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RESEARCH ARTICLE

Preparation of Meloxicam Tablet Formulations and Evaluation of In Vitro Release Similarities

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Summary

Meloxicam is a nonsteroidal-antinflammatory drug, which inhibits COX-2 enzymes and is practically insoluble in water. Immediate-release meloxicam tablet formulations were prepared by wet granulation method and the dissolution profiles of these formulations were compared with the reference formulation (Mobic® lot no: 009621). The objective of this study was to apply several dissolution profile comparison methods to five different immediate-release meloxicam tablet formulations and to identify the advantages and disadvantages of each method. Methods used to compare the dissolution data were, statistical methods (exploratory data analysis method, repeated measures design multivariate approach (MANOVA) and ANOVA-based methods), model dependent methods (zero order, first order, Hixson-Crowell, Weibull and logistic model) and model independent methods (difference factor (f_1), similarity factor (f_2) and Rescignos indices (ξi)).

Key Words : *Meloxicam, dissolution profile comparison methods.*

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Meloksikam Tablet Formülasyonlarının Hazırlanması ve İn Vitro Çözünme Benzerliklerinin Değerlendirilmesi

Özet

Meloksikam COX-2 enzimlerini inhibe eden ve suda pratik olarak çözünmeyen nonsteroidal antiinflamatuvar bir ilaçtır. Meloksikamın hemen salım sağlayan tablet formülasyonları yaş granülasyon yöntemiyle hazırlandı ve bu formülasyonların çözünme profilleri referans formülasyon (Mobic® lot no 009621) ile karşılaştırıldı. Çalışmanın amacı, beş farklı hemen salım sağlayan meloksikam tablet formülasyonuna farklı çözünme profili karşılaştırma yöntemlerini uygulamak ve herbir yöntemin avantaj ve dezavantajlarını tanımlamaktır. Çözünme verilerinin karşılaştırılmasında kullanılan yöntemler, istatistiksel yöntemler (açıklayıcı veri analizi yöntemi, tekrarlayan ölçümlerde çoklu varyans analizi (MANOVA) ve ANOVA yöntemleri), modele bağımlı yöntemler (Sıfır derece, Birinci derece, Hixson-Crowell, Weibull ve Lojistik yöntem) modelden bağımsız yöntemler (Farklılık faktörü (f_1), Benzerlik faktörü (f_1) ve Rescigno İndisi (ξi)).

Anahtar Kelimeler : *Meloksikam, çözünme profili karşılaştırma yöntemleri*

INTRODUCTION

The evaluation of dissolution profiles is a very important quality parameter for solid oral dosage forms. Dissolution tests can be used as quality control and stability indicating tests during the formulation development stage and can also be used for comparing new or generic formulations with an existing product. They can also provide a basis for achieving an in vitro-in vivo correlation. The Food and Drug Administration (FDA) guidelines advise the use of in vitro dissolution testing to ensure pro-

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duct quality in case of certain scale-up and post approval changes (SUPAC) such as manufacturing site changes, increase or decrease in batch size and small quantitative changes in excipients[1,2].

The simplest way to compare dissolution profiles of test and reference formulations is to check the percentage of the dissolved active compound in the dissolution medium after a certain period of time. For rapidly dissolving drug products, the use of single point comparison of the dissolution profiles may be sufficient[3]. However especially in the case of slowly dissolving or poorly water-soluble drugs, comparison of the multiple time points is recommended by the FDA. Comparison of multiple time points or of complete dissolution profiles is necessarily more complex than with a single point test[1,2]. In the literature, different methods are described for comparing dissolution profiles, such as statistical methods and model-dependent and model-independent methods.

The objective of this study was to evaluate the dissolution profile comparison methods of immediate release meloxicam tablet formulations and to identify advantages and disadvantages of each method[4].

