SHORT COMMUNICATIONS

Kinetics of Release of Pentazocine Hydrochloride from Micropellets of Ethylcellulose and Eudragit RL 100

M. MANDAL* and B.K. GUPTA
Dept. of Pharmaceutical Technology
Jadvapur University, Calcutta - 700 032
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Micropellets of Pentazocine hydrochloride were fabricated by the emulsion - solvent - evaporation method using different combinations of ethylcellulose and Eudragit RL 100. The polymer combinations, drug load, and pH of the dissolution medium were found to exert important effects on the drug release profiles. Release kinetics also showed a heterogeneous pattern.

PENTAZOCINE (PZ), an opioid analgesic[1] is extensively used to treat moderate to severe pain of varying aetiologies which include, cancer, trauma, fracture, post-surgical and burns and in addition, preanesthetic medication[2-4]. Since PZ-HCl has a short biological half life of 2-5.7 h[1], it must be administered in a frequent oral dosing schedule of an amount, equivalent to 25-100 mg of PZ every 3-4 h upto 600 mg daily[3]. PZ is commonly administered by the parenteral routes, which may lead to numerous effects such as fibrous myopathy and soft tissue induration at injection site[3]. It was thus envisaged that to obtain enhanced patient compliance, coupled with decreased dosing frequency, a sustained release oral dosage form would provide a proper solution. Another advantage would be a concomitant decrease of fluctuations in the plasma- drug concentrations, so abundantly evident with conventional dosage forms[5]. Literature review reveals many scientific teams working on single/composite polymer matrices[6], and even multiple emulsions, using pentazocine, or its salts, to modulate and control the drug release from the delivery systems.

*** For correspondence**
Jnan Chandra Ghosh Polytechnic
7, Mayurbhanj Road, Calcutta 23.

Ethylcellulose (EC) and Eudragit RL 100 (RL) are polymers accredited as suitable for controlled drug delivery. The present work embodies studies with micropellets of pentazocine hydrochloride prepared with EC and RL, and investigates the effect of factors such as pH and drug load on release profiles as well as, studying release kinetics.

Ethylcellulose 14 c.p.s. (B.D.H., England), Eudragit RL 100 (Courtesy, Rohm Pharma, Germany), Span 80 (Aldrich, U.S.A.), Acetone, Heavy liquid paraffin, Hydrochloric acid, Sodium hydroxide, Monobasic potassium phosphate, petroleum ether 60° - 80° (PET), all of A.R. grade and from S.D. Fine Chem., Bombay.

The micropellets were prepared at an optimum stirring speed of 900 rpm. Initially, different speeds of 700 - 1200 rpm were used. But at higher speeds, the particle size of the micropellets greatly decreased and also, the shape and surface characters were unsatisfactory. Speeds lower than 900 rpm led to clumping, or formulation of very big pellets. The micropellets were prepared by the process developed by Bhattacharyya et al[7]. Different stirrer speeds were used, to choose the optimum for micropelletization. Characterization of micropellets were performed

Table 1
Polymer compositions, drug loads and their effects on physicochemical properties of micropellets of Ethylcellulose - Eudragit RL100 (EC-RL)

Formula Code	Polymer Composition (% w/w)	Theoretical Drug Load (% w/w)	Assay Content (%)	Drug Loss (%)	Product Yield (%)	Entrapment Efficacy (%)	Density (g/cm^3)
T_{4A}	EC100		39.90	9.02	90.99	90.98	0.516
T_{5A}	EC75 + RL25	40	37.18	10.11	89.90	89.89	0.498
T_{6A}	EC25 + RL 75		39.09	9.00	94.02	91.00	0.505
T_{7A}	EC50 + RL 50		36.35	9.95	90.00	90.05	0.486
T_{4B}	EC100		40.65	12.35	84.00	87.65	0.506
T_{5B}	EC75 + RL25		41.60	16.58	82.63	83.42	0.515
T_{6B}	EC 25 + RL75	50	39.75	12.12	89.76	87.88	0.473
T_{7B}	EC50 + RL50		40.53	10.33	89.68	89.67	0.503
T_{4C}	EC100		49.71	12.99	85.30	87.01	0.486
T_{5C}	EC75 + RL25		49.05	10.01	86.48	89.99	0.419
T_{6C}	EC25 + RL75	60	40.65	13.58	80.20	86.42	0.418
T_{7C}	EC50 + RL50		47.07	11.55	81.53	88.45	0.398

