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STUDIES ON CONTROLLED RELEASE FORMULATIONS OF PENTAZOCINE HYDROCHLORIDE

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ABSTRACT

This work embodies studies, performed with micropellet type dosage forms of Pentazocine Hydrochloride (Pz-HCl), using single and composite matrices of Eudragit RS100 (RS) and RL100 (RL). The effects of formulation parameters on various dosage form criteria - namely drug loading, particle size distribution, release profiles etc. have been investigated. Results indicate, that the two polymers can be successfully combined to produce different changes in release kinetics, with simple modifications of coating composition and initial drug loads.

INTRODUCTION

Pentazocine (Pz) is an opioid analgesic (1) of the benzmorphan series (2), used widely in cases of moderate to severe pains (2-4) of various origins, like post-surgical, trauma, cancer, burns, colics, as well as a preanesthetic and anesthetic supple-

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ment (5,6). Pz-HCl has a short biological half life of 2-5.7 hrs. (1,2), and a frequent dosing regime of an amount equivalent to 25-100 mg of Pz every 3-4 hours, upto 600 mg daily (4). The most common route of Pz administration is parenteral (by I.V., I.M., S.C. routes), which may lead to numerous effects like fibrous myopathy woody sclerosis of skin at the injection site (4). Thus, a sustained release oral dosage form would be useful in increasing patient compliance and would also decrease the dosing frequency, with concomitant decrease of plasma drug-level fluctuations, so prominent with conventional dosage forms (7). Previously, Pandit et al. have used a multiple emulsion of Pz (8,9) for achieving prolonged release. For this study, Pz-HCl (which is the orally administered form of Pz usually used), has been used to design a drug delivery system.

Literatures report use of single (10-12), and composite (13-15) matrices of different polymers for modulating drug release from controlled-release systems. This work reports the use of Eudragits as sustained release agents for controlling Pz-HCl release.

EXPERIMENTAL

Materials

Pentazocine Hydrochloride (Courtesy: Win - Medicare Ltd., India), Eudragit RS100 and RL100 (Courtesy: Röhm Pharma, Darmstadt), Span 80 (Fluka), Acetone, Petroleum ether 60°-80°, Hydrochloric acid, Sodium Hydroxide pellets, Dibasic Potassium Phosphate, Heavy Liquid Paraffin (all from S.D. Fine Chem., Bombay and of A.R. grades).

Procedure of micropelletization

The micropellets were prepared by the emulsion - solvent - evaporation method (16-18), using different initial drug loads and polymer ratios (Table 1). The drug was first uniformly dispersed in an acetone - solution of polymers. Next, this drug-

TABLE 1

Effect Of Formulation Variables On Physical Properties Of Micropellets

Formuln. Code	Polymer Composition (% w/w)	Theoretical Drug Load (% w/w)	Assay Content (% w/w)	Product Yield (% w/w)	Drug Loss (%)	Entrapment Efficacy (%)
A_1	RS 100		36.91 ± 0.05	97.60	9.95	90.05
B_1	RS 75 + RL 25		36.87 ± 0.02	99.79	8.17	91.83
C_1	RS 50 + RL 50	40	37.85 ± 0.08	99.15	6.20	93.80
D_1	RL 75 + RS 25		37.23 ± 0.05	98.27	8.55	91.45
E_1	RL 100		39.39 ± 0.06	99.96	1.70	98.30
A_2	RS 100		45.11 ± 0.00	96.72	12.74	87.26
B_2	RS 75 + RL 25		45.20 ± 0.01	99.98	9.62	90.38
C_2	RS 50 + RL 50	50	47.93 ± 0.03	96.77	7.24	92.76
D_2	RL 75 + RS 25		46.23 ± 0.01	95.08	11.54	88.46
E_2	RL 100		47.20 ± 0.07	97.33	8.14	91.86

polymer dispersion was poured in a thin, uniform stream into Heavy Liquid Paraffin (containing 0.1% v/v Span 80), being stirred at 700 rpm for 1 hr. for complete acetone evaporation. Next, 100 ml petroleum ether (60°-80°) (PET) was added dropwise during 1 hr. to rigidize the polymer coating. The paraffin was next decanted off, and the micropellets washed with 3x20 ml PET, filtered, vacuum dried, and stored.

