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COMMUNICATION

Film-Coated Enteric Tablet Formulation of Ketorolac Tromethamine

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ABSTRACT

A great majority of polymers used for pharmaceutical film-coating purposes have been derivatives of cellulose or methacrylate copolymers (Eudragit series) in most recent studies. The type and frequency of the ester substituents in the chemical structure of these polymers determines their water permeability and pH-solubility characteristics; therefore, different members of the series may be employed for taste-masking or as enteric-coating agents or dissolution rate-controlling membranes in sustained-release dosage forms. Ketorolac tromethamine (KT) is a nonsteroidal drug with potent analgesic and anti-inflammatory activity and is absorbed rapidly (T_{max} < 1.0 hr) with an efficiency of >87% following oral and intramuscular administration. The most frequent adverse effects occurring with KT are gastrointestinal disturbances such as peptic ulceration and gastrointestinal bleeding. For this reason, enteric-coated film tablets of KT were prepared in this study by the spray technique. Eudragit S-100 and L-100 were selected as coating materials. Polyethylene glycol (PEG) 4000 was used as a plastifying agent. Core tablets of KT were prepared by the direct compression technique. Tablet specifications were determined and evaluated statistically.

***Key Words**: Enteric coating; Eudragit S 100 and L 100; Film tablet; Ketorolac tromethamine.*

INTRODUCTION

In many of the most recent studies, a great majority of polymers used for pharmaceutical film coating have been derivatives of cellulose or methacrylate copolymers. The different methacrylate copolymers (Eudragit series) offer a range of physicochemical properties and are utilized in many controlled-release applications. The type and frequency of the ester substituents in the chemical structure of these polymers determines their water permeability and pH-solubility characteristics. Therefore, different members of the series may be employed for different purposes, such as taste-masking, enteric-coating agents, or in vitro dissolution rate-con-

trolling membranes in sustained-release dosage forms. The surface chemistry of the polymers is important in terms of their dissolution and coating behavior and hence, further knowledge of the polymer surface chemical structure may aid in the understanding of the interface phenomena of film coating (1,2). Successful film coating depends on the removal of the polymer solvent from the deposited film. Organic solvents have mainly been used because of the ease of evaporation, but recently, an increase in the use of aqueous solvent systems has occurred (3).

The development of an ideal perorally administered drug delivery system providing constant release of drug has been the focus of much research. The objective is to provide constant drug delivery during passage through the gastrointestinal tract (GIT) irrespective of variations in pH, surface tension, and viscosity within the GIT (4). Eudragit is an aqueous dispersion of an acrylic resin consisting of poly-(ethylacrylate-methylmethacrylate) esters. The polymer is neutral in character and is not sensitive to changes in pH. A unique application and characterization of Eudragit E-30 D film coatings in sustained-release formulations was studied by Ghebre-Sellassie et al. (5). Okhamafe and York (6) prepared a review article about interaction phenomena in pharmaceutical film coatings and testing methods. A method has been developed to assess the adhesivity of capsules and film-coated tablets. Nondisintegrating tablets were coated with hydroxypropyl cellulose (HPC), hydroxypropropyl-methyl cellulose (HPMC), and the polymethacrylate copolymers Eudragit E-100 and L-100. The influences of film-coating thickness and the amount of poly(oxyethylene) glycol (PEG) added in varying molecular weights were also studied. Even though Eudragit polymers had little adhesive potential, HPC and HPMC film-coatings became more adhesive with an increase in film thickness, the presence of PEG of molecular weight > 1000 markedly reduced adhesiveness (7). Lucero et al. (8) studied the rheological characteristics of a semisolid preparation of Eudragit. The human in vivo single-dose pharmacokinetics of a model tablet coated with four different aqueous enteric-coat polymeric dispersions were assessed, using an uncoated tablet core as control. In vitro release properties were also investigated. The four aqueous polymeric dispersions were cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), 50:50 CAP/CAT, and metachrylic acid copolymer. Naproxen sodium was the model drug (9).

