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INFLUENCE OF SODIUM LAURYL SULPHATE ON INDOMETHACIN RELEASE PATTERN FROM ZINC-INDOMETHACIN COMPLEX AND INDOMETHACIN CAPSULES

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ABSTRACT

A study was carried out to investigate the drug release pattern from zinc-indomethacin capsules with sodium lauryl sulphate (0.25-1.0% by weight of indomethacin) using the rotating basket method (USP XXI). The Drug release data failed to follow commonly used kinetic models that could explain the release pattern. Hence, the results were interpreted on the basis of bi-exponential, first-order kinetic model and found a good correlation between calculated and observed values. It showed that sodium lauryl sulphate enhanced both the faster and slower rate constants of the bi-exponential,first-order kinetic model and the percentage of the drug dissolved according to the faster process was increased. Indomethacin capsules with sodium lauryl sulphate showed also a similar release pattern.

INTRODUCTION

The incidence of untoward effects, including gastrointestinal reactions such as ulceration and haemorrhage, of indomethacin has been reported to vary from a few per cent to 75 per cent of patients (1). Several attempts are being made from time to time to reduce the gastric intolerance property of the drug either by enteric coating or by following new approaches of the drug delivery systems. Zinc preparations are known to possess antiulcer property besides having anti-inflammatory action. Clinical studies have shown that oral administration of zinc sulphate can be beneficial in the therapy of human gastric ulcers (2-4). Hence, it appeared reasonable to develop zinc-indomethacin complex and to study the effect of sodium lauryl sulphate on the drug release kinetics from the capsule formulations.

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MATERIALS AND METHODS

Preparation of the Zinc-indomethacin Complex: To a solution of indomethacin[1] (3.24g, 9mmol) in ethanol (250 ml) at 0°C was added slowly zinc acetate (1.02g, 4.6 mmol)(E.Merck,Bombay) solution in 50% v/v ethanol (100 ml) cooled to 0°C. The mixture was allowed to stand for 2 hr. The resulting white precipitate was filtered, washed with water and then with ethanol (50% v/v), and dried under vacuum to give 2.85g (81.43% w/w yield); of the zinc complex. M.p. 232-234°(decomp.) Anal.($C_{38}H_{30}N_2O_8Cl_2Zn$).

Capsule Formulations: Four formulations of zinc-indomethacin complex (56 mg,equivalent to indomethacin,50 mg) capsules using sodium lauryl sulphate (0,0.125,0.25 & 0.5 mg for formulation I,II,III & IV, respectively) (Sisco, Bombay) and lactose to adjust capsule weight to 137.5 mg were prepared.Another set of formulations(V,VI,VII & VIII) using indomethacin (50mg) in place of the complex were also prepared in a similar fashion.The capsules were evaluated according to compendial specifications (5).

Dissolution Test: Dissolution profiles were determined for each product on six individual capsules at 37±1°C using a rotating basket method (USPXXI) and at a stirrer speed of 100 rpm. The medium used was 750 ml of the mixture of phosphate buffer, pH 7.2 and distilled water (1:4). At various time intervals, samples (5 ml) were withdrawn and replaced by fresh solvent, and analysed using UV-Vis spectrophotometer (Perkin Elmer,Model Lambda 3) at 314 nm.

Data Analysis: The following mathematical models (i) zero-order kinetics (Eqn.1);(ii) first-order kinetics (Eqn.2);(iii) Hixon-Crowell's cube-root equation (Eqn.3);(iv) square-root of time equation (Eqn.4), and (v) bi-exponential,first-order kinetic model(Eqn. 5)were employed to test the fitness of the dissolution data.

$$w = w_o - k_o t \quad (1)$$

$$\ln w = \ln w_o - k_1 t \quad (2)$$

$$\sqrt[3]{w} = \sqrt[3]{w_o} - k_2 t \quad (3)$$

$$Q = K\sqrt{t} \quad (4)$$

$$w = Ae^{-k_3 t} + Be^{-k_4 t} \quad (5)$$

Where,w_o & w=undissolved amounts of the drug at time, t_o & t, respectively; Q=amount of the drug dissolved at time,t;k_o,k_1,k_2,k_3,k_4