MATERIALS and METHODS

Materials

Meloxicam (Dr. Reddy's Laboratory/India) was selected as a model drug. Mobic®, which is a commercially available immediate-release tablet formulation of meloxicam, was selected as reference tablet formulation (lot no: 009621). Five different test formulations (MX1, MX2, MX3, MX4, MX5) were prepared with wet granulation method. Sodium lauryl sulfate and sodium lauryl sulfate-sodium citrate mixture were used to enhance the solubility instead of sodium citrate alone, which is used in Mobic®. Higher amounts of lactose and microcrystalline cellulose were used in the inner and outer phases of granulation. Aerosil and magnesium stearate were used as lubricants. The labeled amount of the drug substance is 15 mg per tablet for test and reference formulations. All other chemicals and reagents were analytical grades. The dissolution testing of tablets was performed using the USP apparatus 2 (n=12) at a stirring speed of 50 rpm; 900 mL of dissolution medium (pH 7.6 phosphate buffer) at 37±0.5°C was used for each experiment. Dissolution samples were collected at 5, 10, 15, 30, 45, 60 and 90 min for analysis and replaced by an equal volume of fresh dissolution medium.

Methods used to compare dissolution profiles

Statistical Methods

Exploratory data analysis method was evaluated using both graphical and numerical illustration of the test and reference formulation dissolution data. The graphic for each formulation must have the standard error bars at each dissolution time point. As a complement to the graphical summary of the dissolution profile data, data may also be summarized numerically. In the numerical summary statistics, mean and standard deviation of the dissolution data at each dissolution time point for the test and reference formulations can be presented. It is also possible to present the difference between the mean dissolution profiles and a 95% confidence interval for the differences at each dissolution time point[5].

Multivariate approach was applied, and sources of variation, time, drug product and interaction of time and drug product were investigated. In this model, the dissolved percentages were the dependent variable and time the repeated factor[6].

A single group univariate repeated measures analysis was applied. The differences among drug formulations were tested by the comparison of the dissolved percentages at each time point. Then post hoc procedures were applied to determine at what point the differences arose. Dunnett's t-test was also used for the pairwise comparisons as test product against reference product[7]. For statistical methods SPSS 10.0 for Windows was used.

Model Independent Methods

As model independent approaches two fit factors (difference factor (f_1) and similarity factor (f_2)) and Rescigno's indices (ξi) were used to compare the difference between dissolved drug percentage per unit of time for test and reference products. Eq 1 and Eq 2 define the f_1 and f_1 values, where n is the number of sampling times, and R_t and T_t are the individual or mean dissolved percentage at each time point for the reference and test dissolution profiles, respectively. Eq 3 defines ξi, where t_n is the final dissolution time point and ξi (I=1, 2) can be considered as a function of the weighted average of the vertical differences between the test and the reference mean profiles at each time points[5,8,9].

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} x\ 100 \qquad \text{Eq. 1}$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} x\ 100 \right\} \qquad \text{Eq. 2}$$

$$\xi_i = \left[\frac{\int_0^{t_n} |R_t - T_t|^i \, dt}{\int_0^{t_n} |R_t + T_t|^i \, dt} \right]^{1/i} \quad i = 1,2 \qquad \text{Eq. 3}$$

Model Dependent Methods

The model dependent methods are based on different mathematical functions, which describe the dissolution profile. Selection of the suitable function is the first step of the method and evaluation of the dissolution profiles depending on the derived model parameters is the second. The mathematical models (Table 1) first order, Hixson-Crowell, Weibull and logistic models were fitted to individual dissolution data with the non-linear regression module and zero order with linear regression module of Statistica 5.0 for Windows (10,11).

