed loops setup of the FTC on dissolution of MX from IR products:

The FTC was operated either: (1) as an open loop setup with fresh solvent from the reservoir continuously passes through the cell or (2) as a closed loop setup, where a fixed volume of solvent is recycled. For operation of FTC dissolution apparatus in the open loop setup; fresh dissolution medium (phosphate buffer pH 7.5) was pumped continuously and sample fractions were collected at the following time intervals 10, 20, 30, 45, 60, 90, 120 min. While, for the closed loop setup, 900 mL phosphate buffer (pH 7.5) was recycled, 10 mL samples were collected at the specified time intervals and were replaced by the same volume of the fresh dissolution medium. This factor was studied for R and G1 using Pattern-C (fig. 1).

RESULTS AND DISCUSSION

MX, a non steroidal anti-inflammatory drug, was used as water insoluble model drug in this study. It is indicated for short term symptomatic treatment of exacerbations of osteoarthrosis as well as long term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis [37,38].

MX is an acidic drug (pKa, 1.1), practically insoluble in water at physiological pH (12 µg/mL) and has a zwitterionic property with two pKa values (pKa1 =1.09, pKa2 =4.18) [39,40]. The percentage of ionized drug and the solubility increase with increasing pH until the highest solubility reported is reached in phosphate buffer pH 10, decreasing pH leads to an increase in the ratio of non-ionized to ionized drug combined with a decrease in solubility [39]. Previous pharmacokinetics studies have shown that MX has prolonged absorption with T_{max} of longer than 5h, indicating the slow absorption of MX after an oral administration [41,42]. In most studies, the dissolution of MX is carried out in phosphate buffer of pH 7.5.

In this study, the dissolution tests were carried-out using either the open or the closed loops setup of the FTC. When the system operates in the open loop setup, the data collected represents the amount dissolved/released at specific time intervals (estimate of dissolution rate) and is non cumulative form [19,43]. Data can be transformed to the cumulative form; in this case, any mistakes associated with the estimation of the total drug released during a specific time interval will be transferred to the next time interval. If a model is to be fitted to the data, by converting them to the cumulative form, the fundamental assumption of independence of errors is violated [18,19]. Data collected when the system operates in the closed loop setup is in cumulative form.

Comparative *in-vitro* dissolution study of MX products

Fig. 2 showed the percent of MX dissolved from the generic products (G1-G5) versus the innovator product (R) using the open loop setup of the FTC. The FTC was operated using large cell at laminar flow (free tablet position); as illustrated in Pattern-A (fig. 1). The dissolution profiles of the five generic products showed different behaviors, and could be divided into two classes. Class I (G3 and G4) and Class II (G1, G2 and G5). After 30 min, Class I showed higher percent of MX dissolved (82.636%, 90.521% and 87.231% for R, G3 and G4, respectively) and Class II showed lower percent of MX dissolved than the acceptance criterion in the USP and the requirement for an IR dosage form (61.168%, 43.220% and 56.082% for G1, G2, G5, respectively). Although, the dissolution study period was extended up to 180 min, however, the products of Class II did not show a pronounced increase in % MX dissolved. Meanwhile, in a previous study using large cell [11], it was found that the reference products of diclofenac sodium SR tablets (Voltaren 100 mg) manufactured in two different manufacturing sites (Novartis-Egypt, Novartis-Switzerland), showed remarkable differences in the release rate of diclofenac sodium SR. This might open a question about the performance of the two products *in-vivo* [44].

The dissolution profiles of the 5 generic products were compared with the innovator R using the similarity factor f_2. Fig. 3 showed the f_2 results with the following values 33, 25, 56, 50 and 35 for G1, G2, G3, G4 and G5, respectively. The f_2 values of G3 and G4 products were found to be within the FDA acceptance limit (50-100). These values revealed that Class I had a similar dissolution profiles to R, while the Class II revealed dissimilar dissolution profiles. In this respect, we could conclude that the two Classes might give different data *in-vivo*.

