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CHANGES IN DRUG RELEASE RATE: EFFECT OF STRESS STORAGE CONDITIONS ON FILM COATED MINI-TABLETS

D L MUNDAY[1] A R FASSIHI[2]

1. School of Pharmacy,Cape Technikon, Cape Town;
2. Department of Pharmacy,University of Witwatersrand Medical School,Johannesburg, S. Africa

ABSTRACT

Film coated theophylline mini-tablets were exposed to stress storage conditions to investigate the effect of changes in temperature and relative humidity (RH) on drug release and the integrity of film coatings. The mini-tablets (3mm in diameter, weighing 20±1 mg) were film coated with polymers such as ethylcellulose with PEG (2:1), ethylcellulose with Eudragit L (2:1) and Eudragit RL. Samples were exposed isothermally at 28,35 and 45°C (constant RH ranging between 55 and 60%) for 21,90 and 180 days, as well as cyclically alternating them every 24h at 45°C, 55% RH; 28°C, 20% RH; and 5°C, 10% RH for 90 days. Dissolution

2. To whom correspondence should be directed.

profiles determined after storage were compared with those 24h after initial coating. All samples showed that the coating integrity was maintained. However, dissolution was significantly impeded to a degree directly proportional to temperature, whilst the effect of RH appeared insignificant.

INTRODUCTION

The practice of coating powder, pellets, granules and tablets with a thin film of a polymeric material in order to perform a specific pharmaceutical function is becoming increasingly widespread[1,2].

An investigation into the effect of storing film coated mini-tablets at varying temperatures and relative humidities on the rate of drug release was carried out. Previous workers[3],demonstrated the effects of ageing by storing enteric-coated aspirin tablets at different temperatures and relative humidities. Dissolution times increased significantly and it was suggested that temperature is the primary factor causing "baking" of the coating resulting in dissolution being impeded.

In this study the effects of stress storage conditions for relatively short to long time periods on experimental sustained release formulation of theophylline mini-tablets[4] are reported. The mini-tablets were film coated with polymeric agents commonly used in the pharmaceutical industry such as ethylcellulose and polymers of methacrylic acid esters.

TABLE 1.

Composition of the coating materials and the amount of coatings expressed as % w/w.

Coating Composition	Amount of coating (%w/w)*
Eudragit RL	1.5
Ethylcellulose + PEG 1540 (2:1)	0.5 + 0.25
Ethylcellulose + Eudragit L (2:1)	2.0 + 1.0

* ±SD of amount of polymer coating was always less than 0.15.

MATERIAL, METHODS AND EQUIPMENTS

Theophylline anhydrous obtained from Holpro Chemical Corporation was used to prepare mini-tablets (3mm in diameter) by the methods previously described[5]. Small batches of mini-tablets were film coated using an Aeromatic Film Coating Dryer (Switzerland) by the upward spray method. Optimum conditions were maintained to obtain smooth uniform coatings. Table 1 shows the compositions of the coating materials and their amounts expressed as percent w/w.

The Eudragits were obtained from Rohn Pharma, Darmstadt, and the ethylcellulose (NF grade) 10 cps from Hercules, Wilmington. The polyethylene glycol 1540 was supplied by Riedel-De Haen AG, Seelze-Hannover. Acetone and isopropanol (analytical grade) were used as solvents in the coating process and were used as received.

In-vitro Dissolution:

The dissolution tests were conducted using apparatus II of the USPXXI (Hanson Research Corporation, Northridge, CA.). Distilled water (1L) was the dissolution medium at 37 ±0.5°C. Samples consisting of ten coated mini-tablets were contained in the wire mesh basket. Samples of dissolution medium were removed at regular time intervals, diluted, and assayed for theophylline by UV Spectrophotometry at 275nm. Distilled water was added in order to maintain constant volume.