Table 1. Applied mathematical models[11]

Method	Equation
Zero Order	% *Diss* = k.t
First Order	% *Diss* = 100 ($1-e^{-kt}$)
Hixson - Crowell	$\% \textit{Diss} = 100 \left[1 - \left(1 - \frac{k.t}{4.6416} \right)^3 \right]$
Weibull	$\% \textit{Diss} = 100 \left[1 - e^{-(t / T_d)^{\beta}} \right]$
Logistic	$\% \textit{Diss} = 100 \left[\frac{e^{(\alpha + \beta \log t)}}{1 + e^{(\alpha + \beta \log t)}} \right]$

% Diss : Percent dissolved at time t
k : Dissolution rate constant
T_d : Time at which 63.2% of the material is dissolved
α : Scale factor
β : Shape parameter

RESULTS and DISCUSSION

Statistical Methods

Exploratory data analysis method was found to be a useful method to compare dissolution profiles in both graphically and numerically[5]. Figure 1 shows that the dissolution profiles of test and reference formulations were significantly different because there is no overlap in the error bars at each dissolution time point and because the 95% confidence interval for the mean difference at given dissolution time points does not contain zero (Table 2).

Table 2. Summary of statistics for dissolved percentages for test and reference formulations

Time (min)	Formulations	Difference	Standard deviation of the difference	Standard error of the difference	95 % confidence interval for difference	
					LB	UB
5	MX1-REF	26.753	3.353	.968	24.622	28.883
	MX2-REF	21.881	1.350	.390	21.023	22.739
	MX3-REF	22.299	1.342	.388	21.446	23.152
	MX4-REF	17.451	4.325	1.249	14.703	20.199
	MX5-REF	16.715	1.249	.361	15.921	17.509
10	MX1-REF	29.845	2.132	.616	28.490	31.199
	MX2-REF	19.667	1.119	.323	18.956	20.378
	MX3-REF	21.887	1.262	.364	21.085	22.689
	MX4-REF	12.962	5.269	1.521	9.614	16.309
	MX5-REF	4.472	.739	.214	4.002	4.942
15	MX1-REF	19.913	3.406	.983	17.748	22.077
	MX2-REF	14.731	1.086	.314	14.041	15.421
	MX3-REF	10.989	2.289	.661	9.535	12.444
	MX4-REF	1.058	3.795	1.096	-1.354	3.469
	MX5-REF	-2.370	1.374	.397	-3.243	-1.497
30	MX1-REF	-.748	3.792	1.095	-3.157	1.662
	MX2-REF	-2.789	1.529	.442	-3.761	-1.818
	MX3-REF	2.918	1.952	.564	-4.159	-1.678
	MX4-REF	2.389	6.683	1.929	-1.857	6.635
	MX5-REF	-2.173	1.513	.437	-3.134	-1.211
45	MX1-REF	.666	3.045	.879	-1.269	2.601
	MX2-REF	1.325	2.681	.774	-.378	3.028
	MX3-REF	1.138	2.657	.767	-.550	2.827
	MX4-REF	1.458	1.498	.432	.506	2.409
	MX5-REF	1.373	1.391	.401	.489	2.256
60	MX1-REF	.259	3.482	1.005	-1.954	2.472
	MX2-REF	.405	1.876	.542	-.787	1.597
	MX3-REF	.570	1.972	.569	-.683	1.823
	MX4-REF	.356	1.594	.460	-.657	1.369
	MX5-REF	.471	1.521	.439	-.96	1.437
90	MX1-REF	.577	3.015	.870	-1.339	2.492
	MX2-REF	.253	.911	.263	-.326	.831
	MX3-REF	.434	1.875	.541	-.757	1.626
	MX4-REF	.175	.941	.272	-.423	.773
	MX5-REF	.307	1.488	.429	-.638	1.252

LB: lower bound, UP: upper bound

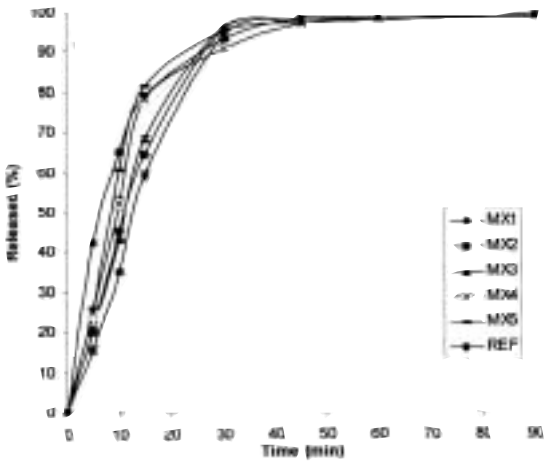

Fig. 1. Mean dissolution profiles for test and reference formulations (error bars represent standard errors at each dissolution time point).