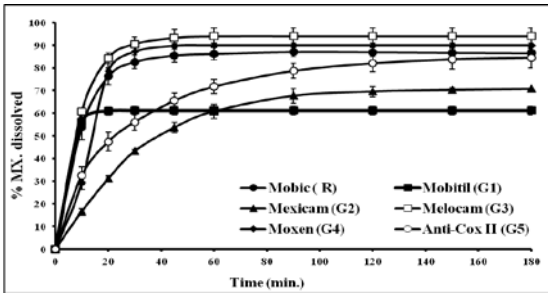

Fig. 2: Dissolution profiles of MX from IR products (7.5 mg MX / product) using the open loop setup of FTC (for cell design see Pattern-A)

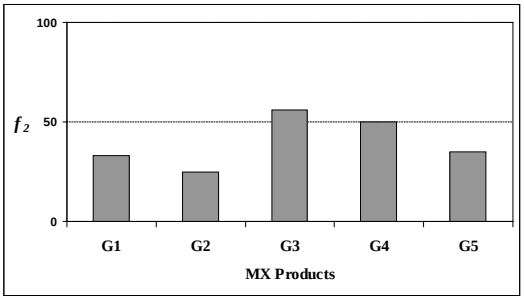

Fig. 3: Comparison between dissolution profiles of different MX generic products (G1 – G5) versus R (Mobic®) expressed by similarity factor "f_2".

The dissolution efficiency (D. E.) was calculated for each individual cell, and hence, the mean D. E. for each product with its 95% confidence intervals (C. I.) was compared by measuring the difference between the mean D. E. and confidence intervals of the innovator product and the tested products [36]. If the differences of the mean dissolution efficiencies as well as the 95% confidence intervals are within appropriate limits (±10%), one can conclude that the dissolution profiles of the reference and test are equivalent [36]. As shown in table 1, both conditions have been satisfied only for two products, G3 and G4. The values of the mean D. E. Were found to be within the appropriate limits; D. D. E. were 7.18 and 1.76 and D. C. I. were 6.93 and 5.75 (±10%) for G3 and G4, respectively. Therefore, the dissolution profiles of G3 and G4 were similar with each other and with the innovator as per these methods.

Therefore, and according to the calculated f_2 as well as D. E., it could be concluded that the two generic products G3 and G4 might probably be interchangeable with each other and with the innovator product R. However, product G1, G2 and G5 might not be interchangeable with the innovator.

Table 1: Mean dissolution efficiencies with 95% confidence intervals

Tested products	Mean D. E. (%) with C. I.	D. D. E.	D. C. I.
R (Mobic®)	81.51 (75.57, 87.44)	0	0
Mobitil (G1)	59.18 (54.69, 63.67)	22.33	32.75
Mexicam (G2)	58.20 (54.32, 62.03)	23.31	33.12
Melocam (G3)	88.69 (80.51, 96.87)	7.18	6.93
Moxen (G4)	83.27 (81.69, 84.85)	1.76	5.75
Anti-Cox (G5)	70.55 (62.30, 78.79)	10.96	25.14

D. E.: Dissolution Efficiency, **C. I.:** Confidence Intervals, **D. D. E.**= Difference of the mean D. E. between the innovator and the tested product, **D. C. I.** Difference in confidence intervals and is calculated

by considering the maximum possible mean D. E. value of Innovator and minimum possible mean D. E. value of other products.

The FDA provides guidelines for dissolution tests for oral IR dosage forms, but also realizes the need for individualizing the method on a case by case basis leaving the justification of a given methodology up to the scientist. Therefore, the individual scientist is challenged to design an appropriate test based on the objectives to be accomplished, e. g., quality control, IVIVC, showing bioequivalence, etc.

Therefore, we proposed other FTC features to investigate possible dissolution similarity or dissimilarity between R and a selected generic product from Class II, that might affect the final judgment. G1 was selected on the basis that it exhibited dissimilar dissolution profile versus R (f_2=33). Four different patterns (A-D) were investigated using G1 versus R.

