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STUDIES ON THE QUANTIFICATION AND COMPARISON OF DISSOLUTION PROFILES OF TWO BRANDS OF MELOXICAM TABLETS

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ABSTRACT

A simple model independent approach using a similarity factor (f_2) and a difference factor (f_1) to compare dissolution profiles as proposed by Moore and Flanner was used to evaluate the in vitro equivalence of two brands of meloxicam tablets. Our results showed that the two meloxicam formulations are not equivalent in vitro. Thus it is recommended that the same formulations should be evaluated to in vivo studies in order to find whether a co-relation exists between in vitro dissolution and in vivo bioavailability.

Keywords: Comparison of dissolution profiles, model independent method, difference factor, similarity factor.

INTRODUCTION

Rationale

Generally the goal of biopharmaceutical studies is to develop in vitro systems that closely resemble in vivo situations. The advantages to be gained in developing in vitro tests that are predictive of drug absorption in man are considerable and have stimulated an over whelming number of investigations by pharmaceutical scientists through out the world. These efforts have focused largely on disintegration and dissolution tests. The documented inability of disintegration tests to provide an index of bioavailability intensified interest in the development of dissolution tests, which might better serve as predictors of drug absorption. The aim of the present work is to study in vitro and in vivo behavior of two brands of meloxicam tablets. The results of in vitro evaluation are presented in the present paper while the in vivo investigation would be presented elsewhere.

Meloxicam [4 – hydroxy – 2 – methyl – N - (5 – methyl - 1, 3 – thiazol – 2 - yl) -2 H -1, 2 – benzothiazine - 3 - carboxamide 1 ,1-dioxide] is relatively a new non-steroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthesis via relatively selective inhibition of cyclo-oxygenase-2 (COX-2), imparting analgesic, antipyretic and anti-inflammatory properties (Engelhardt *et al*., 1995). Meloxicam is a zwitterion in the pH range 1 to 4 and an anion above pH 4 (Luger *et al.,* 1996; Albengres *et al.,* 1993). It is available in > 90 countries worldwide (Frank Degner *et al*., 2000).

Meloxicam is practically insoluble in water, leading to poor dissolution, variations in bioavailability, and gastric irritation on oral administration. A number of workers tried to improve solubility and dissolution rate of meloxicam by using various techniques.

In one study, three meloxicam-ethanolamine salts were prepared and their in vitro dissolution profiles were examined at pH 1.2 and 6.8. The pharmacokinetic profiles of meloxicam following an oral administration of meloxicam or its ethanolamine salts were also evaluated in rats (Han and Choi 2007). The dissolution rates of meloxicam and its ethanolamine salts were similarly slow at pH 1.2, however, at pH 6.8, ethanolamine salt formation significantly enhanced the dissolution rate of meloxicam. Meloxicam

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diethanolamine salt exhibited the highest dissolution rate at pH 6.8. The faster dissolution of meloxicam via ethanolamine salt formation at pH 6.8 appeared to be correlated well with more rapid absorption of meloxicam in rats. T_{max} of meloxicam was significantly ($p<0.05$) shortened following an oral administration of ethanolamine salts. Furthermore, ethanolamine salts exhibited a trend toward the increase in AUC (0-4) (initial exposure), while the overall exposure (AUC(0-24)) was similar between meloxicam and its salts. It was concluded that the ethanolamine salts of meloxicam, particularly diethanolamine salt of meloxicam, facilitated the rapid absorption of meloxicam while maintaining the prolonged exposure and may be used for the earlier onset of action for meloxicam.

In the attempt to reduce its gastric side effect and to increase aqueous solubility, physical mixture and solid dispersion of the meloxicam were prepared with polyethylene glycol 6000 (Vijava Kumar and Mishra, 2006). The results indicated that both physical mixture and solid dispersion possess better analgesic and anti-inflammatory properties with less ulcerogenic potential when compared with pure meloxicam.