Micropellet Characterization Studies

1. Sieve Analysis : This was performed using a nest of standard sieves, of numbers 18, 22, 30, 44 in a sieve shaker. The fractions retained on each sieve were weighed, and particle size calculated by Hatch-Choate equation.

2. Scanning Electron Microscopic Studies (S.E.M.) : Surface morphology of micropellets were examined, using a Scanning Electron Microscope (SEM-Hitachi S-415A), by first gold coating the pellets at 200 A° thickness, using a sputter coater. The tilt was 15°, working distance 15 mm, accelerating voltage 15 KV. The secondary electron imaging technique was used.

3. Content Determination Of Micropellets : Content of the micropellets were determined with accurately weighed 100 mg of micropellets, using 0.1 (N) HCl, at 278 n.m., in a Hitachi 200-20 U.V.-Vis double beam spectrophotometer, and calculations done, based on a standard curve.

4. Dissolution Rate Testing : This was performed using 100 mg micropellets from formulations in a Modified USP XIX Dissolution Rate Testing Apparatus, using 500 ml of bath fluid [0.1 (N) HCl or pH 7.2 Phosphate buffer U.S.P.], prewarmed and maintained at 37±1°C. A 40 mesh S.S. wire basket at 100 rpm was used, and 10 ml aliquots, withdrawn at suitable intervals were diluted, and analyzed spectrophotometrically at 278 nm (for acidic media) or 298 nm (for alkaline media).