Effect of cell size

Fig. 4 showed the dissolution profiles of MX obtained from studying the effect of the cell size of 12.0 and 22.6 mm on the amount of MX dissolved from R and G1 using the open loop setup (c. f. Fig. 1, Patterns-A & B for cell designs). Different cell sizes showed small differences on MX dissolution rate from R (fig. 4A). Where the percent of MX dissolved after 30 min was 79.15% and 82.64% and after 1 h was 85.89% and 86.20% from the small and large cells, respectively. The f_2 value between the two dissolution data was 64 indicating similar dissolution profiles obtained from the two patterns. Similarly, in a previous study done by Emara et al. [11], there was also no difference in the release rate of diclofenac sodium from Voltaren® 100 mg SR tablets (Novartis-Switzerland), upon using either the small or large cell. The authors attributed their result to the fact that the saturation concentration of diclofenac sodium was rather high to be affected by the cell size.

On the other hand, the dissolution rate of MX from G1 using the two cells (large, small) showed remarkable difference, i. e. dissimilar dissolution profiles within the product with f_2 value of 27 (fig. 4B). The percent of MX dissolved from G1 after 30 min was 90.19%, and 61.17%, and remained constant up to 2 h from the small and large cell, respectively. Similar results were published previously [26,27,45,46], a study by Cammarn et al. [26], showed that the dissolution rates of salicylic acid in large cell were significantly lower than those seen in small cells, moreover, the dissolution rate is insensitive to flow rate in these larger cells. Another study by Bielen et. al. [27] reported that the dissolution rates of salicylic acid and prednisone tablets in the large cell were significantly lower than those in the small cell.

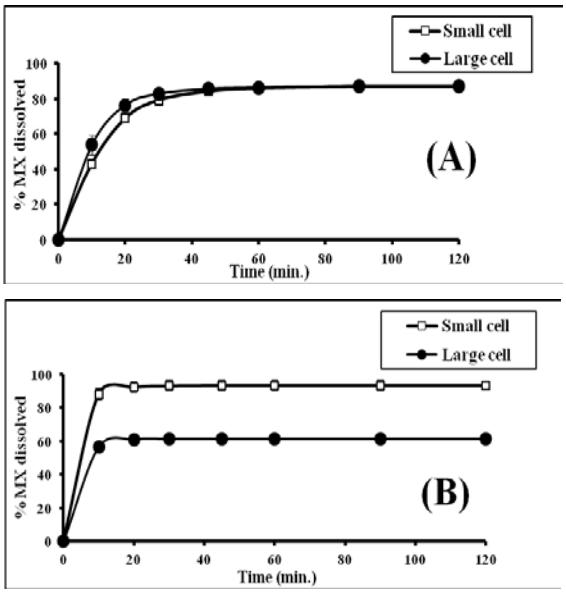

Fig. 4: Effect of cell size on the dissolution rate of MX using the open loop setup of FTC: (A) Mobic®, R; (B) Mobitil®, G1 (for cell design see Patterns-A & B).

Also, in another study [45], the release rates of nifedipine controlled-release product in the large cell were significantly lower than those in the small cell. Wu et al. [46], reported that the dissolution rates of theophylline and naproxen tablets in the large cell were significantly lower than those in the small cell at flow rate 8 mL/min. The results indicated that as the diameter of cell increased, the Reynold's number [47] and the mean dissolution rate decreased, hence, the small cell gave higher dissolution than the larger cell and these results were observed for both theophylline, (high solubility) and naproxen (low solubility) [46]. Emara et al. [11] reported that, in the small cell the fresh dissolution medium is recirculated faster, and the concentration of a given drug in the diffusion layer around the tablet is affected by the concentration gradient. This gives rise to more drug diffusion, which is expected to increase the amount of drug released.

Upon comparing the dissolution similarity between G1 versus R (i. e. between products), it was found that f_2 values were 37 and 33 using small and large cells, respectively, which indicated dissolution dissimilarity between G1 and R under these operational conditions.

It is worthy to point out here that although the two products (R & G1) contain the same drug in the same dosage from (IR), however, the two products behave differently with regard to the cell size. In this respect, we could conclude that the two products might give different *in-vivo* data.