[All values are mean of triplicate determinations]

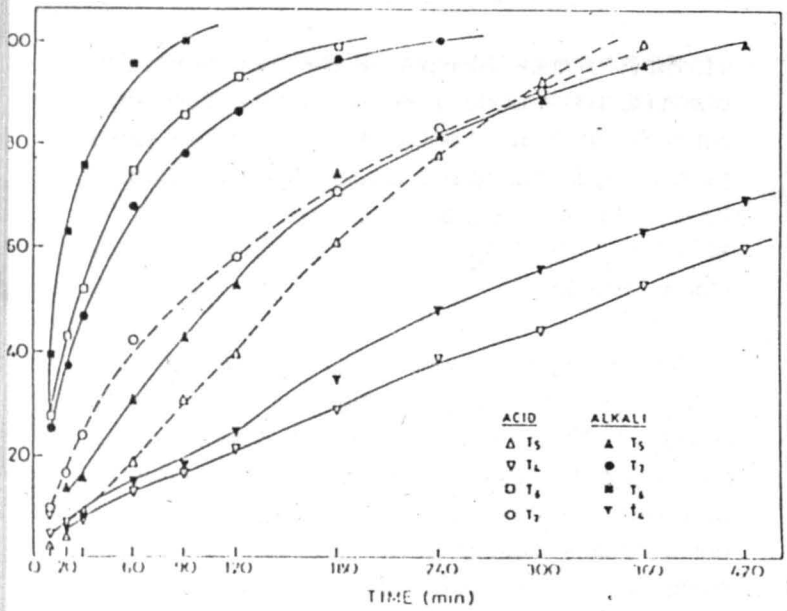

Fig. 1 : Effect of pH and polymer combination on release profiles of EC-RL micropellets (Mesh 30 batches)

as described elsewhere[8]. Three drug loads of 40, 50, 60% w/w were used (Table 1).

From Fig. 1, it is evident that the rate and extent of drug release increased in terms of increasing proportions of RL 100. The 40% w/w drug load is represented in the figure, and same graded release pattern is observed with increase in percentage of RL 100. Formulation T_{4A} showed the slowest release, followed by other formulations with the highest being shown by T6A, containing 75% RL 100. The percent RL versus t_{50} plot showed an inverse relation between the two (Fig. 2).

Preliminary studies indicated that 50 and 60% w/w drug-loaded formulations of EC-RL released the drug extremely fast, in comparison to the 40% drug loaded batches, and also their shapes and size distribution patterns were unsatisfactory. Thus, the batches T_{4B} - T_{7B} and T_{4C} - T_{7C} were discarded

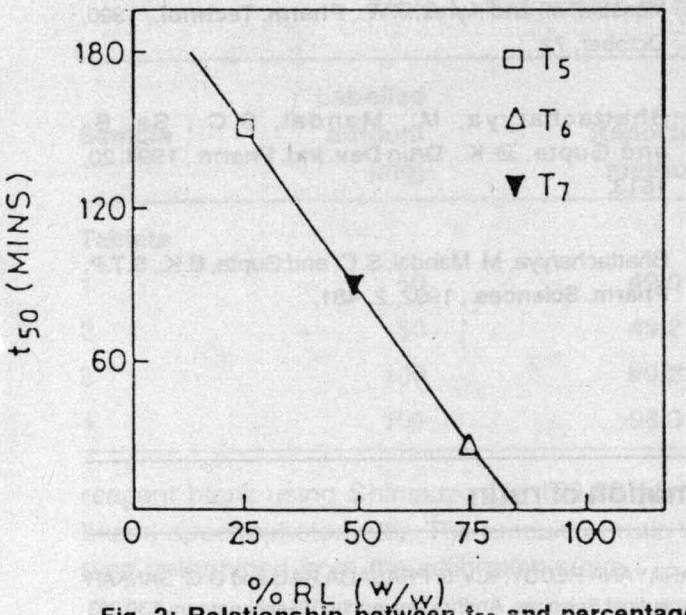

Fig. 2: Relationship between t_{50} and percentage of RL100 for EC-RL formulations

and further studies carried out only with the 40% drug load (T_{4A} - T_{7A}). Henceforth, the formulations will be described as T_4, T_5, T_6, T_7.

