DISSOLUTION PROFILE COMPARISON: MODEL DEPENDENT AND MODEL INDEPENDENT APPROACHES

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ABSTRACT

Similarity in Dissolution behavior of drugs has long been sought from the percpective of both bioavailability and quality control considrations. The objective of this study was to apply several profile comparison to dissolution data of three different batches of Indomethacin (SR) which two of them were German products as the refernce batches. Dissolution was performed using the United States Pharmacopiea (USP) monograph method on tablets and capsules. Two general approaches to compare dissolution profiles were examined: Model-independent approaches and Model-dependent approaches. The model-independent methods included dissolution efficiency (DE) and the fit factors (F_1 and F_2). The model-dependent approaches included Weibull and Exponential models. It is concluded that according to the fit factors and model-dependend approaches, the dissolution of test batches are significantly different with one of the reference batches and is almost similar to the other one.

KEYWORDS

Dissolution profile comparison , Indomethacin,Model dependent , Model independent.

INTRODUCTION

Indomethacin is a non steroidal, anti-inflammatory drug with anti-pyretic and analgesic properties. It has been used effectively in the treat ment of moderate to sever rheumatoid arthritis, ankylosing spondylitis, osteora thritis, bura sitis and in patent ductus arteriosus[1]. Indocid ® was first released in 1982 as an extended release preparation of Indomethacin with the advantage of once or twice a day dosing[2]. The USP, stated that the dissolution behaviour of oral solid dosage froms had been shown to be a useful criterion for controlling the formulation and process variables which can influence the bioavailability of the drug of the particular dosage from. In 1985 it was suggested the equivalence in dissolution behavior was sought in light of both bioavailability and quality control[3]. In this study, dissolution profiles of drugs are compared by several model-dependendent and model-independeut methods. Model-independent approaches such as (a) ANOVA approaches (b) the difference factor and the fit factors, F_1 and F_2 and (c) the two indices of Rescigno (δ_1 and δ_2).

In addition, some model dependent approsches are used including zero-order, First order, crowell, Higuchi, quadratic, Weibull and Exponential models. Where as model-independent approaches,

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make no assumption regarding the shape of the dissolution curve, the model-dependent methods involve the use of definit equations in which parameters defining the curve's shape, are optimised.

EXPERIMENTALS

1. Materials

Amuno Retard and Indomet- Ratio pham 75mg capsules (German products) were obtained commertially as the reference batches. Three batches of Indomethacin 75mg tablets. (Aria pharma ceuticals, Iran) were used to perform dissolutin tests, as the test products. (Batch No: 7907044, 7911071, 7911070)

2. Methods

2.1. Dissolution media:

All dissolution studies were carried out in a phosphate buffer medium by dissolving 27.22 gr KH_2PO_4 in 1000 mL water and adjusting to the pH=6.2 using sodium hydroxide.

2.2. Dissolution studies

The dissolution studies were performed on nine tablets of each batch using the USP monograph method. Using the rotating basket (USP Apparatus 1). The temperature of the dissolution medium was maintained at $37^{o}C \pm 0.5$ and the agitation rate was 75 rpm. Samples of 3.0 ml were removed from the dissolution medium at , 1, 2, 4, 12 h. The absorbance of all samples were measured at 318 nm and concentration of Indomethacin calculated by reference to a linear calibration line (Table 1).

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Table .1

Dissolution (% Released) for Indomethacin (SR) test and reference batches.

Tablet	Time	Batch 44	Batch 71	Batch 70	Indomet	Amuno
1	1	19.44	21.87	8.19	36.23	17.01
	2	30.13	30.76	24.48	41.68	28.36
	4	44.51	43.1	40.45	52.63	45.03
	12	66.66	62.71	61.65	68.24	68.38
2	1	20.1	23.69	14.53	37.29	16.16
	2	31.61	34.56	26.19	44.83	26.21
	4	45.88	51.19	37.17	52.96	42.34
	12	74.49	71.15	61.65	65.63	65.11
3	1	22.77	26.77	17.28	34.33	16.03
	2	35.14	36.58	29.13	42.61	26.59
	4	49.61	50.13	40.52	50.87	42.86
	12	70.78	69.71	67.75	63.66	65.49
4	1	21.87	22.52	19.64	37.61	16.43
	2	34.29	33.19	31.55	45.16	26.99
	4	45.88	47.85	43.12	51.39	41.74
	12	72.26	67.16	68.53	62.54	63.06
5	1	21.80	13.95	14.83		
	2	34.11	25.78	27.53		
	4	48.96	42.75	38.71		
	12	70.56	66.24	66.37		
6	1	31.03	16.17	14.66		
	2	38.61	27.04	26.81		
	4	51.84	41.05	39.63		
	12	71.01	61.97	65.73		
7	1	33.71	15.32	17.41		
	2	46.8	28.87	30.12		
	4	59.04	39.86	40.32		
	12	81.63	65.83	68.97		
8	1	28.53	17.87	15.85		
	2	40.65	30.31	28.49		
	4	52.96	41.07	40.32		
	12	74.16	66.37	68.97		
9	1	26.71	23.44	13.36		
	2	39.6	35.21	25.47		
	4	52.36	49.61	37.75		
	12	73.36	69.50	63.33		