Effect of type of flow

Fig. 5 showed the effect of turbulent versus laminar flow (free tablet position) on the amount of MX dissolved from R and G1 using the open loop setup (cf. Fig. 1, Patterns-B & C for cell design). The type of flow had almost no effect on MX dissolution rate from R (fig. 5A), where the f_2 value was 69 indicating similarity between the two types of flow. The percent of MX dissolved was 79.15% and 73.82% in 30 min and after 1h was 85.89% and 82.05% for the laminar and turbulent flow conditions, respectively. On the other hand, the amount of MX dissolved from G1 increased pronouncedly upon applying laminar flow condition (fig. 5B). Where the percent of MX dissolved from G1 was found to be 93.09% and 81.12% in 30 min and remained constant up to 2 h when the laminar and turbulent flow were applied, respectively. The f_2 value was 43 which indicated dissimilar dissolution profiles, upon changing the type of flow.

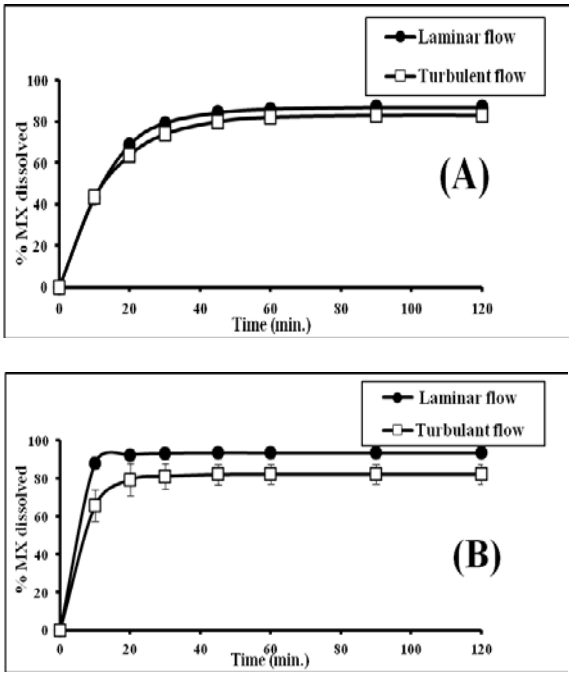

Fig. 5: Effect of type of flow on the dissolution rate of MX using the open loop setup of FTC; (A) Mobic®, R; (B) Mobitil®, G1 (for cell design see Patterns-B & C).

Upon comparing the dissolution similarity between G1 versus R (i. e. between products), using the same FTC operational feature, it was found that f_2 values were 37 and 48 when laminar flow and turbulent flow was applied, respectively, which indicated dissolution dissimilarity between G1 and R under these operational feature.

Similarly, Morihara et al. [28] studied the dissolution of salicylic acid from USP calibrator tablets and reported that the dissolution rate was higher when the tablet rest on top of the glass beads (i. e., laminar flow) than leaving the tablet free in the cell without glass beads. In another study [11], changing the type of flow had almost no effect on the amount of diclofenac sodium released from Voltaren® SR tablets. Thus, for each drug/product system, the optimum criteria, features and conditions of the FTC should be considered precisely to discriminate between different products and detect any minor change of excipients or manufacturing site of the product, which might give different *in-vivo* results.

Effect of tablet position

The effect of tablet position within the glass beads as well as the amount of glass beads loaded in the FTC using open loop setup (fig. 1, Patterns-A & D) was demonstrated in fig. 6. It was found that the dissolution of MX from R and G1 were much lower when the tablet was buried in the glass beads than when the tablet rest on top of glass beads, the percent of MX dissolved after 30 min from R was 8.27% and 82.63% for the two tablet positions, respectively (fig. 6A). Also, for G1 after 30 min, the percent of MX dissolved was 3.66% and 61.17% for the two tablet positions (Patterns-A & D), respectively, and remained constant up to 2 h (fig. 6B). The similarity factor f_2 for R was 9 indicating dissimilarity between the dissolution profiles within the product (fig. 6A). Also, f_2 for G1 was 13, indicating dissolution dissimilarity obtained from changing tablet position within FTC (fig. 6B).