In general, all formulations gave higher release in alkali, in comparison to the acid media (Fig. 1). In both acidic and alkaline medium, release from T_6 was the highest and T4 was the least.

From these results, it can be concluded that drug load increments adversely affected particle size distribution, shifting it towards fines, and also enhanced drug loss. Polymer composition variedly influenced drug release. EC being more hydrophobic than RL, produced marked slowing of release rates. With addition of RL to EC matrix, there was thus, enhanced release of drug. Two factors, namely the pH of dissolution medium, and swelling character of EC affected drug release here. The alkali medium induced profound swelling of the EC matrix, leading to increased drug release. The high alkali value of RS, provided a synergistic effect, since RL swells in alkali to a greater extent than in acids. The particle size of micropellets had an inverse relation with drug

Fig. 3: Scanning Electron Microscopy of micropellets

release. The release kinetics of the EC-RL batches were significant, Since the data could not be totally fitted to a single kinetic model. A mixed pattern of zero and first order kinetics was thus put forward based on statistical calculations. The first order release from matrix systems is often found in literature, but zero order is rather rare. Thus explanations supporting zero order kinetics were proposed basing on the multiple hole theory, which was further substantiated by the scanning electron microscopy which was shown in Fig. 3.

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Spectrophotometric estimation of rutin

M. NARAYANA REDDY, K.V.S. PRASADA RAO and D.G. SANKAR
Dept. of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530 003

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A simple spectrophotometric method has been developed for the estimation of rutin from pharmaceutical dosage forms using the chromogenic agent, 3-methyl benzothiazolin-2-one hydrazone (MBTH). The coloured complex exhibits maximum absorption at 500 nm and obeys Beer's law in the concentration range of 10-50 mcg/ml of rutin.

RUTIN (5,7,3',4'-tetrahydroxy flavonol-3-rhamnoglucoside) is used in pharmaceutical formulations for its vitamin P activity. Various spectrophotometric methods have been reported[1-7] for the determination of rutin in pharmaceutical preparations. MBTH reagent was utilised for the spectrophotometric determination of some phenols using various oxidants[8,9]. It was extended to other phenolic compounds with ceric ammonium sulphate by Michael[10]. The present work was taken up to apply above mentioned reaction to the spectrophotometric determination of rutin.

3-Methyl benzothiazolin-2-one hydrazone (MBTH) 2 mg/ml solution was prepared by dissolving 200 mg of MBTH in 100 ml of distilled water.

Ceric ammonium sulphate, 10 mg/ml solution was prepared by dissolving 1 g of ceric ammonium sulphatea in 100 ml of 0.72 M sulphuric acid.

An accurately weighed portion (20 mg) of rutin was dissolved in 95% ethanol and the volume was made upto 100 ml with the same solvent so as to obtain a concentration of 200 mcg/ml. Alternatively, 20 tablets were accurately weighed, finely powdered and the powder corresponding to 20 mg of rutin was warmed with 95% ethanol, filtered and the total volume was brought to 100 ml (200 mcg/ml) with ethanol.

Volumes of standard rutin (200 mcg/ml) solution ranging from 0.5 - 2.5 ml were transferred into a series of 10 ml volumetric flasks. A 3 ml portion of MBTH solution was added to each flask and shaken gently for two minutes. Then 3 ml of ceric ammonium sulphate solution was added successively to each flask and diluted to the mark with distilled water. The absorbance was measured in each case at 500 nm, within the stability period (5- 25 min) against