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COMPARATIVE EVALUATION OF SOME COMMERCIALLY AVAILABLE BRANDS OF RIFAMPACIN TABLETS

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Abstract: The objective of this study was to evaluate some commercially available brands of Rifampacin Tablets. In *in- vitro* release studies of physical parameters of tablet i.e. disintegration, dissolution rate, crushing strength, thickness and diameter, uniformity of weight and assay of the active ingredients of four brands of commercially available Rifampacin tablet i.e. A, B, C & D were performed. For this purpose, Dissolution rate was studied in phosphate buffer at pH 6.0, 6.5 and 7.4 using USP rotating basket at 100 rpm. The data was analyzed by Cube-Root law and calculated dissolution rate constant predicting *in vitro* behavior of the drug released from these preparations. In this particular case two types of dissolution mechanisms were founded; in first 20 minutes, the fast release phase and after 20 minutes the slow release phase. According to the degree of dissolution of D and B proved to be the best of the available commercial brands.

Key Words*:* Rifampacin, disintegration, dissolution rate, analysis, weight variation.

Introduction

In-vitro tests of tablet are performed **(a)** For research: to elucidate the mechanism involved in disintegration and dissolution process when a tablet or capsule is exposed to a fluid under suitable conditions in-vitro or in-vivo after oral administration **(b)** For development purpose: to guide the pharmaceutical formulator in the preparation of optimum dosage form of drug for clinical trial **(c)** For quality control purpose: to ensure that a given tablet (or capsule) dosage form is essentially uniform as regard to their thickness, diameter, hardness, weight variation, disintegration, dissolution, and percentage purity of the active ingredients from lot to lot **(d)** For predictive purpose: as an in-vitro test is most acceptable representative evaluation of in-vivo performance of a dosage form and has replaced a series of in-vivo clinical testing of the products (Wagner, 1971). Many investigators (Yirtalo *et al*., 1975) have considered it as having a biological significance because these in-vitro tests stimulate the process going in GIT and hence these tests predict about bioavailability of the drug in the body. In in-vitro study, dissolution is an important tool in the evaluation of the best formulation and also in the understanding of possible risks related to specific GI environment, dose dumping, food effects on bioavailability and interaction with other drugs (Sungthongjeen, *et al*., 1999).

According to the Morrison and Campbell (Wagner, 1971) in-vitro tests can be used to explain the difference in the results which may predict what will happen with next drug administered in the same dosage form. Today dissolution studies are the most frequently used tools in the development, characterization and utilization processes of controlled release formulations (Rouf *et al*., 2008).

Tuberculosis (T.B.) is an infection largely due to *Mycobacterium Tuberculosis* belonging to the class mycobacterium. It is present worldwide

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with an extremely high prevalence in Asian countries where 60-80% of children below than age of 14 years are infected. Tuberculosis is spread predominantly by droplet infection. The prevalence of Tuberculosis increases with poor social conditions, inadequate nutrition and over crowding (Edward and Boucher, 1995).

Rifampacin is one of the drugs of choice for the treatment of tuberculosis which acts by binding to and inhibiting DNA dependant RNA polymerase in prokaryotic but not eukaryotic cell, by binding to the guanine residues in DNA and blocks the movement of RNA polymers thus preventing transcription and consequently inhibiting protein synthesis. Human RNA polymerase is not affected (Rang *et al*., 1999).

Materials

Rifampacin Powder donated by Schozoo laboratories Lahore, Sodium hydroxide and Sodium dihydrogen Phosphate were supplied by E. Merck and Distilled water used was obtained from an all glass electrically heated still and stored in 5 liters well leached and stoppered bottle, pH 5.8 ± 0.1 as determined by Corning pH meter and surface tension 72 ± 0.2 mN/m at 20ºC.

The Erweka Hardness Tester and Disintegration Test Apparatus supplied by Erweka apparatus Gmbh Heusentamm Germany, which was manufactured under specification (B.P.2002). UV-Spectrophotometer Agilent 2005 was used for the analysis of the sample taken using software Version-2005, courtesy Agilent, Germany. Dissolution apparatus was six vessels dissolution tester tube II based on U.S.P XIX rotating paddle method. Four brands of commercially available Rifampacin tablet (450mg) i.e. A,B,C and D were purchased from the local medicine market (table 1).