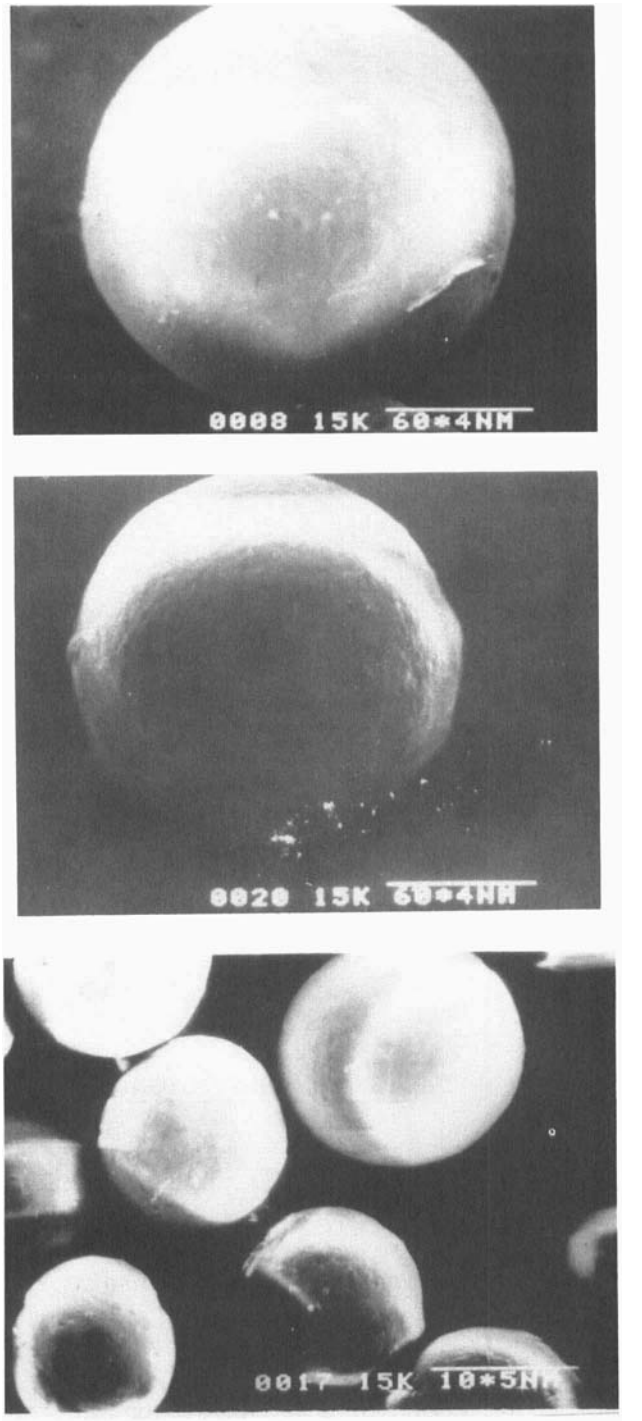

FIGURE 1
Scanning Electron Micrographs of Pentazocine Hydrochloride Micropellets. Key, Plate 1, FN. A_2 (x50)
Plate 2, FN. D_2 (x50)
Plate 3, FN. C_2 (x30)

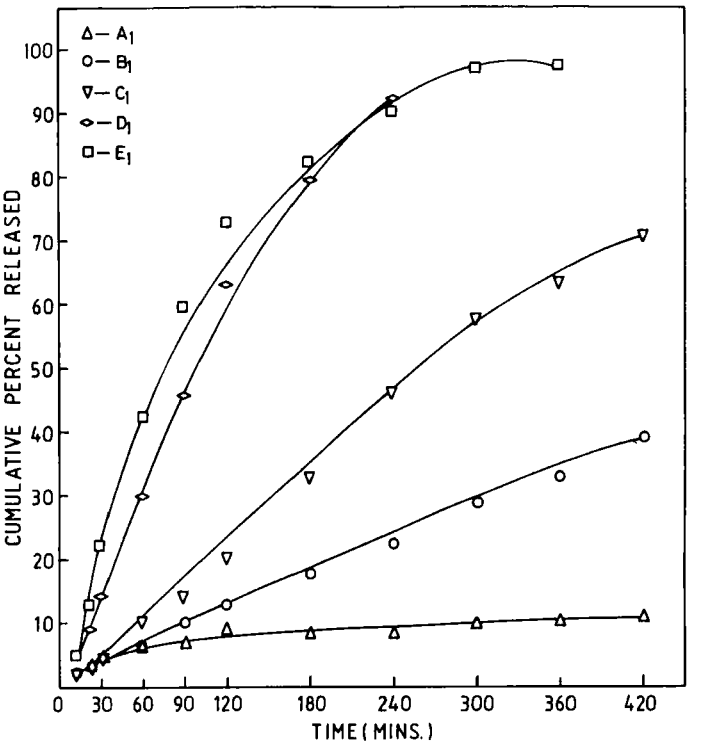

FIGURE 2
Effects of polymer combinations on release profiles of formulations (initial drug load of 40% w/w) in 0.1(N) HCl.

RESULTS AND DISCUSSION

A) Effect of formulation variables on physical properties of micropellets

1. Variation of polymer comibnations: When the total polymer amount was held constant with variations only in ratios of RS and RL, there were minimal changes in product yield, drug entrapment, or drug loss. In all cases, except formulations A_2 and D_2 (Table 1), drug entrapment was over 90%, and the pattern of drug loss could not be definitely corelated with changed polymer combinations. Product yield was excellent, being above