[1]Supplied by Ranbaxy Laboratories Ltd,New Delhi(India)

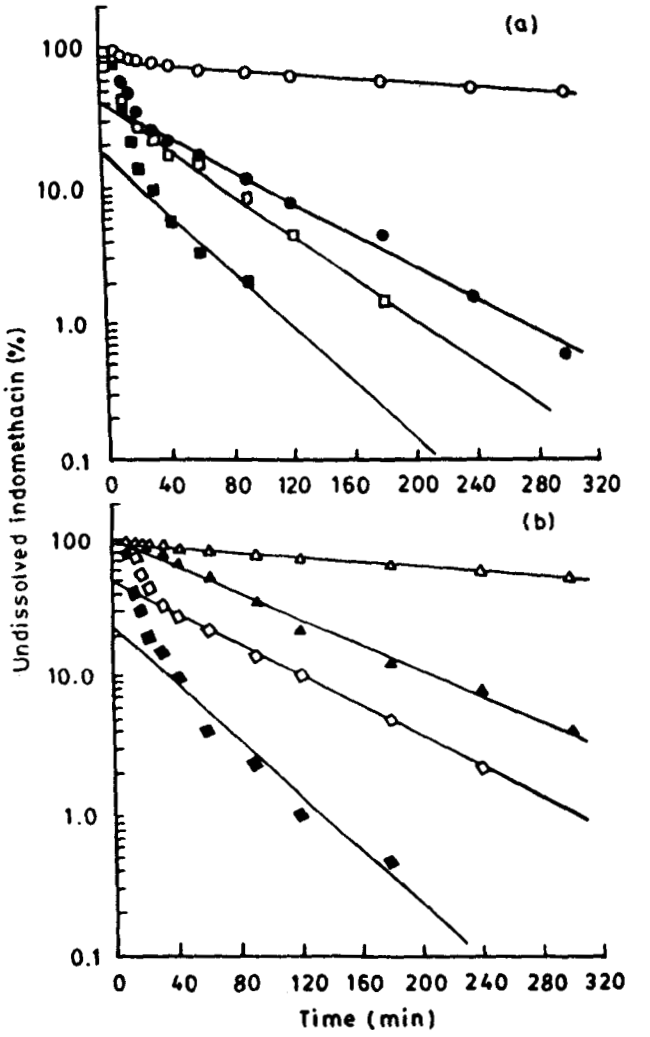

FIGURE 1

Undissolved amounts of indomethacin from capsules of formulations (a):0.1:●,II;□,III;■, IV;(b): Δ,v, ▲,VI; ◇,VII; and ●,VIII. The straight line relates to first-order kinetics.

and K=corresponding release rate constants. Lag-time was defined as the calculated value of t corresponding w=100% (or Q=0).

Student's 't' test was used for statistical analysis of the data.

RESULTS AND DISCUSSION

All the formulations conformed to compendial specifications. The results(Fig.1)showedthat the rate and extent of the drug release was

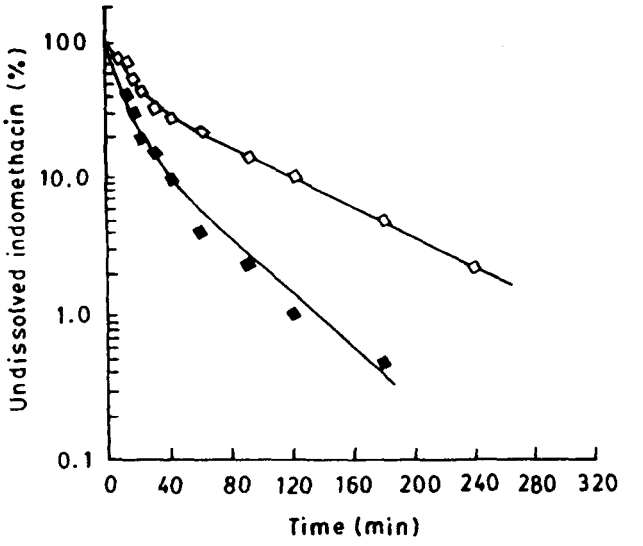

FIGURE 2

Undissolved amounts of indomethacin from capsules of formulations: ◇ ,VII and ◆,VIII. The curve relates to bi-exponential,first-order kinetics.