In another study, the solid binary systems were prepared at various drug concentrations (5-40%) with polyethylene glycol 6000 by different techniques (physical mixing, solvent evaporation) (Vijava Kumar and Mishra 2006). The formulations were characterized by solubility studies, differential scanning calorimetry, fourier transform infrared spectroscopy and in vitro dissolution rate studies. The solid dispersions of the drug demonstrated higher drug dissolution rates than physical mixtures and pure meloxicam, as a result of increased wettability and dispersibility of drug in a solid dispersion system. In order to modulate the gastric side effect of meloxicam and to increase its aqueous solubility, physical mixture and solid dispersion of the drug were prepared with skimmed milk (Mishra and Vijava, 2006).The analgesic, anti-inflammatory and ulcerogenic effects were assessed for physical mixture and solid dispersion in comparison to pure meloxicam. The results indicated that solid dispersion possess better analgesic and anti-inflammatory properties with less ulcerogenic potential as compared to pure meloxicam. In another study, when physical mixture and solid dispersions with skimmed milk were prepared and investigated (Vijava Kumar and Mishra 2006), results showed that the solubility of solid dispersion of the drug was almost three times greater than the pure drug. Similarly, the solid dispersion of the drug indicated a significant improvement in the dissolution of the drug as compared to the physical mixture and the pure drug. When physicochemical characterization of meloxicam-mannitol binary systems were studied by using mannitol as a carrier in different ratios, in physical mixtures and melted forms (Nassab *et al.*, 2006). The results showed that the amount of mannitol and the particle size of meloxicam were important factors in the rate of dissolution. To the perfect dissolution of meloxicam, the melt technology was used which resulted in mixed crystals. It was found that the interaction (adhesion) between mannitol and meloxicam for physical mixtures was not enough to the perfect dissolution. A multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate (Florite RE) and sodium alginate, for time and site specific drug release of meloxicam (Sharma and Pawar 2006). Meloxicam was adsorbed on the Florite RE (FLR) by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR powder was used to prepare calcium alginate beads by ionotropic gelation method, using 3(2) factorial design. Developed formulations were evaluated for yield, entrapment efficiency, image analysis, surface topography, mechanical strength, apparent density, buoyancy studies and dissolution studies. Formulations show a lag period ranging from 1.9 to 7.8 h in acidic medium followed by rapid release of meloxicam in simulated intestinal fluid USP, without enzymes (SIF). Complete drug release in SIF occurred in less than 1h from the formulations.

Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polyvinylpyrrolidone K-30 has also reported in the literature (El-Badry and Fathy 2006). The results were primarily due to increase wettability, the solubilization of the drug by the carrier, and formation of meloxicam amorphous form. Some workers studied the characteristics of microparticles obtained by adsorption of meloxicam, on a porous silicate carrier Florite RE (FLR) and development of a tablet formulation using these microparticles with improved drug dissolution properties (Sharma et al 2005). The study also revealed the use of FLR as a pharmaceutical excipient. Meloxicam was adsorbed on the FLR in 2 proportions (1:1 and 1:3), by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR microparticles were evaluated for surface topography, thermal analysis, X-ray diffraction properties, infrared spectrum, residual solvent, micromeritic properties, drug content, solubility, and dissolution studies. Dissolution of drug from microparticles containing 1:3, drug:FLR ratio was faster than microparticles containing 1:1, drug:FLR ratio. These microparticles were used for formulating directly compressible tablets. Prepared tablets were compared with a commercial tablet. All the prepared tablets showed acceptable mechanical properties. Disintegration time of prepared tablets was in the range of 18 to 38 seconds, and drug dissolution was much faster in both acidic and basic medium from prepared tablets as compared with commercial tablet. The results suggested that FLR provides a large surface area for drug adsorption and also that a reduction in crystallinity of drug occurs. Increase in surface area and reduction in drug crystallinity result in improved drug dissolution from microparticles. In another work, beta-cyclodextrin (beta-CD) as a vehicle, either singly or in blends with lactose (spray-dried or monohydrate), for preparing a meloxicam tablet was evaluated (Ghorab et al 2004). The tablets were prepared by direct compression and wet granulation techniques. The effect of beta-CD on the bioavailability of meloxicam was also investigated in human volunteers using a balanced 2-way crossover study. The powder blends and granules of all formulations showed satisfactory flow properties, compressibility, and drug content. The dissolution rate of meloxicam was significantly enhanced by inclusion of beta-CD in the formulations up to 30%. Another study also showed that dissolution properties of meloxicam-cyclodextrin binary systems were superior when compared to pure meloxicam (Naidu *et al.,* 2004).

Comparative dissolution

Although immediate release solid dosage forms are routinely subjected to tests such as content uniformity, weight, hardness, friability and disintegration, the test that is most often associated with the assessment of *in vivo* performance is the dissolution test.