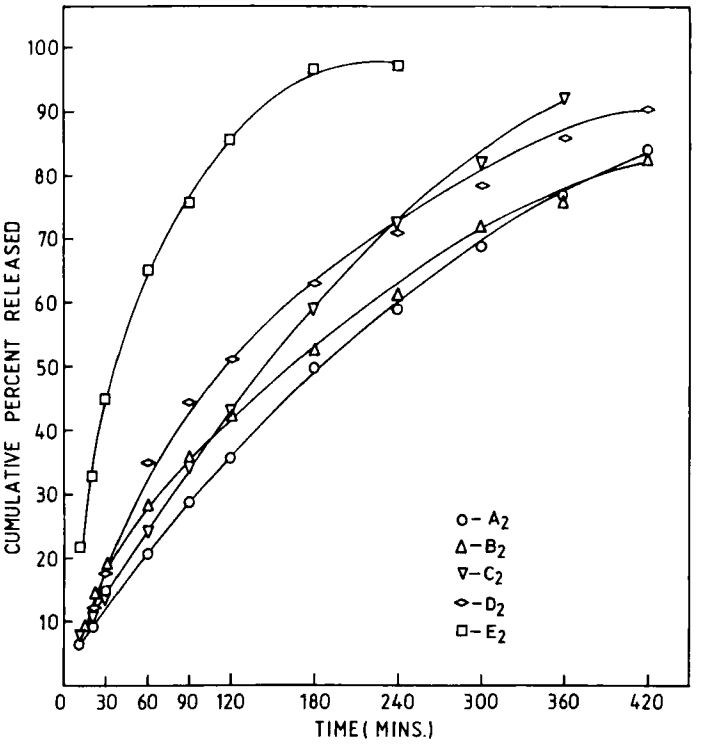

FIGURE 3
Effects of polymer combinations on release profiles of formulations (initial drug load of 50% w/w) in 0.1(N) HCl

95% in all cases, thus validating the manufacturing process. S.E.M. shows spherical micropellets being formed at all combinations, with uniform coatings (Fig. 1, Plates 1,2,3).

2. Variations of initial drug load : A change in drug load from 40% w/w to 50% w/w, brought about no significant changes in product yield. The drug loss in case of the 50% w/w batches was a bit higher than the 40% w/w batches, and consequently, drug entrapment was also slightly low, though no definite relation was found between drug loss and polymer variations at a particular drug load.

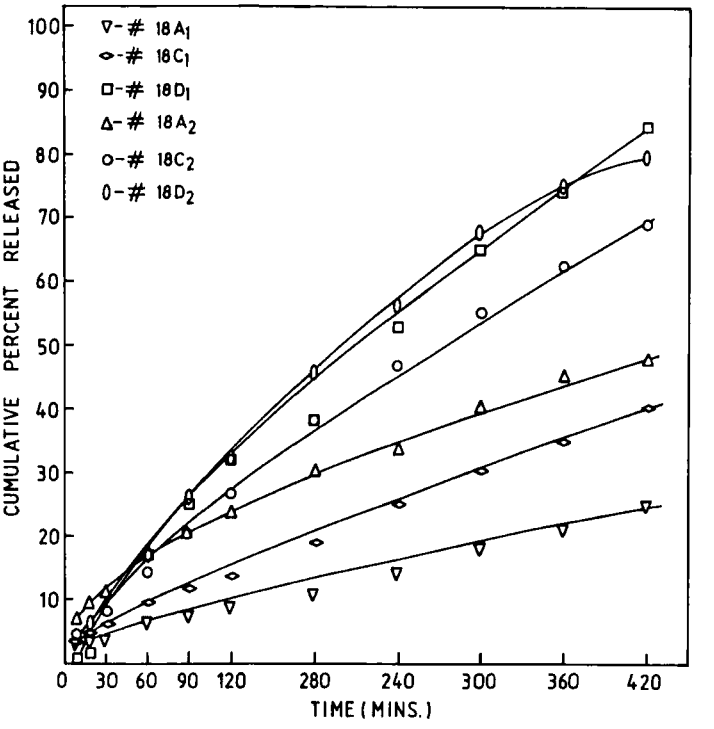

FIGURE 4
Effects of initial drug loads on release profiles of formulations [in 0.1(N) HCl].

B) Effect of formulation and other variables on release of Pz-HCl from micropellets

1. Effect of polymer combination variations on release of drug: Eudragits RS and RL exert a significant effect on modulation of release from formulations. The batches with RL100% (E_1 and E_2) depict maximum Pz-HCl release, and RS100% batches (A_1 and A_2), show minimum release (Fig. 2,3). This can be attributed to greater permeability of RL (19,20) due to larger number of quaternary ammonium groups than RS, thus having less retardant effect on drug release than RS. When gradually increasing amounts of RL are incorporated into the RS matrix, Pz-HCl