Ketorolac tromethamine (KT) is a nonsteroidal drug with potent analgesic and anti-inflammatory activity and is absorbed rapidly ($T_{max} < 1.0$ hr) with an efficiency of $>87\%$ following oral and intramuscular administration (10–15). Kamath et al. (16) studied spectrophotometric determination of KT.

In this study, film-coated enteric tablets of KT were prepared by the spray technique. Eudragit S-100 and L-100 were selected as coating materials. PEG 4000 was used as a plastifying agent. Core tablets of KT were prepared by the direct compression technique. Tablet specifications were determined and evaluated statistically.

MATERIALS AND METHODS

Methods

Ketorolac tromethamine was obtained from Dr. Reddy's Laboratories Ltd. Eudragit S-100 and L-100 (Rohm Pharma, Germany), polyvinyl-pyrrolidone, magnesium stearate, lactose, and starch (E Merck) were used. All the other chemicals were of analytical grade. A spectrophotometer (UV-Visible Recording Spectrophotometer, UV-160 A, Shimadzu), pH meter (Bilmar Model 101), pulverizer (Aymes), cubic mixer (Erweka), tablet machine (Erweka), friabilator (Roche), and hardness apparatus (Monsanto) were also used.

Preparation of Core Tablets

Content of the core tablet was

Ketorolac tromethamine: 0.0100 g
Starch: 0.0250 g
Magnesium stearate: 0.0020 g
Lactose: 0.1520 g
Polyvinylpyrrolidone: 0.0110 g

All ingredients were mixed in a cubic mixer and core tablets with a weight of 200 mg were directly compressed on a single-punch tablet machine. Tablet specifications (friability, KT content, crushing strength, weight deviation) were determined. Results are given in Table 1.

Table 1

Uncoated Tablet Specification (n = 10)

Hardness	3.5 kg
Average weight	201.0 ± *2.2532 mg (*SD)
Friability	0.2292%
Amount of KT	10.3745 mg
Disintegration time	5 min (in SGM)

Film Coating

Two film-coating solutions were prepared:

1. Eudragit L 100: 5.00 g
   Ethanol (96%): 86.25 g
   Polyethylene glycol 4000: 1.25 g
   Distilled water: 7.50 g
2. Eudragit S 100: 5.00 g
   Ethanol (96%): 86.25 g
   Polyethylene glycol 4000: 1.25 g
   Distilled water: 7.50 g

Tablets were divided into two groups and were separately coated with these solutions by the spray technique. After coating, coated-tablet specifications were investigated and the results are shown on Table 2.

Determination of KT Amount in Coated Tablets

The spectrophotometric method (16) was used to determine the amount of KT in coated tablets. For this purpose 15.0 mg KT was accurately weighed and dissolved in buffer solution (pH 1.2) and the volume was adjusted to 100 ml in a volumetric flask. Six samples of 1–6 ml were taken from this stock solution and diluted to 50 ml with pH 1.2 buffer solution. Absorbances of these samples were measured at 318 nm. Regression equations and regression coefficients were calculated. The same procedures were repeated with pH 7.5 buffer solution. The results are given in Table 3. Then 10 tablets were finely powdered and 210 mg (corresponding to average one-tablet weight) was dissolved in buffer solution (pH 7.5), and the volume was adjusted to 100 ml. A 3-ml sample was taken from this solution and diluted to 50 ml with pH 7.5 buffer solution. Absorbances of these samples were measured at 323 nm. Amount of KT was calculated by using regression equations.

In Vitro Dissolution Studies

Dissolution tests were performed according to the basket method described in USP XXII, apparatus I. Four hundred milliliters of simulated gastric medium (SGM) without enzymes and simulated intestinal medium (SIM) were used as the dissolution media (USP XXII). SGM was the dissolution medium for the initial 2-hr period and then SIM for the following 4 hr at 37 ± 0.5°C and 50 rpm. The amount of KT was determined according to the spectrophotometric method mentioned above.

RESULTS AND DISCUSSION

Uncoated tablet specifications are given in Table 1. According to the results, core tablet specifications fit to the pharmacopeial limits.