statistically highly significant ($p<0.001$) at and after 5 min in the capsules containing sodium lauryl sulphate. As a rule, the higher the sodium lauryl sulphate levels, the more rapid the release of the drug. An eight to seventeen-fold and five to seven-fold increase in the drug release was noted from the complex and indomethacin capsule with sodium lauryl sulphate, respectively.

According to the above mentioned kinetic models, the best linear correlation coefficients (range 0.9015-0.9955) were observed for the first-order kinetics. This model, however, did not describe the whole dissolution profile of indomethacin which is evident from Fig.1, relating to the capsules of formulations I to VIII, but, Fig.2 shows the dissolution rate pattern seemed to be biphasic. Hence, the dissolution rate data were interpreted on the basis of a bi-exponential first-order kinetics, analogous to that generally employed to describe pharmacokinetics after rapid intravenous injection of a drug. The results obtained on the basis of this model (Table 1) show good correlation observed between the calculated and observed values, and the linear

TABLE 1

BI-EXPONENTIAL FIRST-ORDER EQUATIONS FOR THE RELEASE OF INDOMETHACIN

Formulation	Equation	Initial phase (r)	Terminal phase (r)	Lag-time (min)
I	$y = 23.90e^{-0.08759t} + 81.67e^{-0.00165t}$	0.9973	0.9925	2.8
II	$y = 100.36e^{-0.13906t} + 39.77e^{-0.01348t}$	0.9852	0.9961	3.4
III	$y = 141.71e^{-0.24185t} + 39.54e^{-0.01796t}$	0.9758	0.9976	3.3
IV	$y = 159.11e^{-0.18739t} + 16.12e^{-0.02344t}$	0.9996	0.9673	3.3
V	$y = 10.97e^{-0.04099t} + 91.35e^{-0.00156t}$	0.9859	0.9931	3.6
VI	$y = 7.71e^{-0.01356t} + 94.04e^{-0.01033t}$	0.9005	0.9939	2.1
VII	$y = 87.04e^{-0.11744t} + 46.47e^{-0.01240t}$	0.9758	0.9988	3.6
VIII	$y = 132.75e^{-0.15859t} + 29.96e^{-0.02281t}$	0.9947	0.9778	3.2

correlation coefficients are very high indicating the release of indomethacin from the capsules was biphasic throughout. It is also observed that some of the drug is released via rapid process, and the rest via a slower process. Both the processes separately conformed to first-order kinetics. The intercept of the terminal phase indicates the per cent of the released via the slower process (e.g. for capsules of formulation VII,50%). The results are in consistent with the observations reported by Laakso et al.(6).

It is also evident that small positive lag-time (Table 1) do exist indicating the time required for the dissolution of gelatin shell prior to the leaching or releasing of the drug from the capsules. Rapid deaggregation of the capsule content, after the dissolution of the gelatin shell, resulted in a large exposed surface and caused in fast enhancement in the dissolution area at the initial phase.The terminal phase mainly describes the dissolution of the poorly soluble drug from the aggregates after disintegration and dissolution of the gelatin shell. Incorporation of sodium lauryl sulphate (1% by weight of indomethacin) in formulations IV and VIII enhanced not only the percentage of the initial phase to 18-22% compared to 1-3% in formulations I and V having no sodium lauryl sulphate but also the release rate constants of both the terminal and the initial phases (Table 1), which can be explained by the fact that according to Noyes and Whitney's

equation the dissolution rate is directly related to the solubility of the drug.

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