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Stability Studies of Rifampicin Mucoadhesive Nasal Drops

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Stability studies of rifampicin mucoadhesive nasal drops were performed by using accelerated stability testing analysis. Effect of temperature and antioxidants were studied. As the temperature increases the rate of degradation was increased and at individual temperatures the rate of degradation was more with increasing time.The stability was improved to certain extent by adding one or more antioxidants such as ascorbic acid and sodium sulfite. The pH changes are within pH 5 and pH 6 due to the influence of polymer (HPMC K4M).The optimally formulated nasal drops could have 90% active drug at the end of 17 days if stored at 36°.

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container to remain with in its physical, chemical, microbiological, therapeutic and toxicological specifications[1]. Assurance that the packaged products will be suitable and stable for its anticipated shelf life is inevitable and must come from a well designed stability profile. Linter[1] suggested that a well designed stability testing plan is an essential and pertinent expansion of the quality assurance programme. Effect of temperature and antioxidants were studied in this investigation on the stability of mucoadhesive rifampicin nasal drops and the shelf life of the product is determined.

EXPERIMENTAL

Rifampicin of Universal Pharmacy, Nagpur, HPMC K4M of Cadila Labs, Ahmedabad, ascorbic acid and sodium sulfite of Loba Chemie, Mumbai and Tween 80 of Robert Johnson Company were used in the present investigation.

Method of preparation of rifampicin mucoadhesive nasal drops : The formulae of nasal drops is shown in Table-1. HPMC K4M was soaked in water for about 3 h. Rifampicin was placed in a graduated measuring cylinder and thoroughly mixed with Tween 80 by keeping on a vortex mixer till a smooth paste was prepared. Ascorbic acid was dissolved in water and added to the paste and mixed. Finally the volume was made up with distilled water. The suspensions were transferred to an a amber-coloured bottle taking care to see that the air space left was minimum by selecting the right size container. The suspensions obtained were uniform without rapid settling. The whole preparation and distribution was carried out during night with diffused light.

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Stability studies; effect of temperature:

In each of the thoroughly cleaned amber-coloured vials 5 ml of the formulation was placed and then the containers were tightly closed and subjected to different temperatures of 8, 36, 45, 55 and 65° to study the degradation kinetics. Samples were withdrawn from the vials maintained at mentioned temperatures at the intervals of 3, 6, 9, 12, 15, and 18 days and the rifampicin content was estimated.

Effect of antioxidants: Three types of rifampicin formulations (i.e, S, A and B) were prepared by using different antioxidants and their composition are given in Table-1. Same procedure was followed as mentioned above for carrying out the study.

Estimation of rifampicin in formulation : To 0.5 ml of sample, 0.3 ml of methanol was added and extracted

TABLE 1 - COMPOSITION OF THE FORMULATION FOR THE STUDY OF EFFECT OF TEMPERATURE AND pH STUDY

Ingredients (g)	Formulations Fo	S	A	B	C
Rifampicin	–	1	1	1	1
HPMC K4M	1.25	1.25	1.25	1.25	1.25
Tween 80	0.3	0.3	0.3	0.3	0.3
Ascorbic acid	0.1	0.1	0.5	0.1	–
Sodium sulfite	–	–	–	0.4	0.5
Water	100	100	100	100	100

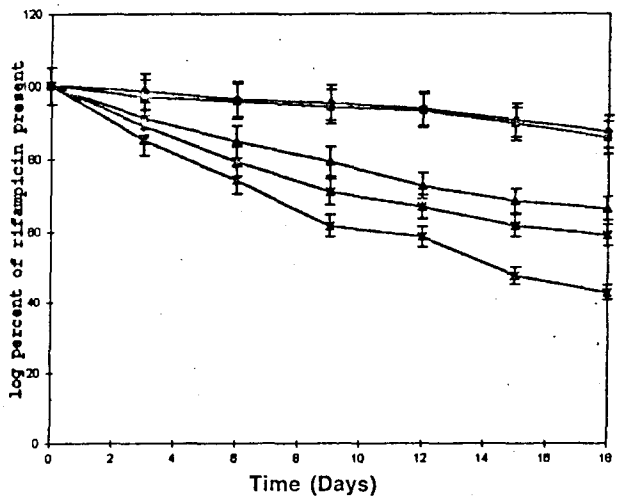

Fig. 1 : Degradation of Rifampicin at various temperatures

Rifampicin nasal drops were stored at 8° (-o-), 36° (-□-), 45° (-Δ-), 550 (-x-) and 650 (-x-). Samples were withdrawn at regular intervals and analysed for rifampicin content.

with a mixture of diethylether and chloroform (7:3) 3 to 4 times, till the entire rifampicin is extracted into the organic solvent. It was dried in a vacuum oven and was reconstituted in 200 µl of methanol. Twenty microlitres of reconstituted sample spot was resolved by thin layer chromatographic technique using chloroform and methanol (4:1) as mobile phase and silica gel as layer. Rifampicin spot was identified by keeping pure rifampicin as standard and that area of silica gel was scrapped out and extracted with 5 ml of methanol. Absorbance of this methanolic solution was measured at 465 nm wave length using spectrocolorimeter.