In vitro dissolution testing provides useful information at several stages of the drug development process. Under certain conditions it can be used as a surrogate for the assessment of Bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of t (time) related to the amount of drug dissolved from the pharmaceutical dosage system. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms. In some cases, that equation can be deduced by a theoretical analysis of the process, for example zero order kinetics. In most cases, with tablets, capsules, coated forms or prolonged release forms that theoretical fundament does not exist and some times a more adequate empirical equations is used. The kind of drug, its polymorphic form, crystalline nature, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetic (Salomon and Doelker, 1980; El-Arini and Leuenberger, 1995). A water-

soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water-soluble drug the self-erosion of the matrix will be the principal release mechanism. To accomplish these studies the cumulative profiles of the dissolved drug are more commonly used in opposition to their differential profiles. To compare dissolution profiles between two drug products model dependent, statistic analysis and model independent methods can be used (Costa and Lobo, 2001).

Comparative dissolution profiles are used as (Shargel *et al*., 2005).

1) The basis for formulation development of bioequivalent drug products and proceeding to the pivotal *in vivo* bioequivalence study
2) Comparative dissolution profiles are used for demonstrating the equivalence of a change in the formulation of a drug product after the drug product has been approved for marketing and
3) The basis of a bio-waiver of a lower – strength drug product that is dose proportional in active and inactive ingredients to the higher – strength drug product.

Moore and Flanner (1996) developed a simple model independent approach using a similarity factor (f_2) and a difference factor (f_1) to compare dissolution profiles. These new 'fit factors' directly compare the difference between the percent drug dissolved per unit time for a test and a reference formulation. Fit factors were adopted by FDA Center for Drug Evaluation and Research (CDER) and the similarity factor was also adopted by the European Medicines Evaluation Agency (EMEA) Committee for Proprietary Medicinal Products (CPMP) as an assessment criterion of similarity between two *in-vitro* dissolution profiles (CPMP, 1999, FDA, 1997). The difference factor (f_1) calculates the percent difference between the two curves at each time point and is a measure of the relative error between the two curves,

$$f_1 = \left[\frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right] x100$$

Where n is the number of time points, R_t is the dissolution value of the reference formulation at time t and T_t is the dissolution value of the test formulation at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the curves,

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} x100 \right\}$$

For curves to be considered similar, f_1 values should be close to 0 and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100), which means an average difference of no more than 10% at the sample time points (Shah *et al.,* 1998), ensures equivalence of the two curves and thus of the performance of the test and reference products (FDA, 1997).

The present work describes the in vitro evaluation of two brands of meloxicam tablets using a simple model independent approach as proposed by Moore and Flanner (Moore and Flanner, 1996).

EXPERIMENTAL

Material and reagents

Sodium hydroxide was obtained from Merck and meloxicam reference standard was obtained through the courtesy of Hilton Pharma (Pvt.) Ltd., Karachi, Pakistan.

Instruments

Analysis was performed on UV spectrophotometer (Model UV-150-02, Shimadzu, Japan). The dissolution tests were performed by using USP paddle apparatus (Erweka, Gmbh, Germany).

Study products

Meloxicam 7.5 mg tablets (A) was a commercial product which was selected as

Test formulation (batches A-1, A-2 and A-3) while (B) was the innovator product which was selected as Reference formulation (batches B-1, B-2 and B-3)

Dissolution

Extent of dissolution of tablets was determined by the method reported by Hanchu and Xiaobing in 2000 (Hanchu and Xiaobing, 2000) with modification in stirring rate. To the best of our knowledge this was the only method reported in the literature at the time of dissolution studies.

Preparation of standard stock solution

Amount equivalent to 10 mg of meloxicam was weighed accurately using meloxicam standard powder and dissolved in 100 ml 0.01M sodium hydroxide solution to produce a concentration of 100 µg/ml.

Preparation of standard working solution

25 ml of meloxicam standard stock solution (100 µg/ml) was pipette out and completely transferred to a 50 ml volumetric flask and completed to the mark with 0.01 M sodium hydroxide solution to produce a concentration of 50 µg/ml.

Preparation of standard calibration curve

Six volumetric flask (10 ml) was labeled as 0, 5, 10, 15, 20 and 25 µg/ml and to each volumetric flask following amounts of meloxicam working standard solution (50 µg/ml) was added and completed to 10 ml with 0.01 M sodium hydroxide solution. Each volumetric flask was then vortex for five minutes and the contents were measured at 270 nm by spectrophotometer using 0.01 M sodium hydroxide solution as blank.