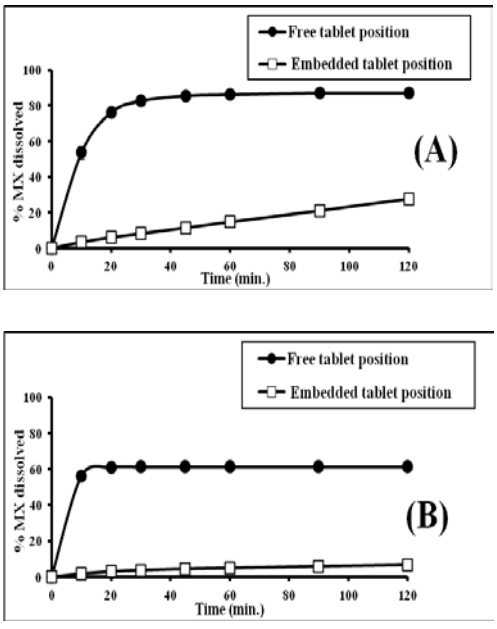

Fig. 6: Effect of different tablet position on the dissolution rate of MX using the open loop setup of FTC: (A) Mobic®, R; (B) Mobitil®, G1 (for cell design see Patterns-A & D).

Upon comparing the dissolution similarity between G1 versus R (i. e. between products), using the same FTC operational feature, it was found that f_2 values were 48 and 33 using embedded tablet position (Pattern-D) and free tablet position (Pattern-A), respectively, which indicated dissolution dissimilarity between G1 and R under these operational feature.

The increase in the dissolution rate of the free tablet position (Pattern-A) might be due to the movement of the tablet. As long as the saturated aqueous layer surrounding the tablet changed faster, in the free position, this will create another fresh unsaturated layer which led to observed increase in MX dissolution rate [45].

These results were similar to previous studies [11,45]. Emara et al. [11] reported that the release rate of diclofenac sodium from SR tablets was significantly lower when the tablet was buried in the glass beads than placed on the top of the glass beads. Also, it was found that the release of nifedipine was decreased when the tablet was embedded in the glass beads [45]. However, a study carried out by Morihara et al. [28] showed that, the dissolution of salicylic acid from USP calibrator tablets was the highest when the tablet was buried in the glass beads, followed by placement on top of glass beads. These variable results between salicylic acid [28] in one hand and diclofenac sodium, nifedipine [11,45] and our current study on MX in the other hand, might throw light or open a door for the importance of optimizing all the operational conditions of the FTC to obtain reliable, reproducible results and eliminate any erratic dissolution data that could be occurred when the method was not properly adjusted.

Effect of the open and closed loops setup

The FTC apparatus can operate in two different modes: (1) as an open loop setup with fresh solvent from the reservoir continuously passes through the cell and (2) as a closed loop setup where a fixed volume of liquid is recycled. The open setup is selected for samples that require high volume of media (i. e., low solubility compounds), and the closed loop setup is selected when a low volume of medium is required [19].

Fig. 7 showed the effect of open and closed loops setup of the FTC on the amount of MX dissolved from R and G1 using Pattern-C (fig. 1). It was found that, the amount of MX dissolved was slightly increased on applying the closed loop setup (fig. 7 A & B) for both R and G1. In case of R, the percent of MX dissolved after 30 min was 73.82% and 84.75% and after 1 h was 82.05% and 90.27% when the open and closed loops setup were applied, respectively (fig. 7A). For G1, the percent of MX released after 30 min was 81.12% and 94.72% and after 1 h was 82.15% and 94.72% for open and closed loops setup, respectively (fig. 7B). The similarity factor f_2 for R was 47 indicating dissimilarity between the dissolution profiles within the product (fig. 7A). Also, f_2 for G1 was 46, indicating dissolution dissimilarity obtained from the open and closed loops setup (fig. 7B).