According to the results of the multivariate approach (MANOVA) (Table 3), the dissolved percentages were found to be significantly different at each time point ($p<0.05$); time and drug product interaction was also found to be significantly different ($p<0.05$) between test and reference formulations.

Table 3. Multivariate test results

Effect	Statistics	Value	F	Sig
Time	Pillai's Trace	1.000	57000.078	0.000
	Wilks' Lambda	0.000	57000.078	0.000
	Hotelling's Trace	6650.009	57000.078	0.000
	Roy's Largest Root	6650.009	57000.078	0.000
Time	Pillai's Trace	2.949	13.151	0.000
X	Wilks' Lambda	0.000	45.190	0.000
Formulation	Hotelling's Trace	68.553	114.385	0.000
	Roy's Largest Root	52.325	478.400	0.000

The results of univariate ANOVA showed that the drug products were significantly different in terms of dissolved percentages at each time point ($p<0.05$). The effect of time-drug product interaction was also investigated and the dissolution profiles were not parallel ($p<0.05$). As for post hoc procedures, the results of pairwise comparisons of test products against the reference product by Dunnett's t-test are given in Table 4. It was found that the percents dissolved of all the test and reference formulations were significantly different until time point 15 ($p<0.05$) and that the dissolution profiles were parallel at the time points after 30 min ($p<0.05$).

Model Independent Methods

The values of f_1 and f_2 factors and ξi for test products versus reference were calculated from the means of dissolved percentages at each time point using Eq. 1, 2 and 3 and are listed in Tables 5, 6 and 7. f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure the equivalence of the dissolution profiles. Since f_2 is sensitive to the measurements obtained after each formulation has dissolved more than 85%, limiting to no more than one sampling time point after 85% dissolution is a useful recommendation[9]. When these two fit factors were employed in data treatment, it became apparent that the selection and determination of the dissolution end points play a critical role in the calculation of the values.

The indices ξi (i=1, 2) lie between zero and one. Values of xi (i=1, 2) close to zero indicate similarity between mean dissolution profiles.

Table 5. Similarity factors (f_2) for reference versus test product

Last point for dissolution (min)	f_2 values				
	MX1	MX2	MX3	MX4	MX5
15	32.488	32.488	39.007	48.075	52.803
30	34.902	41.486	41.336	50.346	55.026
45	36.874	43.438	43.293	52.256	56.907
60	36.874	43.436	43.290	52.253	56.899
90	36.872	43.436	43.288	52.252	56.896

Table 6. Difference factors (f_1) for reference versus test product

Last point for dissolution (min)	f_2 values				
	MX1	MX2	MX3	MX4	MX5
15	41.03	30.18	29.59	16.88	12.63
30	27.63	21.13	20.78	12.11	9.20
45	20.61	15.97	15.67	9.34	7.17
60	16.40	12.76	12.55	7.48	5.79
90	13.68	10.60	10.46	6.23	4.84

Table 4. Multiple comparisons of test product against reference product by Dunnett's test