Conc.(µg/ml)	Vol of Working Std. Sol. (ml)
00.0	0.00
05.0	1.00
10.0	2.00
15.0	3.00
20.00	4.00
25.0	5.00

Calibration curve data and calibration curve parameters for meloxicam in 0.01M sodium hydroxide solution demonstrate that calibration curve was linear in the concentration range from 5 to 25 µg/ml. The correlation coefficient was found to be 0.9999. The calibration plot is given in figure 1.

Dissolution methodology

Dissolution tests were carried out with 3 batches of each of the reference and the test formulation of meloxicam. The dissolution tests were performed at 37^{o}C using USP paddle apparatus with six replicates. The dissolution medium was 500 ml 0.01 M sodium hydroxide maintained at 37^{o}C. The stirring rate was set at 50 rpm. 10 ml of dissolution samples were withdrawn at 5, 15, 30 and 45 minutes and replaced with equal volume of the fresh medium to maintain a constant total volume. Samples were filtered and assayed by UV spectrophotometer at 270 nm wavelengths. Cumulative percentages of the drug released from the dosage forms were calculated. Experimental data were analyzed by using a simple model independent approach as described earlier.

RESULTS

The dissolution behaviour of the drug from test and reference formulations of meloxicam 7.5 mg tablets are presented in table 1 and table 2 respectively, while the release profiles of the both the formulations are shown in figure 2. It was evident that all the products tested showed greater than 80% of the labeled amount of meloxicam dissolved in 30 minutes. A comparison of the cumulative dissolution of both formulations is presented in table 3. For visualization of the difference/ similarity of dissolution patterns of two products the two profiles are shown on the same plane in figure 3.

The (f_1) and (f_2) values were 16.85 and 30.89 respectively, thus they were not within the established limits, that is 0 to 15 for (f_1) and 50 to 100 for (f_2) that ensure similarity of

Table 1
Dissolution behaviour of test formulations of meloxicam 7.5 mg tablets (Batch No.A-1, A-2 and A-3) in 0.01 M sodium hydroxide solution using paddle method at 50 rpm and 37°C (n=6 tablets)

S. No.	Batch No.	Percent drug dissolved at different time intervals (min.)			
		5	15	30	45
1.	A-1	30.72	72.09	84.65	92.20
2.	A-2	34.78	81.15	85.74	93.99
3.	A-3	38.85	78.47	89.08	93.16
Mean		34.78	77.24	86.49	93.12
SD*		4.07	4.65	2.31	0.90

Table 2
Dissolution behaviour of reference formulations of meloxicam 7.5 mg tablets (Batch No.B-1, B-2 and B-3) in 0.01 M sodium hydroxide solution using paddle method at 50 rpm and 37°C (n=6 tablets)

S. No.	Batch No.	Percent drug dissolved at different time intervals (min.)			
		5	15	30	45
1.	B-1	79.16	83.63	90.00	95.22
2.	B-2	86.82	88.95	91.28	93.62
3.	B-3	80.48	83.56	87.35	92.19
Mean		82.15	85.38	89.54	93.68
SD*		4.09	3.09	2.00	1.52

Table 3
Cumulative mean dissolution behaviour of reference (Batch No.B-1, B-2 and B-3) and the test (Batch No.A-1, A-2 and A-3) formulations of meloxicam 7.5 mg tablets in 0.01 M sodium hydroxide solution using paddle method at 50 rpm and 37°C (n=18 tablets)

Time (min)	Extent of percent dissolution			
	Reference Formulation		Test Formulation	
	Mean	SD*	Mean	SD*
5	82.15	4.09	34.78	4.07
15	85.38	3.09	77.24	4.65
30	89.54	2.00	86.49	2.31
45	93.68	1.52	93.12	0.90

*SD = Standard deviation.

pattern or pattern-equivalence of the two profiles.

DISCUSSION

In recent years, drug release/dissolution from solid dosage forms has been the subject of intense and profitable scientific developments. Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. The quantitative analysis of the values obtained in dissolution/release tests is easier

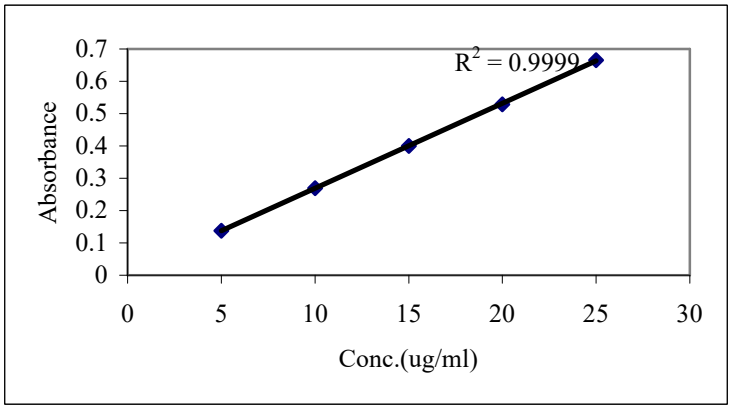

Fig. 1: Calibration plot of meloxicam.