Table 1: Technical data of four brands of Rifampacin tablets of 450 mg.

Brand's Name (450mg)	Batch No.	% Friability	Uniformity of weight(mg)	Crushing strength (kg)	Disintegration time (min)	Assay (%)
A	008	0.22±0.12	0.830±1.60	80.00	7.00	101.00
B	126	0.20±0.03	0.568±0.22	82.50	7.50	102.00
C	002	0.25±0.04	0.906±1.30	115.00	7.30	99.60
D	4555 X 5	0.31±0.02	0.540±0.42	62.50	8.00	101.40

Table 2: Comparison of %age dissolved of four brands of Rifampacin tablets at pH (6.0, 6.5 and 7.4)

Brands	A			B			C			D		
Time (minutes)	pH			pH			pH			pH		
	6	6.5	7.4	6	6.5	7.4	6	6.5	7.4	6	6.5	7.4
5	15	14.8	15	19.7	28	18.9	18.9	19	19	9.6	10	12.1
10	26	28.4	29	28.7	47.3	26.3	31.2	29	39.1	23	22.6	23
15	46	44.8	43	47.3	63.2	45.1	45.4	44	45	36	35	36.2
20	60	61.6	59	61.5	80.3	57.2	63.8	65	62	50	53	53.2
40	79	76.5	74	77.9	89.1	75.6	81.1	84	79	66.4	64	64.8
60	89	82.8	78.8	85.3	95.1	87.4	93.1	91	88	75	74	73.4
90	94	93.2	89	95.6	97.2	90.7	95.3	93	90	86	84	82.3
120	98.8	97.8	98	99.7	99.6	99.2	99.1	99.1	97	99	98.2	99.1

Methods

The diameter, thickness and crushing strength of ten randomly selected tablets was measured with a micrometer

(vernier caliper) and Erweka hardness tester. Twenty tablets were rotated in a friabilator (Emmy Pharma) at 25 rpm for 4 minutes. The tablets were then dedusted and the loss of weight due to fracture or abrasion was recorded as % age weight loss (% Friability). Twenty tablets were randomly taken then the individual and total weight was determined using Sartorius balance and average weight was calculated. The result was compared with B.P. specification of Weight Variation Test (B.P. 2002).

The U.S.P. disintegration method was used in which tablets (n=6) from each brand was kept in basket assembly suspended in a beaker containing distilled water maintaining at 37±0.5ºC with up and down frequency of 27 to 33 cycles per minute the time required to complete disintegration of six tablets within U.S.P. specifications (U.S.P.XXI. 1988).

The dissolution rate study of Rifampacin tablets was determined by U.S.P XIX Rotating Paddle Method. One tablet in each of six vessels was placed containing phosphate buffer at different pH (6.0,6.5 & 7.4) and maintaining temperature at 37± 0.5ºC the volume of each vessel was maintained. At 900 ml. A sample aliguot of 5ml was drawn by a pipette at different time intervals and the fresh dissolution medium was replaced after each withdrawal. The drawn samples were stored in the refrigerator until analyzed spectrophotometrically at 475 nm for Rifampacin contents.

Assay of Rifampacin

0.1gm of Rifampacin powder was dissolved in sufficient methanol to produce 100 ml, diluted 2 ml of the solution to 100 ml with phosphate pH 7.4 and measured the absorbance of the resulting solution at λmax 475 nm (UV-Spectrophotometer Agilent 2005 was used for the analysis of the sample taken using software Version-2005, courtesy Agilent, Germany).

Results and Discussion

Among four commercial brands of Rifampacin tablets, A brand disintegrated most rapidly (7.00 minutes) and D brand disintegrated at the slowest rate (8.00 minutes). These brands of Rifampacin were found to comply with the pharmacopoeial requirements as regards to their variation in weight and assay contents as shown in tables 1 and 2.

The percent of Rifampacin dissolved in the dissolution medium at different time intervals, was calculated and plotted against time. The dissolution profiles for each of brands of tablets are given in table 2 and shown graphically in figs. 1, 2 and 3.