The pH of the formulation 'S' and blank 'F_0' at room temperature was measured at every 2 day intervals using a pH meter till 25 days to see if there is any change.

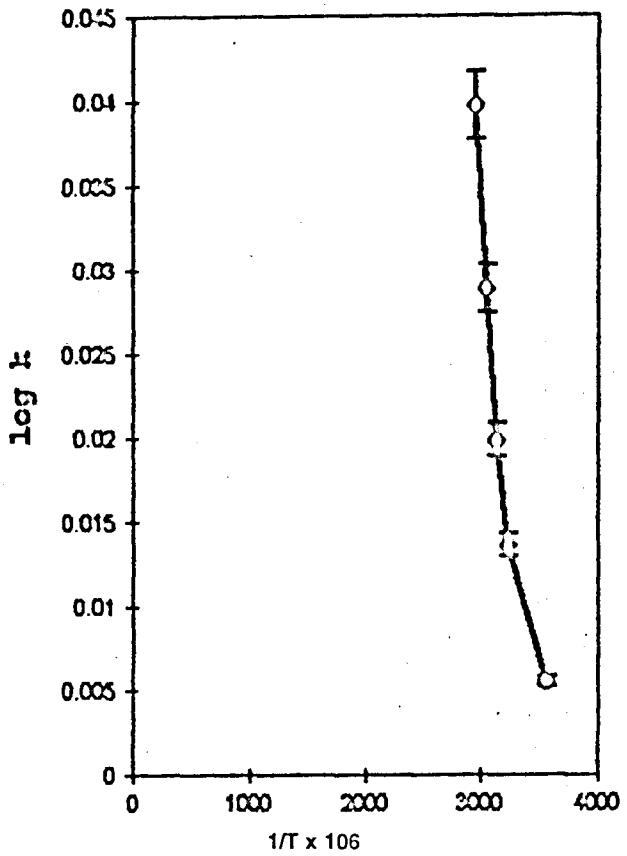

Fig. 2 :Temperature dependent degradation of Rifampicin : arrhenius plot showing decreased chemical stability

RESULTS AND DISCUSSION

Chemical stability of pharmaceutical products is generally evaluated by accelerated stability testing. The method of accelerated stability testing of pharmaceutical products based on the principles of chemical kinetics was demonstrated by Garret and Carper[2]. According to this technique, the specific decomposition rate

TABLE 2 - DEGRADATION OF RIFAMPICIN FORMULATIONS S, A AND B AT VARIOUS TEMPERATURES

Formulation	Temp.	% of Rifampicin present						
		0 day	3 day	6 day	9 day	12 day	15 day	18 day
S	8°	100	98.42±1.26	96.31±0.64	95.26±0.75	93.68±1.56	90.52±0.12	87.36±2.54
A		100	95.48±2.35	97.89±1.13	97.2±1.56	96.62±0.76	95.79±1.25	94.96±0.76
B		100	99.46±0.98	98.82±1.52	98.1±0.79	97.91±0.84	97.16±2.13	96.66±1.23
S	36°	100	96.84±1.24	95.78±0.67	94.21±0.85	93.15±1.53	89.47±1.24	85.78±0.86
A		100	97.62±0.98	97.11±1.25	96.86±0.47	96.31±1.62	95.92±0.86	94.22±1.54
B		100	98.82±1.24	98.16±1.67	97.93±0.84	97.54±1.62	97.02±0.64	96.48±1.42
S	45°	100	91.05±0.87	84.73±1.11	79.47±1.64	72.63±0.96	68.42±1.42	66.31±3.12
A		100	94.69±1.46	90.86±1.18	88.22±0.67	85.1±0.35	83.96±2.31	75.77±1.26
B		100	96.51±2.50	95.06±1.26	94.59±0.84	93.76±0.54	91.09±2.01	90.11±1.25
S	55°	100	88.94±1.24	79.47±0.86	71.05±1.24	66.84±1.42	61.57±1.24	58.94±0.84
A		100	92.63±2.31	87.31±0.79	84.47±4.63	80.99±0.54	76.83±1.25	71.92±0.86
B		100	93.04±2.13	90.58±1.45	88.95±0.86	85.44±0.63	83.61±1.24	80.77±1.74
S	65°	100	85.26±1.25	74.21±0.86	61.57±1.84	58.42±0.42	47.36±2.31	42.63±1.54
A		100	89.96±1.12	86.42±1.43	78.31±1.46	73.15±0.12	65.71±1.25	56.92±1.42
B		100	90.86±0.97	87.43±1.53	81.44±1.25	77.92±0.46	72.16±1.35	68.33±1.42

