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COMPARATIVE EVALUATIONS OF AQUEOUS FILM COATED TABLET FORMULATIONS BY HIGH HUMIDITY AGING

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Compressed tablets of ticlopidine hydrochloride were coated with three aqueous film coating formulations and aged under 95% relative humidity at 23° and 37°. The in vitro dissolution of the drug from tablets coated with the formulation containing polymethacrylic acid esters before aging was slower than the tablets coated with the formulations containing hydroxypropyl methylcellulose or ethylcellulose dispersion. On aging, the in vitro drug dissolution of the coated and uncoated tablets decreased and the decrease depended on the film forming excipient in the coating formulation and the temperature of aging. The tablets coated with the formulation containing polymethacrylic acid esters dissolved very slowly after aging. Higher moisture contents of the tablets after aging under 95% relative humidity at 23° compared to 37° resulted in a consistently lower tablet crushing strength. The tablets coated with the formulation containing 10% hydroxypropyl

methylcellulose showed a smaller decrease in the tablet crushing strength on aging compared to the other two formulations.

INTRODUCTION

There has been a considerable increase in the polymer film coating of tablets over the past decade. Recent government regulations on the use and recovery of organic solvents, ever-increasing price and, occasionally, their spotty availability had a large impact on the tablet film coating development. Aqueous film coating is rapidly becoming the method of choice and this in turn has led to the development of much more efficient coating units and low viscosity water-soluble and water dispersible polymers.

Hydroxypropyl methylcellulose, a water soluble polymer available in lower viscosity types, is one of the most commonly used film forming excipients used in aqueous film coating. Although it is generally believed that the polymers of higher nominal viscosity produce better films, the lower viscosity grade material permits higher polymer loadings in the coating solutions. Since lower-viscosity grade materials allow a considerable reduction in the coating time, compromise decisions may not lead to the most optimum properties of the final films. A recent report (1) indicated that very small differences were observed between

permeability and mechanical properties of the low and high viscosity polymers.

An interesting approach that may be useful in overcoming the small differences in the quality of the film utilizes aqueous polymeric dispersions of essentially water-soluble polymers. One such product based on polymeric acid esters and another based on ethylcellulose are currently commercially available. Higher polymer contents can be accommodated in these symptoms without marked increases in viscosity. However, because of the insoluble nature of these polymers, water-soluble materials that permit ultimate film breakdown in the gastrointestinal tract must be used in the final formulation.

The methods used to evaluate film coatings have been summarized (2-5), but the principal methods used for isolated films are the film permeability to gases (usually water vapors), mechanical properties (strength, plasticity, elasticity) and diffusion of drug molecules across a concentration gradient. For applied films, the properties of the coated tablets and the drug dissolution rate are usually used to characterize the film coatings, although some attempts have been made to test film adhesion to tablet surfaces and mechanical properties of films on tablets (6-8).

The purpose of this investigation was to evaluate film coated

tablets prepared with a low viscosity water-soluble polymer, hydroxypropyl methylcellulose, and two water dispersible polymers based on ethylcellulose and polymethacrylic acid esters. The in vitro dissolution rate of the three film coated tablet formulations were compared by aging under 95% relative humidity at 23° and 37°. The results of these studies indicated that the tablets coated with the formulation containing polymathecrylic acid esters dissolved most slowly before aging and dissolution became very slow after aging. Tablets coated with the formulation containing 10% hydroxypropyl methylcellulose (low viscosity grade) or ethylcellulose colloidal dispersion also became slower in dissolution on aging and the results were dependent on the temperature of aging.

MATERIALS AND METHODS

Materials

The drug, ticlopidine hydrochloride (chloro-2-benzyl)-5 tetrahydro- 4,5,6,7 thieno(3,2c) pyridine hydrochloride) was obtained from Sanofi Research and was at least 98% pure. Hydroxypropyl methylcellulose (Methocel E-5, premium) from Dow Chemical Co., ethylcellulose dispersion (Aquacoat ECD 30) from FMC Corp. and polymethacrylic acid esters dispersion (Eudragit E 30 D) from Rohm Pharma were used as film forming agents. Crystalline lactose (regular grade) from Foremost Co., citric acid anhydrous from Pfizer, povidone (K 29-32) from BASF, talc

from J. T. Baker were all USP grade. Corn starch from Staley Manufacturing Co., magnesium stearate from Mallinckrodt Inc., and polyethylene glycol 8000 from Union Carbide were all N.F. grade. Other excipients were diethyl phthalate from Monsanto, silicone antifoam emulsion (AF 75) from General Electric, and FD and C yellow #5, FD and C red #40 and opaspray K-1-4210A from Colorcon Inc.

Preparation of Granules

The tablet core formula contained 64.1% ticlopidine hydrochloride, 22.4% lactose, 10% corn starch, 2% povidone, and 0.5% magnesium stearate. The drug and the lactose were mixed in a planetary mixer for 10 minutes. Citric acid and povidone were dissolved in water and this solution used to granulate the powder mixture. The wet granulation was passed through a screen with an aperture of 1.7 mm and dried in a forced air oven at 50^{o} to about 3% moisture. The dried granules were passed through a 1.18 mm aperture screen. The starch and the magnesium stearate were mixed by geometric dilution and blended with the dry granulation for 5 minutes. The granulation moisture was determined with a moisture balance (Cenco, Central Scientific Co., Chicago, IL 60623). The moisture content of the granulation blend was 2.6%.