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2.3. Statistical methods

Fit factors: Fit Factors or similarity indices were introduced by moor and Flanner[4] in 1996 and are defined as follows.

$$F_2 = 50.\log\{[1+\frac{1}{n}\times\sum(R_t - T_t)^2]^{-0.5}\times 100\}$$

Where R_t is the percentage of dissolved product for a reference batch. at the time point t.
T_t is the percentage of dissolved product for the test batch. n is the number of time points and wt is the waight factor.
The factor F_1 is the average % difference over all time points in the amount of test batch dissolved as compared to the reference batch.

$$F_1 = \{[\sum_{t=1}^{n}| R_t - T_t |]/[\sum R_t]\}\times 100$$

The F_1 value is zero when the test and reference profils are identical and increases proportionally with the dissimilarity between the two profiles. The F_2 value is between 0 and 100. The value is 100 when thetest and the reference profiles are identical and approaches zero as the dissimilarity increases. The F_1 limit of so is recommended as a criterion of equivalence and it is 10 for F_1[5].

Dissolution efficiency : This concept was proposed by khan and Rhodes[6] and is defined as follows:

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100}\times(t_2 - t_1)}\times 100$$

where y is the percentage of dissolved product. DE is then the area under the dissolution curve between time points t_1 and t_2 expressed as a precentage of the curve maximum dissolution. y_{100} over the same period.
3.3. Model dependent approaches:
some models result in the comparison between two dissolution curves being represented by a single number. whereas most model dependent approaches result in each curve being repenresented as two or more emperical parameters.
weibull function is described as follows:

$$x/100 = 1 - e^{-\alpha\times t^{\beta}}$$

where $x_{(t)}$ = percent dissolved with respect to time t.
α = Scale factor corres pondingto the apparent rate constant .
β = Shape factor
For convenience, the linearized form of weibull function:

$$\ln(-\ln(1-m))=\ln\alpha+\beta\ln t$$

was fitted to the individual unit dissolution data to generate the parameters.
The other model used was Enponential with the function

$$x/100 = 1 - e^{-\alpha(t)}$$

that X is the percent dissolveel with respect to time t. The parameter α was calculated for all of the batches after fitting the dissoution data in to model[7.]

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Using one-way ANOVA (α=0.05) statistically significant differences were found.

RESULTS

1. Analysis of data using F1 and F2:

For each test batch the F_1 and F_2 values were calculated two times. One with the Amuno Retard as the reference batch and the other with theIndomet-Ratio pharm as the refference batch. So the test batches were compared with both reference bathces by the means of F_1 (Table 2) and F_2 approach (Table 3).

Table .2

Fit factor (F1) between test batches and references Amuno and Indomet

	Amuno			Indomet		
Tablet	**Batch 44**	**Batch 71**	**Batch 70**	**Batch 44**	**Batch 71**	**Batch 70**
1	9.16	11.38	10.52	20.79	18.57	32.29
2	16.86	22.64	5.23	23.01	16.76	28.26
3	21.10	24.41	5.04	15.99	12.85	25.02
4	18.37	15.94	10.50	19.58	16.17	21.70
5	19.13	6.046	2.28	17.25	26.54	27.33
6	30.72	4.42	2.38	11.17	24.82	27.00
7	50.20	3.26	8.08	16.43	25.51	24.84
8	33.31	6.10	5.09	13.6	22.81	26.82
9	30.41	20.73	4.98	14.37	14.96	28.08