Experimental Storage Conditions:

Samples consisting of about 10g of film coated mini-tablets of each coating material and thickness were contained in open petri dishes and subjected to the following experimental conditions: 1. Isothermal storage at 28°C,35°C and 45°C with the RH maintained constant at between 55-60%. 2. Cyclic condition: (i) Samples were exposed to 45°C at 55% RH for 24 hrs, then at 28°C and 20% RH for 24 hrs, and then at 5°C and 10% RH for 24 hrs after which the cycle was repeated. (ii) Exposure alternating every 24 hours between 45°C and 55% RH, and 28°C and 0% RH.

The relative humidity was controlled within ±5% by storing the samples in dessicators containing appropriate mixtures of sulphuric acid and water using incubators set at the required temperature. The complete absence of moisture was produced using phosphorous pentoxide. Samples were submitted to dissolution testing 24 hours after

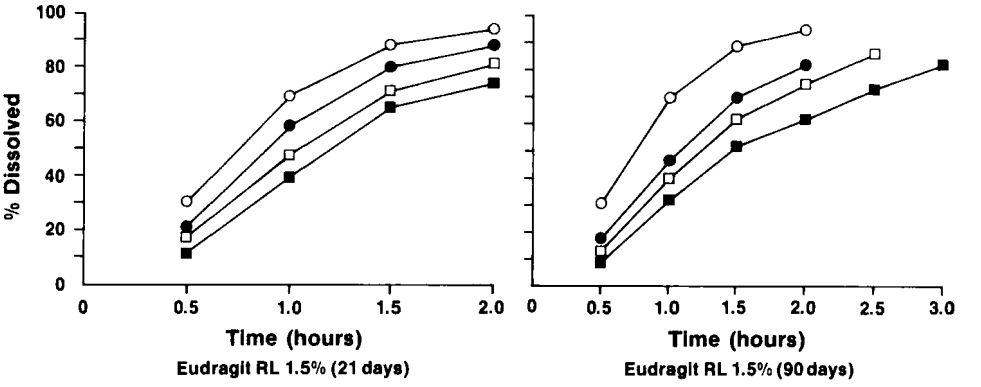

Fig 1. Changes in drug release profiles resulting from the exposure of mini-tablets film coated with Eudragit RL 1.5% to isothermal stress storage conditions for periods of 21 days and 90 days. o , Initial profile (24h after coating); ● , 28°C; □ , 35°C; ■ ,45°C.

coating (initial profile), and then dissolution profiles obtained after 21, 90 and 180 days under isothermal conditions and after 90 days of cyclical storage.

RESULTS AND DISCUSSION

Examples of dissolution profiles of the mini-tablet samples exposed to stress storage conditions (isothermally and cyclically) showing the percentage theophylline released as a function of time in hours (h) are shown in Figs. 1 and 2. From each dissolution profile under various storage conditions, the time in hours for 50%

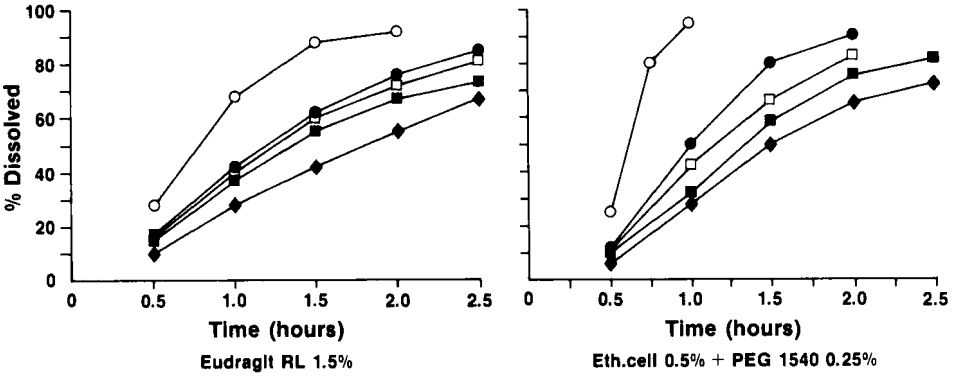

Fig 2. Changes in drug release profiles resulting from the exposure of mini-tablets film coated with various polymeric materials to experimental conditions: ○,Initial(24h after coating);●, cyclic 45°C/25°C/5°C 90 days;□, 28°C 180 days;■, 35°C 180 days,◆, 45°C 180 days.