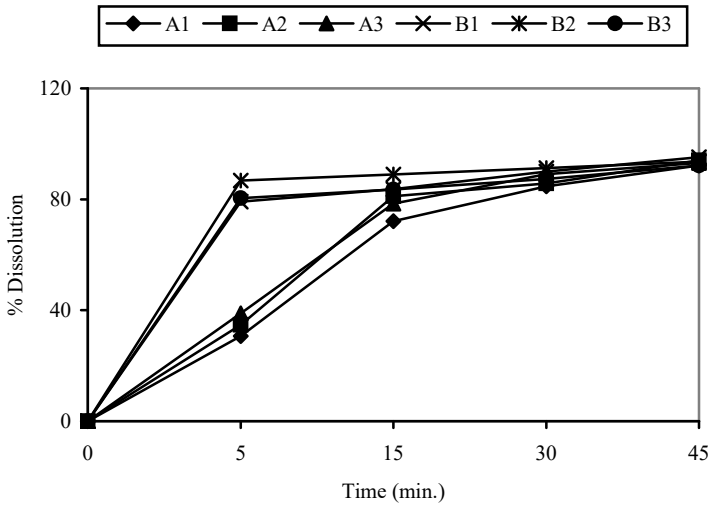

Fig. 2: Mean dissolution profiles of different batches of meloxicam 7.5 mg tablets: B-1, B-2 and B-3 of the reference formulation and A-1, A-2 and A-3 of the test formulation.

when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. The present study was designed to analyze data obtained for dissolution profiles using mathematical methods of analysis described by Moore and Flanner (1996). These authors have described difference factor (f_1) and similarity factor (f_2), which can be used to characterize drug dissolution/release profiles.

Fit factors are essentially a quantitative method, reflecting the differences between corresponding values in the two curves. They do not indicate the sense of the deviation, and yield the same value irrespectively of the test curve being placed below or above the reference (Moore and Flanner, 1996). Thus, they do not directly take into consideration the shape of the curve, and not allow for a variation in the spacing between sampling

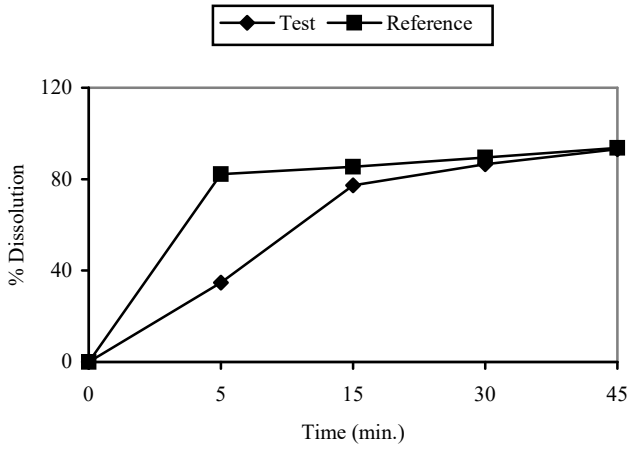

Fig. 3: A comparison of cumulative percent dissolution profiles of the drug from test and reference products.

times (Costa and Lobo, 2001 and Costa, 2001). Also, they do not take into account variability within test and references batches.

Inspite of these limitations fit-factors have been very useful in comparing dissolution curves once they present a great advantage of reducing complexity by providing a single number to describe two curves that consist of several points (Moore and Flanner, 1996). Our results revealed that the two-meloxicam formulations are not equivalent *in vitro*. The conclusion drawn from mathematical analysis could also be very evidently verified by visual examination of the two patterns of cumulative dissolution-extent profiles of the drug from the test and reference products given in figure 3. Thus it is recommended that the same formulations should be subjected to *in vivo* studies in order to find whether a co-relation exists in this case between in vitro dissolution and *in vivo* performance of the products.

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Note for guidance on quality of modified release products: A. Oral dosage forms; B. Trandermal dosage forms; section I (Quality), EMEA Committee for Proprietary Medicinal Products (CPMP), London, UK, 1999.

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