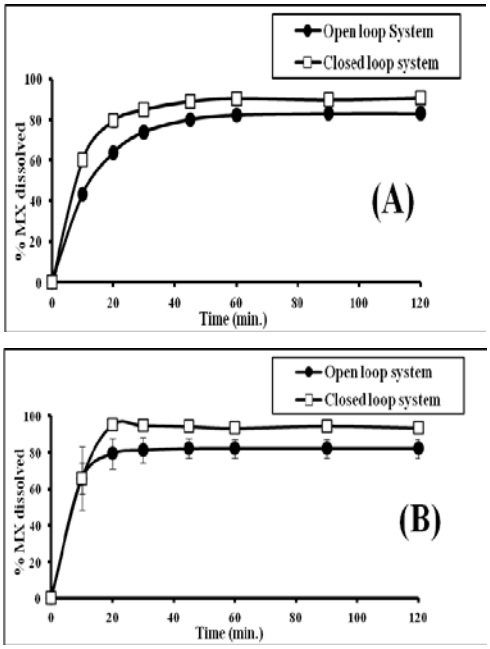

Fig. 7: Effect of the open and closed loops setup of FTC on the dissolution rate of MX: (A) Mobic®, R; (B) Mobitil®, G1 (for cell design see Pattern-C).

Fig. 8 comparing the dissolution similarity between G1 versus R (i. e. between products), upon using the same FTC operational feature in each case, it was found that only the closed loop setup gave f_2 value of 55, while f_2 value for the open loop setup was 48. Therefore, the closed loop setup gave similar dissolution profiles for G1 and R.

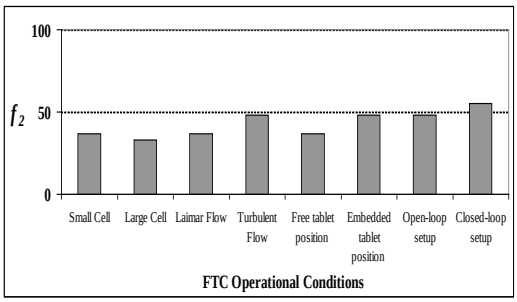

Fig. 8: Comparison between dissolution profiles of MX products (G1 against R) expressed by similarity factor "f_2" at different FTC operational conditions.

Based on these results, it is better to use the closed loop setup as to save time and chemicals used to prepare the dissolution medium as well as provide the simpler test procedure and less time consumed for the pre-filtration step. Where each cell requires a volume of 900 mL or 1500 mL of dissolution medium for closed and open loop setup, respectively. A study done by Qiu et al. [23], to compare the dissolution profiles of paracetamol tablets (using the closed and open loops at three different flow rates of 4, 8 and 16 mL/min) showed similar dissolution profiles in both open and closed loops setup. All of the similarity factor f_2 values at different flow rates are greater than 50, indicating their similarity.

Fig. 9 summarized the effect of different FTC operational conditions on the dissolution profiles within each MX product (R or G1) by similarity factor f_2 values. It was worthy to mention that the dissolution profile of MX from R was highly affected by changing the tablet position, slightly affected by the open and closed loops setup and not affected by cell size and type of flow. On the other hand, the dissolution profile of MX from G1 was affected by all the previous operational conditions.

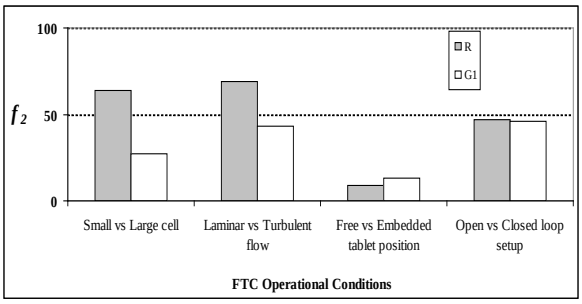

Fig. 9: Effect of FTC operational conditions on the dissulotion profiles within each MX product (R or G1) expressed as Similarity factor "f_2".

CONCLUSION

This study opens an important question about the optimization of the FTC to obtain reliable and discriminative results reflecting the major as well as the minor formulation variables prior to the bioequvilance testing. Upon applying specific and well controlled conditions of the FTC, it was found that the generic products Melocam® (G3) and Moxen® (G4), showed dissolution similarity compared to the innovator (Mobic®).

The *in-vitro* testing was extended to focus on other FTC operational conditions and its impact on the similarity / dissimilarity between the selected product G1 and R. The calculation of f_2 values for R and G1 upon applying different conditions of FTC, revealed that a one single *in-vitro* dissolution test out of seven, gave similar dissolution profiles (Pattern-C with closed loop setup). Moreover, the dissolution rate of product R was much less affected by changing the FTC operational conditions than product G1.

CONFLICT OF INTERESTS

Declared None

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