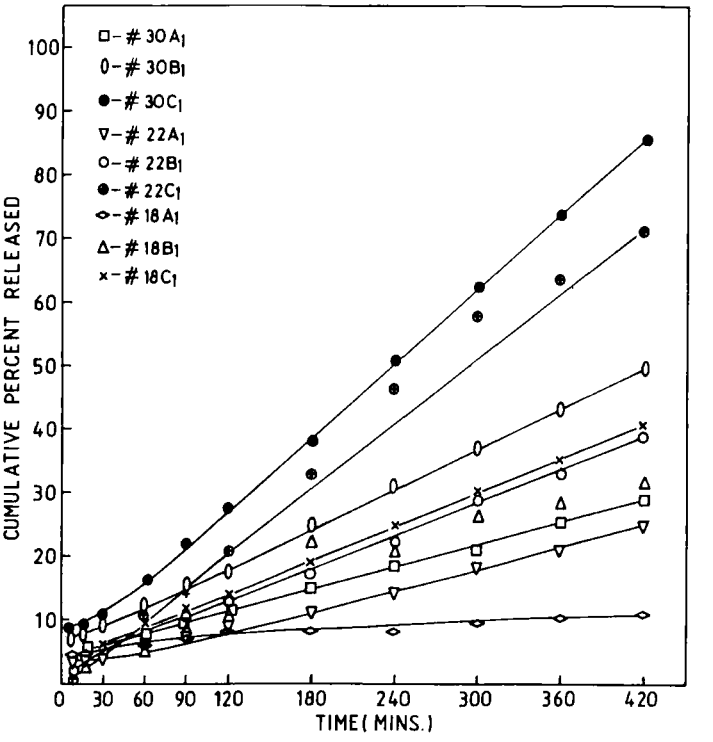

FIGURE 5
Effects of particle size on release profiles of formulations (initial drug load 40% w/w) in 0.1 (N) HCl. The symbols # represent mesh numbers.

release is enhanced due to drug - leaching by dissolution medium, which gains facilitated entry through open channels created by RL in the nearly - impermeable RS matrix. Moreover, RL being more prone to swelling in the dissolution medium, causes faster drug release by implied hydrodynamic pressure.

2. Effect of initial drug load on release rate : From Fig. 4, the effect of varying drug loads on release profiles are seen. For a specific particle size, the formulations A_2, C_2, D_2 gave a higher release than corresponding A_1, C_1, D_1 batches. Thus,

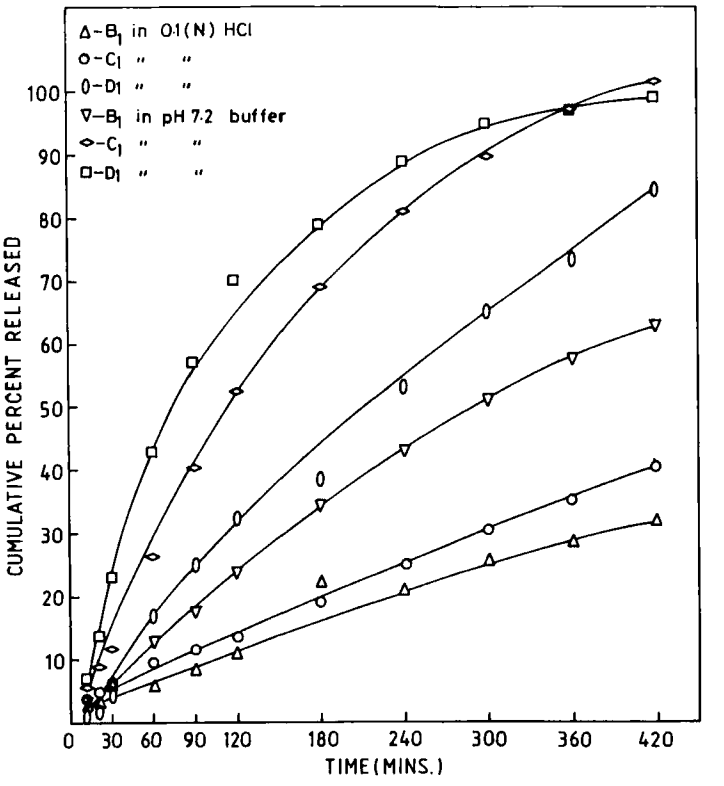

FIGURE 6
Effects of pH on release profiles of formulations (initial load of 40% w/w).

with increase of drug load, a higher release was obtained [like Chang et al (21)], due to reduction in diffusion pathlengths, since the total polymer amount was held constant.