S : Formulation containing 0.1% ascorbic acid
A : Formulation containing 0.5% ascorbic acid
B : Formulation containing 0.1% ascorbic acid and 0.4% sodium sulfite

TABLE 3 - PH CHANGES IN RIFAMPICIN FORMULATION AT ROOM TEMPERATURE

Time	pH Changes			
(days)	Fo	S	B	C
1	5.4	5.31	6.72	6.74
3	5.51	5.3	6.42	6.52
5	5.76	5.25	6.21	6.34
7	5.86	5.19	6.31	6.25
9	5.79	5.32	6.45	6.78
11	5.85	5.35	6.21	6.45
13	5.8	5.39	6.34	6.48
15	5.79	5.41	6.01	6.1
17	5.85	5.36	6.54	6.21
19	5.82	5.27	6.21	6.66
21	5.69	5.2	6.31	6.87
23	5.63	5.15	6.02	6.21
25	5.6	5.13	6.85	6.87

S: Formulation containing 0.1% ascorbic acid A: Formulation containing 0.5% ascorbic acid
B: Formulation containing 0.1% ascorbic acid and 0.4 % sodium sulfite
C: Formulation containing 0.5% sodiumsulfite

constant *k* values for the decomposition of a drug in solution at various elevated temperatures are obtained by plotting some function of concentration against time. The logarithms of the specific rates of decomposition are then plotted against the reciprocals of the absolute temperatures and the resulting line is extrapolated to room temperature[3]. The results of chemical evaluation were shown in figures-1 and 2. It can be observed from the figures that the chemical stability invariably decreased in all formulations till eighteenth day. As the temperature increased the rate of degradation was increased and at individual temperatures the rate of degradation increased with increase in time. Temperature-dependent degradation rate changes are apparent from Arrhenius plot (figure-2).

The main degradative pathway for rifampicin is oxidation. So an attempt was made to enhance the stability by inclusion of different antioxidants and varying their concentration. Therefore, the effect of antioxidants was studied. Influence of antioxidants on the chemical stability of the formulation was shown in Table-2. Formulation 'S' was taken as the standard. Formulation 'A' and 'B' containing different antioxidants, degradation was compared with reference to standard. Formulation 'S' turned dark as temperature increased or on ageing and some sort of precipitation was observed at elevated temperatures. Stability was improved to some extent by adding one or more antioxidants to this formulation. Formulation 'B' containing antioxidant sodium sulfite was found to be more stable than others.

Formulations have been studied for pH changes at room temperature with respect to the blank formulation. The results are shown in Table-3. From the results it was observed that the pH changes are within pH 5 and pH 6. Previous studies indicate that rifampicin undergoes drastic degradation between pH range of 3-4 whereas it is considerably stable in the pH range of 6-7[4]. Ascorbic acid was used as antioxidant in formulations to improve the stability of rifampicin. The addition of ascorbic acid decreased the pH of the formulations, but not below pH 5. pH of the formulation, changed with time but the pH never went below pH 5. Ascorbic acid appeared to have improved rifampicin's chemical stability. This indicates that though the pH was lowered by ascorbic acid, it definitely helped to increase the overall stability of rifampicin. To compensate this decrease in pH by ascorbic acid, an

alkaline antioxidant, sodium sulfite was used which has shown a drastic increase in the chemical stability of rifampicin. The addition of sodium sulfite resulted in an increase in the pH of formulation (B), pH changes observed in the formulation with time never were below pH 6. Nevertheless, the stability profile was similar to that of formulation-S. From the table-3, it was also observed that, formulation-C (0.5% sodium sulfite) has shown almost the same pH value w th that of formulation-B (0.1% ascorbic acid and 0.4% sodium sulfite). This indicates that though the pH increased after the addition of sodium sulfite, pH changes with time were abolished and overall stability of formulation was improved.

A mucoadhesive rifampicin nasal drop dosage form could be designed with reasonable stability, pourability and bioadhesion without any undesirable discomfort. The optimally formulated nasal drops formulation could have 90% active drug, rifampicin at the end of 17 days if stored at 36°, 30 days at 20° and 76 days at 8°.

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