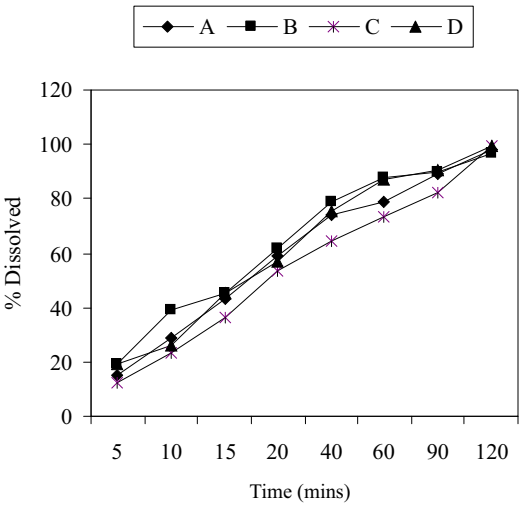

Fig. 1: % age dissolved of Rifampacin tablets 450 mg at pH 7.4 at 37 ± 0.5ºC.

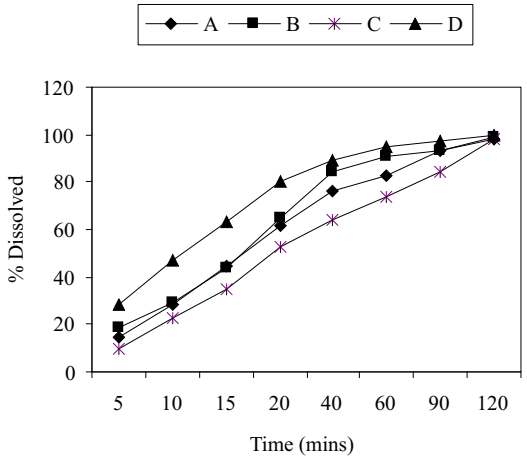

Fig. 2: % age dissolved of Rifampacin tablets 450 mg at pH 6.5 at 37 ± 0.5ºC.

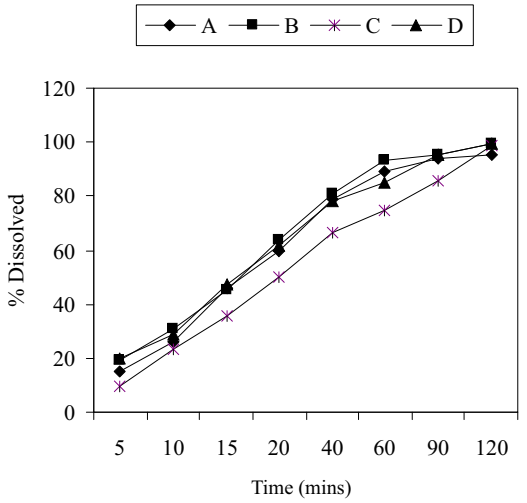

Fig. 3: % age dissolved of Rifampacin tablets 450 mg at pH 6.0 at 37 ± 0.5ºC.

From the table 2 and figs. 1, 2 and 3, it is evident that all the tablets showed a biphasic release pattern of Rifampacin i.e. in first 20 minutes fast phase was observed and in the later phase slow release of Rifampacin was observed which are consistent with earlier studies of this laboratory (Rabbani *et al*., 1997) on Co-trimoxazole tablets were biphasic release pattern was noted both for Trimethoprim and Sulphamethoxazole.

This dissolution test is based on the assumption that the media used will provide sink condition i.e. there is no influence of concentration gradient (Hanson, 1982) for the drug and diffusion layer model of dissolution mechanism is applicable which is mathematically shown by the following relationship:

$$d_c / d_t = K S (C_s - C_t)$$

Where d_c / d_t is the dissolution rate, K is the constant, S is the surface area, C_s is the solubility of drug in the medium and C_t is the concentration of drug in the medium at time, the constant K has been shown to be equal to D/h where D is the diffusion coefficient of drug and h is the thickness of the diffusion layer (Burner and Tolloczko. 1900).