3. Effect of particle size on release profiles : Figure 5 shows a comparative profile for batches A_1 and C_1 at mesh sizes 18, 22, and 30. With increase in particle size, the release of formulations decreased appreciably, thus bearing out the inverse relationship between surface area and dissolution (22). The mesh 30 formulations showed fastest release in cases of both

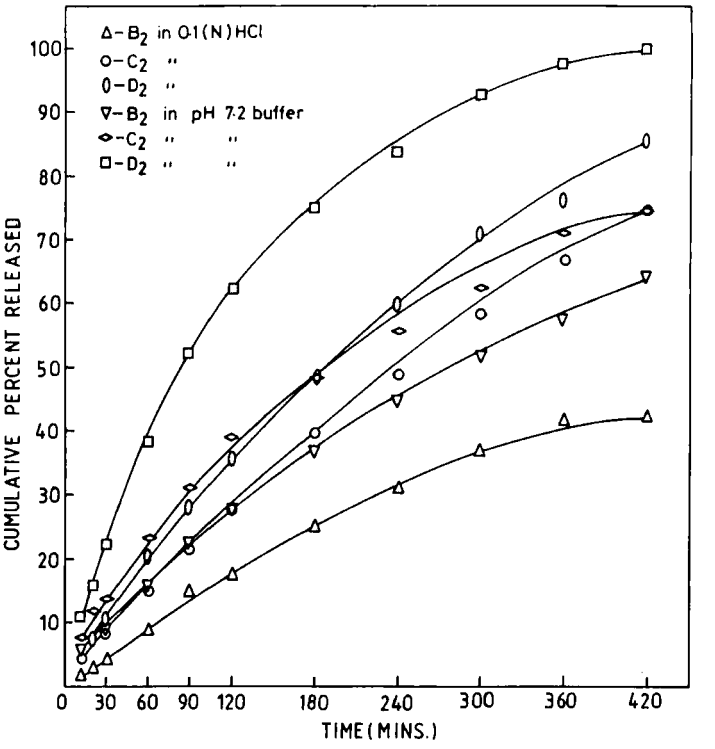

FIGURE 7
Effects of pH on release profile of formulations (initial drug load of 50% w/w).

A_1 and C_1, and mesh 18 batches, the slowest release. Similar results were obtained with the 50% w/w batches.

4. Effect of pH on release profiles : Figures 6,7 show the release profiles of B_1, C_1, D_1 and B_2, C_2, D_2 in acidic and alkaline media. The figures depict, that release is greater in pH 7.2 phosphate buffer than in 0.1 (N) HCl. Actually, Pz-HCl undergoes a greater degree of ionization in alkaline media than in acidic media, hence leading to a greater solubility in the former medium.

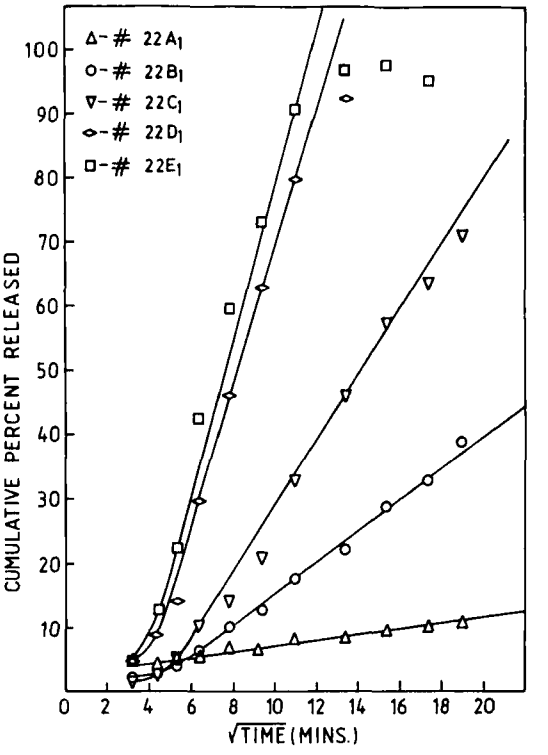

FIGURE 8
Release profiles of formulations following Higuchi kinetics [in 0.1(N) HCl]