TIME (min)	Formulations (I)	Difference (I-J) (J)	SE	Sig	95% CI LB	UB	
0	MX1	REF	.000	.000	1.000		
	MX2	REF	.000	.000	1.000		
	MX3	REF	.000	.000	1.000		
	MX4	REF	.000	.000	1.000		
	MX5	REF	.000	.000	1.000		
5	MX1	REF	-26.753	1.103	.000	-29.593	-23.912
	MX2	REF	-21.881	1.103	.000	-24.721	-19.041
	MX3	REF	-22.299	1.103	.000	-25.139	-19.459
	MX4	REF	-17.451	1.103	.000	-20.291	-14.611
	MX5	REF	-16.715	1.103	.000	-19.555	-13.875
10	MX1	REF	-29.845	1.096	.000	-32.669	-27.022
	MX2	REF	-19.667	1.096	.000	-22.490	-16.843
	MX3	REF	-21.887	1.096	.000	-24.710	-19.063
	MX4	REF	-12.962	1.096	.000	-15.785	-10.138
	MX5	REF	-4.472	1.096	.001	-7.295	-1.648
15	MX1	REF	-19.913	1.044	.000	-22.602	-17.224
	MX2	REF	-14.731	1.044	.000	-17.420	-12.042
	MX3	REF	-10.989	1.044	.000	-13.678	-8.300
	MX4	REF	-1.058	1.044	.766	-3.747	1.632
	MX5	REF	2.3700	1.044	.102	-.319	5.059
30	MX1	REF	.748	1.191	.955	-2.319	3.814
	MX2	REF	2.789	1.191	.087	-.278	5.856
	MX3	REF	2.918	1.191	.067	-.148	5.985
	MX4	REF	-2.389	1.191	.177	-5.456	.678
	MX5	REF	2.173	1.191	.250	-.894	5.239
45	MX1	REF	-.666	.739	.836	-2.570	1.238
	MX2	REF	-1.325	.739	.265	-3.229	.579
	MX3	REF	-1.138	.739	.403	-3.042	.765
	MX4	REF	-1.458	.739	.189	-3.361	.446
	MX5	REF	-1.373	.739	.236	-3.276	.531
60	MX1	REF	-.259	.719	.996	-2.111	1.593
	MX2	REF	-.405	.719	.971	-2.257	1.447
	MX3	REF	-.570	.719	.893	-2.422	1.282
	MX4	REF	-.356	.719	.983	-2.208	1.496
	MX5	REF	-.471	.719	.947	-2.323	1.381
90	MX1	REF	-.577	.638	.834	-2.221	1.068
	MX2	REF	-.253	.638	.994	-1.897	1.392
	MX3	REF	-.434	.638	.939	-2.079	1.210
	MX4	REF	-.175	.638	.999	-1.820	1.47
	MX5	REF	-.307	.638	.985	-1.951	1.338

LB: lower bound, UP: upper bound

Table 7. Rescigno's indices (ξ_i) for reference versus test product

Last point for dissolution (min)	ξ_I values				
	MX1	MX2	MX3	MX4	MX5
15	0.65	0.55	0.53	0.36	0.24
30	0.45	0.37	0.36	0.29	0.15
45	0.37	0.31	0.30	0.25	0.14
60	032	0.27	0.26	0.22	0.13
90	0.28	0.24	0.23	0.20	0.12

The dissolution profile of MX5 was found to be similar to that of the reference for all of the last five time points for dissolution (15, 30, 45, 60 and 90 min). The dissolution profile of MX4 was found to be different for the dissolution up to 15 min (f_2=48.075), whereas it was similar up to 30, 45, 60 and 90 min (f_2=50.346, 52.256, 52.253 and 52.252, respectively).

MX1, MX2 and MX3 formulations were found to be different up to all of the dissolution time points. According to the results of ξi (i=1, 2) MX4 and MX5 formulations were found to be similar to the reference formulation (ξi values closer to zero).

Model Dependent Methods

Mathematical models have been used extensively for the parametric representation of dissolution data. The dissolution data were fitted to these models and the model which best fit the dissolution data of reference and test products was selected according to the following criteria: higher determination coefficient, smaller residual mean square and smaller absolute difference between each fitted and actual percent dissolved. Considering these criteria, Weibull distribution was found to be the best model.

The derived model parameters, Td (time parameter) and β (shape factor), were compared as test product against reference using multivariate confidence region procedure. The similarity region, multivariate statistical distance (MSD) and 90% confidence region were calculated. The upper limit of the confidence interval is higher than the MSD values that, the test formulations are considered to be different from the reference (Table 9)[2].