The diffusion layer stimulates the unstirred water layer of the intestine. This layer is saturated with the drug and the drug concentration is equal to C_s. The C_s-C_t in equation represents the concentration gradient in the bulk dissolution medium. As Rifampacin is slightly soluble (450 mg in 343 ml of water) (William. 1995) and the concentration Ct of the drug in the dissolution medium (900 ml) is effectively zero hence the Ct is negligible as compared to Cs and the above equation may be written as

$$d_c / d_t = DS (C_s / h)$$

Although the above equation is an over simplification of the dynamics of dissolution, yet it is qualitatively useful parameter for dissolution testing.

The change in the characteristics of the medium such as pH that affects the solubility of the drug and rate of its dissolution is not considered here. Keeping in view of this fact and the effect of pH on the absorption of the drug in GIT, this study was also conducted at different pH i.e. 6.0, 6.5 and 7.4 which will stimulate the conditions in different

parts of the intestine hence it will give more realistic picture of the dissolution behaviour of the Rifampacin tablets.

The above equation can be modified to take into account the volume of dissolution medium (V),

$$d_c / d_t = DS/Kh$$

DS/h is constant for Rifampacin; therefore

$$d_c / d_t = KC_s / V$$

The above equation further modified to take into account the weight (W) of the tablet in contact with the volume V of the medium and considering diffusion coefficient D and thickness h of the saturated stationary layer as constant and incorporating D/h into K and considering rate of dissolution as rate of change of weight of solid particles and summing Noye's Whitney equation:

$$d_w / d_t = -KS (C_s)$$

Now Wo-W is the weight of the solid that has dissolved into volume V i.e.

$$(Wo-W) /V = C_s$$

The above equation after necessary mathematical treatment becomes

$$Wo^{1/3} \; W^{1/3} = K_1 t$$

The above Cube Root Law for dissolution would probably explain the biphasic behavior of the Rifampacin tablets quantitatively and results are given in the tables 3-5 and figs. 4-6.

This behavior of dissolution from all brands and two rate constants obtained suggest that in this particular case two types of dissolution mechanism operate. First, the initial fast rate constants might be due to the inclusion of such disintegrant by the manufacturer, which does not swell by exerts its disintegrating action by capillary action because the capillaries are likely to be formed and the liquid is drawn up through these capillaries at a very rapid rate. It ruptures the intergranular bonds and the granules are thrown apart with the resultant breaking up of tablet. The second rate constant might be due to erosion of the granule, which has already been available in the dissolution medium (Lowenthal, 1972).

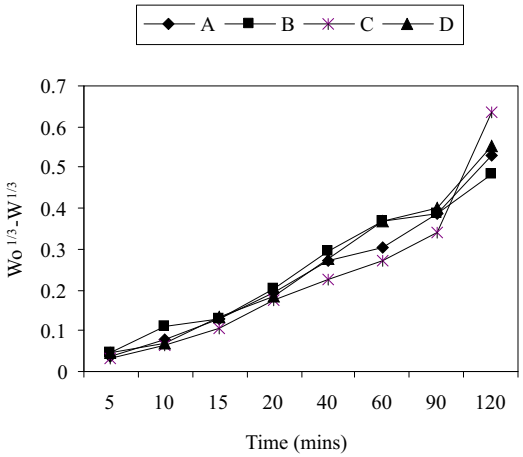

Fig. 4: Cube-root dissolved amount of Rifampacin tablets 450 mg at pH 7.4 at 37 ± 0.5ºC

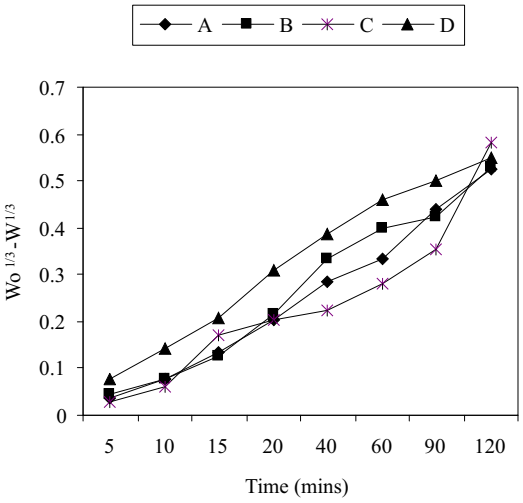

Fig. 5: Cube-root dissolved amount of Rifampacin tablets 450 mg at pH 6.5 at 37 ± 0.5ºC