Kinetics of drug release from micropellets

A number of kinetic models have been used in literatures to describe release kinetics from micropellets and microcapsules (23-26) and we too attempted describing the release profile by a model function. Drug release appeared to fit zero, first order and square root kinetic models, as reported by Kristl (27). But, on application of differential rate treatments and linear regression analysis, ultimately evidence supported the Higuchi matrix model (Fig. 8) and (Table 2), according to the equation $Q = [D\ (2A-C_S t)]^{\frac{1}{2}}$ (28), for diffusion controlled transport in a polymer matrix. Data also appeared to fit first order (Fig. 9)

TABLE 2

Comparison Between Linearization Of Release Data By First Order, Zero Order And $t^{\frac{1}{2}}$ Order Kinetics For Different Formulations

	Corelation Coefficients (r)		
Formuln. Code	Zero Order	Ist Order	$t^{\frac{1}{2}}$ order
A_1	0.915	0.916	0.944
B_1	0.900	0.966	0.994
C_1	0.987	0.990	0.992
D_1	0.984	0.979	0.984
E_1	0.900	0.870	0.933

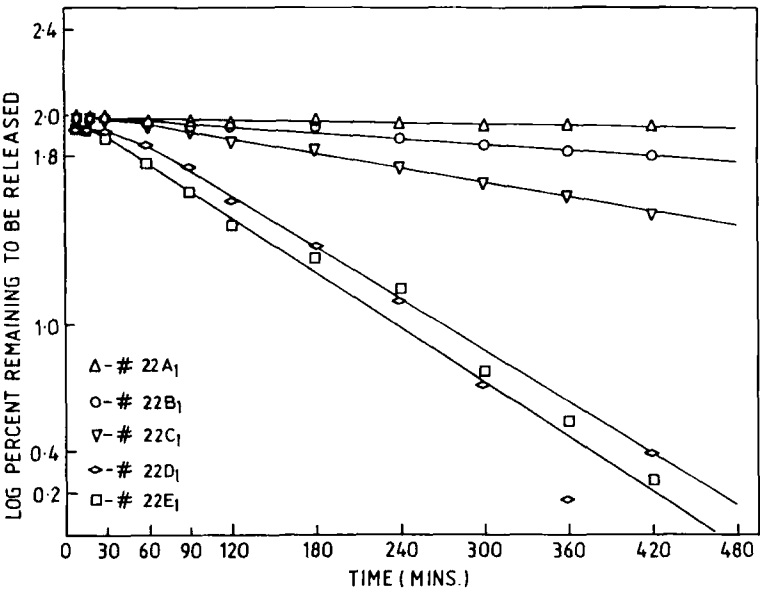

FIGURE 9
Release profiles of formulations by first-order kinetics [in 0.1(N) HCl].

and zero order models, but Higuchi plots gave consistently higher values for corelation coefficients, than for both first and zero order models, in majority of the formulations. The initial slight deflections in the Higuchi plots (Fig. 8) may be due to the slow imbibation of polymer matrix by dissolution medium.

The non-conformity of zero order models by matrix systems, has been confirmed also by Pongpaibul et al (29), the reason being due to the changing distance travelled by the drug from the matrix - core to the surface, which increases with time. So, usually rate of release from matrix follows square root kinetics, as also postulated by Gohary et al (30).

CONCLUSION

From the studies it is clear, that a wide range of properties of formulations can be affected with Eudragits. Extensive

work is still progressing, as we intend to find out the formulations giving optimum sustained action of Pz-HCl. It can be visualized from these studies, that a RS-RL combination would be near-perfect for achieving our purpose. We hope to extend this study to in-vivo trials, and establish an in-vitro - in-vivo corelation.

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