release of theophylline (t50%) was obtained and these results for each storage condition are tabulated (see table 2). The dissolution curves and t50% values demonstrate that a similar change in drug release pattern occurs which is irrespective of the nature of the polymeric film. The ageing process brought about by storage under stress conditions tended to impede the dissolution process. There is no evidence in the literature to suggest that these moderate storage conditions could produce any physical or chemical changes to the anhydrous theophylline which comprises the tablet core. Hence the decrease in the rate of release is therefore presumably due to the slowing

Table 2.

t50% in hours obtained from dissolution profiles under various storage conditions.

Coating composition	Initial Value	Isothermal at 55% RH						Cyclic	
		28°C		35°C		45°C		45°C,55%RH 28°C,20%RH 5°C,10%RH	45°C,55%RH 28°C, 0%RH
		† 21	90 180	21	90 180	21	90 180	90	90
Ethyl-cellulose 0.5% + PEG 1540 0.25%	0.6	$0.8_{1.0}^{1.1}$		$1.0^{1.2}_{1.3}$		$1.1_{1.4}^{1.5}$		1.0	1.1
Eudragit RL 1.5%	0.7	$0.8_{1.1}^{1.2}$		$1.1^{1.3}_{1.4}$		$1.3_{1.6}^{1.8}$		1.2	1.3
Ethyl-cellulose 2% + Eudragit L 1%	2.4	$2.8_{3.6}^{3.9}$		$3.2^{4.0}_{4.2}$		$4.2_{5.0}^{5.1}$		3.8	3.8

† = Number of days stored

in the rate of molecular diffusion of the drug across the polymeric coating material. Support for this assumption is provided by recently published work,[6,7] in which it is suggested that the permeability of polymer systems may be significantly altered by changes in crystallinity, glass transition temperature, polarity, degree of cross-linking and the binding of drugs with some of the functional groups of the polymer. It is likely that such changes in certain of these parameters will occur in the film coatings during the experimental storage period thus causing the dissolution process to be impeded.

The intention of these tests under conditions of continual stress was to determine the integrity

of the film coating. Internal stresses may build up in the film due to differences in the relative thermal expansion of the coating and the substrate. If these stresses exceed the cohesive strength of the film then cracking and loss of film integrity occurs. This would manifest itself by a faster than expected drug release profile, or even an "immediate release" caused by the entire splitting of the coat. This can lead to toxicity or variable bioavailability. However the dissolution curves clearly demonstrate that the integrity of each of the film coatings was maintained even though there are differences in the chemical structures of the polymers used. There was no evidence of cracking or splitting even in the thinner films.

It is apparent from the t50% values in Table 2 that the greatest reduction in release rate occurs in the first 21 days (isothermal storage) after coating. Although there are further reductions in the release rates at 90 days and 180 days these changes appear to become less significant upon prolonged storage. This would suggest that the mechanism responsible for impeded dissolution would eventually achieve equilibrium. It is also clear that the mechanism responsible for reducing drug release is temperature related since the degree to which the drug was impeded became greater as the storage temperature increased. It would appear that the effect of the variable humidity was insignificant. There was only a slight difference between the release rates

determined for both storage procedures under cyclic conditions. This demonstrates that temperature has a significant effect on the retardation of release as the dissolution profiles obtained for samples stored under cyclic conditions corresponded approximately to the average temperature during Isothermal storage.

It is assumed that any change in *in-vitro* dissolution rate will also produce a corresponding change in drug release *in-vivo*. Therefore it is considered important that film coated oral dosage systems, which release the drug by diffusion through a polymeric membrane, should undergo *in-vitro* dissolution testing after programmed storage periods (simulating the shelf life) so that a more realistic assessment of release may be achieved.

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