Cube-Root dissolution rate constants are showing biphasic behavior of all commercial brands of Rifampacin tablets at different pH values as shown in tables 3-5. From the tables it can be suggested that B will be most bioavailable at all pH values. The difference found the dissolution rate constants for the first 20 minutes between the different brands of Rifampacin tested is probably due to the different types of coating materials and thickness of the coating layer employed methyl cellulose, for example a commonly used material for film coating has been reported to retard dissolution of the tablet by Schwartz and Alvino, 1976.

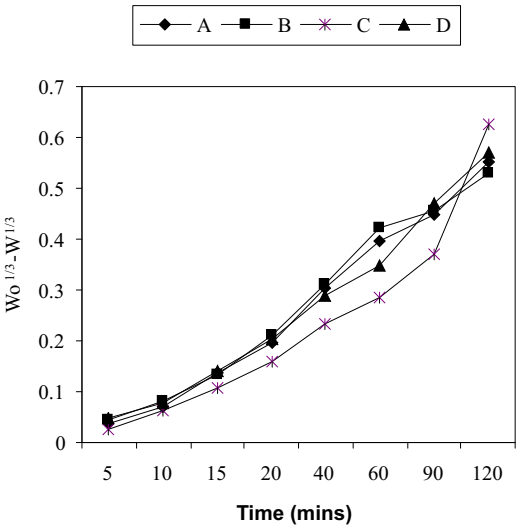

Fig. 6: Cube-root dissolved amount of Rifampacin tablets 450 mg at pH 6.0 at 37 ± 0.5ºC

Table 3: Cube-root Dissolution Rate constants in Phosphate Buffer of pH 7.4, at 37 ± 0.5ºC representing two phases of all brands of Rifampacin tablets 450 mg

Brand's Name	First phase up to 20 minutes ($10^{-3}g^{1/3}$/min)	Second phase after 20 min, ($10^{-3}g^{1/3}$/min)
A	13	4.66
B	9.8	4.97
C	13	3.30
D	14	3.20

Table 4: Cube-root Dissolution Rate constants in Phosphate Buffer of pH 6.5, at 37 ± 0.5ºC representing two phases of all brands of Rifampacin tablets 450 mg.

Brand's Name	First phase up to 20 minutes ($10^{-3}g^{1/3}$/min)	Second phase after 20 min. ($10^{-3}g^{1/3}$/min)
A	14.2	2.7
B	20.2	1.6
C	6.2	4.7
D	17.8	3.6

As Rifampacin is given in once daily dose so on the basis of above discussion it is concluded that these tablets act as slow release drug system i.e. initial fast phase and then slow phase to maintain the drug serum level for a longer period. However, B brand must prove a little better.

Table 5: Cube-root Dissolution Rate constants in Phosphate Buffer of pH 6.0, at 37 ± 0.5ºC representing two phases of all brands of Rifampacin tablets 450 mg.

Brand's Name	First phase up to 20 minutes ($10^{-3}g^{1/3}$/min)	Second phase after 20 min. ($10^{-3}g^{1/3}$/min)
A	11.8	3.73
B	12	3.33
C	10.6	4.30
D	15.6	2.53

Conclusion

From the results and discussion, it can be concluded that the plot of cube-root amounts dissolved ($Wo^{1/3}W^{1/3}$) against time (t) resulting in biphasic release in first 20 minutes is the fast phase and thereafter the slow phase. The difference in the rates of dissolution with the progress of time can be explained on the basis of solubility; since Rifampacin is practically insoluble in water and the dissolution rates are of first order i.e. initial rates are comparatively higher than the successive rates beyond 20 minutes. The tablets brands according to the degree of the dissolution of Rifampacin are arranged in following sequence:

B > C > A>D (at pH 7.4)

D >B>A >C (at pH 6.5)

B > D >A >C (at pH 6.0)

It is further revealed that all of the commercially available brands met the official specification and also this study emphasized the need of constant surveillance on marketed drug product by the government, manufacturers and independent research groups to ensure supply and availability of quality medicines for the patients.

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