Table 2

Coated Tablet Specifications (n = 10)

Method	Eudragit S-100 Coated Tablet	Eudragit L-100 Coated Tablet
Average weight	210.1400 mg SD = ± 1.6365	209.9700 mg SD = ± 1.6365
Disintegration time		
in SGM	none	none
in SIM	10 min	9.5 min

Table 3

Regression Equation, Regression Coefficient, λ_{max} (nm) at Each Medium (n = *10*)
(y = *abs.*, x = *conc.*)

Medium	Regression Equation	Regression Coefficient	λ_{max} (nm)
pH 1.2	$y = 0.0614\,x + 0.0081$	$r = 0.9998$	318
pH 7.5	$y = 0.0528\,x + 0.0023$	$r = 0.9997$	323

Table 4

Dissolution Results of Coated and Uncoated Tablets (n = *10*)

Dissolution Medium	Time (min)	Released %		
		Uncoated Tablet	Coated Tablet	
			Eudragit L-100	Eudragit S-100
SGM	30	80.1387	0.5274	0.0000
	60	90.1791	1.9372	0.1193
	90	98.5642	2.8436	0.8743
	120	98.4965	3.7338	1.5117
SIM	125		14.6631	5.2117
	130		53.3558	19.8626
	135		80.6372	43.7775
	150		99.3009	100.2288
	165		99.7491	101.5149
	180		98.9480	100.7189
	195		99.5763	101.3661

After coating, coated tablet specifications were also determined and the results are presented in Table 2.

Regression equation, regression coefficient, λmax (nm) of each medium (n = 10) are given in Table 3.

Uncoated tablets disintegrated in SGM in 5 min. Coated tablets did not disintegrate in SGM within 2 hr, but they disintegrated in SIM in 10 min. Dissolution studies were carried out on coated and uncoated tablets and the results and profiles are given Table 4 and Fig. 1. According to the results, KT in uncoated tablets totally dissolved in SGM, whereas 1.5–3.7% of KT in coated tablets dissolved in SGM. A great amount of KT (96.3–98.5%) dissolved in SIM.

Dissolution studies carried out on Eudragit L-100 and S-100 coated tablets indicated that the release profiles depend not only on the physicochemical properties of the drug, particularly solubility, but also on the additive to eudragit resin in the dry film. Moreover, the integrity of the coating material, and hence the release rates, were found to be independent of the pH of the dissolution medium. We attempted to produce film-coated enteric tablets of KT. The results were found to be satisfactory.

The increasing application of film coating to solid dosage forms and the insufficient knowledge of their intrinsic characteristics have highlighted the need to adopt a fundamental approach in finding solutions to the problems encountered in film-coating practice. Considerable improvements in the properties of existing film-coating systems would be more readily achieved if adequate information on interaction phenomena is available. This approach may be less time-consuming and more cost-effective than synthesizing entirely new polymers.

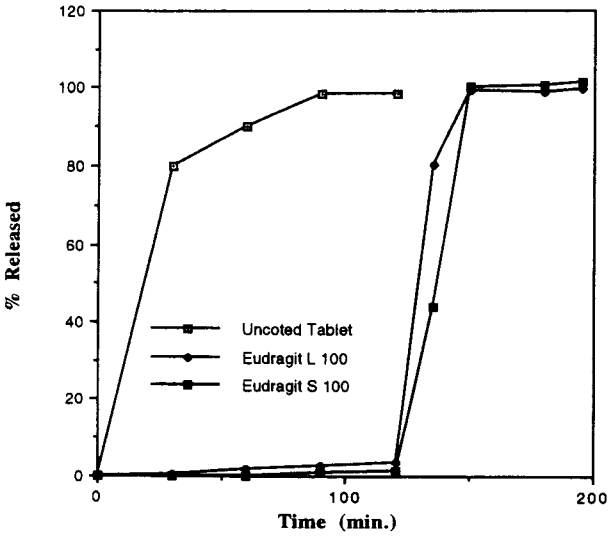

Figure 1. Dissolution profiles of uncoated and coated tablets.

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