Table 9. Comparison of the derived model parameters by multivariate confidence region procedure

Formulations	MSD	Similarity Limit	90% Confidence Interval of MSD	
			LB	UB
MX1-REF	2.871	0.531	1.966	3.774
MX2-REF	1.79	0.472	0.886	2.694
MX3-REF	1.867	0.537	0.963	2.771
MX4-REF	1.888	0.864	0.983	2.792
MX5-REF	0.391	0.417	-0.513	1.295

CONCLUSION

Dissolution testing is used as a quality control procedure in formulation development to assist in selection of a candidate formulation and in research to detect the influence of critical manufacturing variables such as excipient type, mixing effect and binder effect. In spite of the need to compare dissolution profiles, current methods to compare dissolution profiles are not yet well developed. The methods used in this study to compare the dissolution profiles of test and reference formulations were useful but gave different results regarding the similarity of dissolution profiles. According to the results of statistical test methods and model dependent methods, all test formulations were found to be different from the reference formulation while MX4 and MX5 formulations were found similar to the reference using the model independent methods.

Although statistical methods and model dependent methods are more discriminative and provide detailed information about dissolution data, model independent methods have been recommended in the FDA's guidelines and are easy to compute. On the other hand, the most important problem of the model independent method is the selection of the dissolution sample times and their use in profile simila-

Table 8. Parameters of the mathematical models and descriptive statistics of regression for the dissolution data

		REF	MX1	MX2	MX3	MX4	MX5
	r^2	0.552	0.684	0.655	0.643	0.604	0.557
	k	0.840	1.082	1.018	1.016	0.815	0.876
Zero	SE	0.78	0.76	0.76	0.78	0.097	0.089
Order	R_{max}	71.75	70.31	67.98	67.82	78.75	66.88
	RMS	500.63	473.30	477.58	499.84	774.26	644.71
	r^2	0.997	0.967	0.983	0.978	0.975	0.981
	k	0.105	0.058	0.067	0.067	0.079	0.09
First	SE	0.001	0.002	0.001	0.002	0.002	0.002
Order	R_{max}	4.46	20.291	11.89	12.504	21.683	16.031
	RMS	6.179	48.38	22.7	29.83	31.41	23.688
	r^2	0.8228	0.972	0.972	0.966	0.92	0.885
	k	0.079	0.071	0.074	0.074	0.076	0.078
Hixson-SE	0.002	0.001	0.001	0.001	0.001	0.001	
Crowell	R_{max}	23.73	18.72	12.5	16.52	24.03	23.71
	RMS	193.97	34.09	37.72	49.91	102.32	145.68
	r^2	0.695	0.865	0.851	0.840	0.795	0.7421
	k	13.65	12.71	12.99	13.01	13.21	13.46
Higuchi	SE	0.332	0.25	0.25	0.26	0.29	0.32
	R_{max}	31.70	33.14	27.34	27.93	36.85	32.1
	RMS	334.35	197.23	202.18	219.42	260.22	325.28
	r^2	0.999	0.994	0.998	0.9967	0.982	0.996
	Td	9.48	16.21	14.36	14.02	12.13	10.68
Weibull	SE	0.062	0.194	0.117	0.12	0.301	0.095
	b	0.91	0.609	1.41	1.52	1.35	1.54
	SE	0.011	0.043	0.025	0.03	0.088	0.03
	R_{max}	3.75	10.44	4.36	5.87	18.88	6.27
	RMS	1.55	8.58	3.24	4.41	22.31	5.32
	R^2	0.99	0.984	0.988	0.988	0.972	0.996
	α	-2.93	-6.13	-5.05	-5.33	-4.49	-4.72
Logistic	SE	0.062	0.21	0.136	0.147	0.551	0.402
	β	3.66	5.6	4.93	5.2	4.72	5.19
	SE	0.641	0.188	0.126	0.138	0.535	0.41
	R_{max}	4.07	13.2	8.27	7.0	20.91	4.84
	RMS	3.38	14.92	9.33	9.42	17.63	2.13

rity calculations and this needs further investigation. Finally, all of these methods can be used as a very important tool in quality control studies[11-14].

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