Table .3

Similarity factor (F2) between test batches and references Amuno and Indomet

	Amuno			Indomet		
Tablet	**Batch 44**	**Batch 71**	**Batch 70**	**Batch 44**	**Batch 71**	**Batch 70**
1	70.11	67.7	66.27	46.46	48.35	36.92
2	58.86	52.71	80.38	45.75	51.75	40.05
3	54.42	51.13	83.01	51.61	56.97	43.49
4	58.10	59.07	69.54	49.30	51.23	46.73
5	56.37	77.40	92.92	50.24	40.74	41.10
6	46.24	80.52	91.35	61.46	42.25	40.96
7	36.52	88.89	73.61	49.05	42.27	44.00
8	45.13	78.43	81.22	56.80	44.89	42.18
9	46.99	54.49	82.09	55.71	52.83	39.38

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2. Analysis of data using D.E.

Dissolution efficiency data for each test batch and both reference batches are presented in Table 4.

Table .4

Dissolution efficiency (DE) of the test and reference batches

Tablet	Batch 44	Batch 71	Batch 70	Indomet	Amuno
1	46.15	44.51	43.28	52.91	46.52
2	49.57	51.33	40.52	52.65	43.96
3	50.55	50.93	44.54	50.60	44.35
4	49.31	48.35	46.34	51.04	43.16
5	50.00	44.27	42.92		
6	52.68	42.49	42.98		
7	60.47	43.43	45.94		
8	54.24	44.77	44.67		
9	53.82	50.19	41.13		

3. Analysis of data using Model dependent approaches

The dissolution data for each batch was Fitted to the Functions of weibull and exponential models and the function parameters, (α and β for weibull and α for exponential) were determined. and presented in Table 5-6.

Table .5

Weibull model parameters (α & β)

Tablet	Batch 44		Batch 71		Batch 70		Indomet		Amuno	
	α	β	α	β	α	β	α	β	α	β
1	0.21	0.69	0.25	0.55	0.10	1.07	0.44	0.31	0.19	0.72
2	0.22	0.72	0.27	0.62	0.16	0.71	0.46	0.31	0.17	0.71
3	0.27	0.63	0.31	0.54	0.19	0.70	0.41	0.35	0.17	0.71
4	0.25	0.65	0.26	0.59	0.22	0.66	0.47	0.29	0.18	0.67
5	0.26	0.64	0.16	0.79	0.17	0.75				
6	0.36	0.49	0.18	0.68	0.17	0.75				
7	0.41	0.56	0.18	0.73	0.20	0.72				
8	0.34	0.55	0.20	0.67	0.18	0.75				
9	0.32	0.57	0.27	0.59	0.15	0.76				

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Table .6
Exponential model (α) factor

Tablet	Batch 44	Batch 71	Batch 70	Indomet	Amuno
1	-0.07	-0.06	-0.09	-0.06	-0.08
2	-0.10	-0.08	-0.06	-0.05	-0.07
3	-0.08	-0.07	-0.08	-0.05	-0.08
4	-0.09	-0.07	-0.08	-0.04	-0.7
5	-0.08	-0.08	-0.08		
6	-0.07	-0.06	-0.07		
7	-0.11	-0.07	-0.08		
8	-0.08	-0.07	-0.08		
9	-0.08	-0.07	-0.07		

DISCUSSION

1. Results using F1 and F2

For the three test batches were compared with Indomet - Ratio pharm all of the F_1 values exept for the batch 44 were above 10. Therefore one would conclude that the dissolution profiles were not similar and the same result was obtained for F_2 values, all were less than 50 and 50 the dissolution profiles of all test batches exept batch 44 are dissimilar with the reference for the batch Amuno Retard dissimilarity according to F_1 and F_2 values was found only for batches G1 and 44.

2. Results using DE

The dissolution efficiency of almost all batches were similar to Amuno-Retard and Indomet exept batch 70.

3. Results using weibull model

According to weibull function all the batches are different with the reference batch. Indomet in the shape (β) and scale (α) parameters and they are almost all similar to the reference Amuno-Ratio pharm in parameters exept α parameter for batch 44.

4. Results using Exponetial model

Accorching to α parameters of this model, none of the batches are different with AmunoRetard and Indomet.

CONCLUSION

It is concluded that according to the fit factors and model dependend approaches, the dissolution of test batches are significantly different with one of the reference batches and is almost similar to the other one.

ACKNOWLEDGEMENTS

Financial support to this study was provided by Mazandaran University of Medical Sciences.

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