Compression

The tablets were compressed by means of a single punch machine

(Stokes model F4) to a tablet crushing strength of about 13 strong Cobb units using 1.11 mm standard concave punches and die. The target tablet weight was 390 mg. The tablet crushing strength was determined by the Schleuniger 2E hardness tester (Vector Corporation Marion, Iowa 52302).

Coating Solution

The compositions of the tablet coating solutions are given in Table 1. Formulation I contained 10% hydroxypropyl methylcellulose, 2% polyethylene glycol 8000, 4% opaspray and 84% purified water. The hydroxypropyl methylcellulose was added to a part of the water which was preheated to 80°. The remaining water was cooled to 5° and was added to the cellulose dispersion while stirring. The polymer completely dissolved as the dispersion was cooled to 20°. The polyethylene glycol was then added and stirring continued until it was completely dissolved. The opaspray was then added, mixed and the coating suspension was passed through a 0.175 mm aperture screen.

Formulation II contained 22.22% ethylcellulose dispersion, 6.67% hydroxypropyl methylcellulose, 1.33% diethyl phthalate, 7% titanium dioxide/pigment and 62.78% water. The ethylcellulose dispersion and diethyl phthalate were stirred for 15 minututes. To part of the water which was preheated to 75-80°, hydroxypropyl methylcellulose was added. Sufficient cold water

TABLE I

Aqueous Film Coating Formulations

Excipients	Formulation I	Formulation II	Formulation III
Hydroxypropyl Methylcellulose [1]	10	6.67	0.75
Polyethylene Glycol 8000	2		2.25
Opaspray K-1-4210A	4		
Ethylcellulose [2] Colloidal Dispersion		22.22	
Diethyl Phthalate		1.33	
Titanium Dioxide/ Pigment		7	7.5
Talc			9
Magnesium Stearate			3
Antifoam Emulsion AF-75			0.075
Polymethacrylic Acid Esters [3] Dispersion			25
Purified Water	84	62.78	52.425

1) Methocel E-5, Dow Chemical
2) Aquacoat ECD-30, FMC
3) Eudragit E 30 D, Rohm Pharma

was added to the hydroxypropyl methylcellulose to bring the solid contents to 19% and the solution was cooled to 20°C. The ethylcellulose dispersion, hydroxypropyl methylcellulose solution and titanium dioxide/pigment were mixed together and ball milled for about 1 hour.

Formulation III contained 25% polymethacrylic acid esters dispersion, 0.75% hydroxypropyl methylcellulose, 9% talc, 3% magnesium stearate, 7.5% titanium dioxide/pigment, 2.25% polyethylene glycol 8000, 0.075% antifoam emulsion and 52.425% water. The hydroxypropyl methylcellulose and polyethylene glycol were dissolved in water. Magnesium stearate, talc, titanium dioxide and antifoam emulsion were added to the solution. The mixture was ball milled for 1 hour to obtain a uniform dispersion. This suspension was added to the polymethacrylic acid esters dispersion while stirring.

Film Coating

Tablet batches of 6 kg were coated in a 24" Accela-Cota (Thomas Engineering Co.) with a pan speed of 16 rpm. A Binks air gun (model 610) with a 63A fluid nozzel and a 66S air nozzle and an atomizing air pressure of 30-35 psi was used for all 3 coating formulations. A continuous spray delivery of 25-30 g/min was used for formulations I and III and 23-28 g/min was used for formulation II. The flow rate was controlled by means of a peristaltic pump (Harvard Apparatus Model 1210). The inlet

drying air temperature for formulations I and II was 61-63°C and for formulation II, it was 68-70°C. The desired coating weight was 2-2.5% and the coating time for formulation I was 70 minutes and for formulations II and III it was 50 minutes.

Aging and Sampling

The tablets were aged under 95% relative humidity at 23° and 37° in desiccators containing saturated salt solutions. At regular intervals, tablets were sampled for determining *in vitro* drug dissolution, moisture gain, tablet crushing strength and physical appearance. Tablets sampled from the humidity chamber were allowed to equilibrate at ambient room conditions for 24 hours before performing dissolution studies.

In vitro Dissolution

The USP method II was used. For each sampling point, 6 tablets were tested. The apparatus consisted of USP paddles driven by a multiple - spindle drive with a variable speed control (model 72R, Hanson Research Corp., Northridge, CA), 1-liter round-bottom plastic flasks (Elanco, Indianapolis, In) and a water bath. The dissolution medium was 700 ml of deaerated water equilibrated at 37° and stirred at 50 rpm. The dissolved drug was analyzed by recording the absorbance at 236 mm using an automated monitoring system consisting of peristaltic pump (model 1210, Harvard Apparatus, Millis, Ma),

1 mm spectrophotometer flow cells and automatic sample changer/spectrophotometer (Model 25, Beckman Instruments, Fullerton, Ca). The absorbances were plotted on a recorder every minute until complete dissolution was achieved. The mean percent dissolved and the standard deviations at several time points along the dissolution curve were calculated.

The dissolution apparatus was calibrated using USP dissolution calibrator tablets (prednisone 50 mg). The mean dissolution and the standard deviation were within the required specifications.

RESULTS AND DISCUSSION

The results of the in vitro dissolution of ticlopidine hydrochloride from tablets coated with formulation I (10% hydroxypropyl methylcellulose as film forming excipient) before and after aging under 95% relative humidity at 23° and 37° are given in Fig. 1-2. The initial dissolution rate of the drug is influenced by the film coating and remained essentially unchanged at the 5 minute time point after aging. However, at latter time points, there was some decrease in the dissolution rate as a result of aging.

The dissolution profiles of the drug from tablets coated with formulation II (ethylcellulose colloidal dispersion and

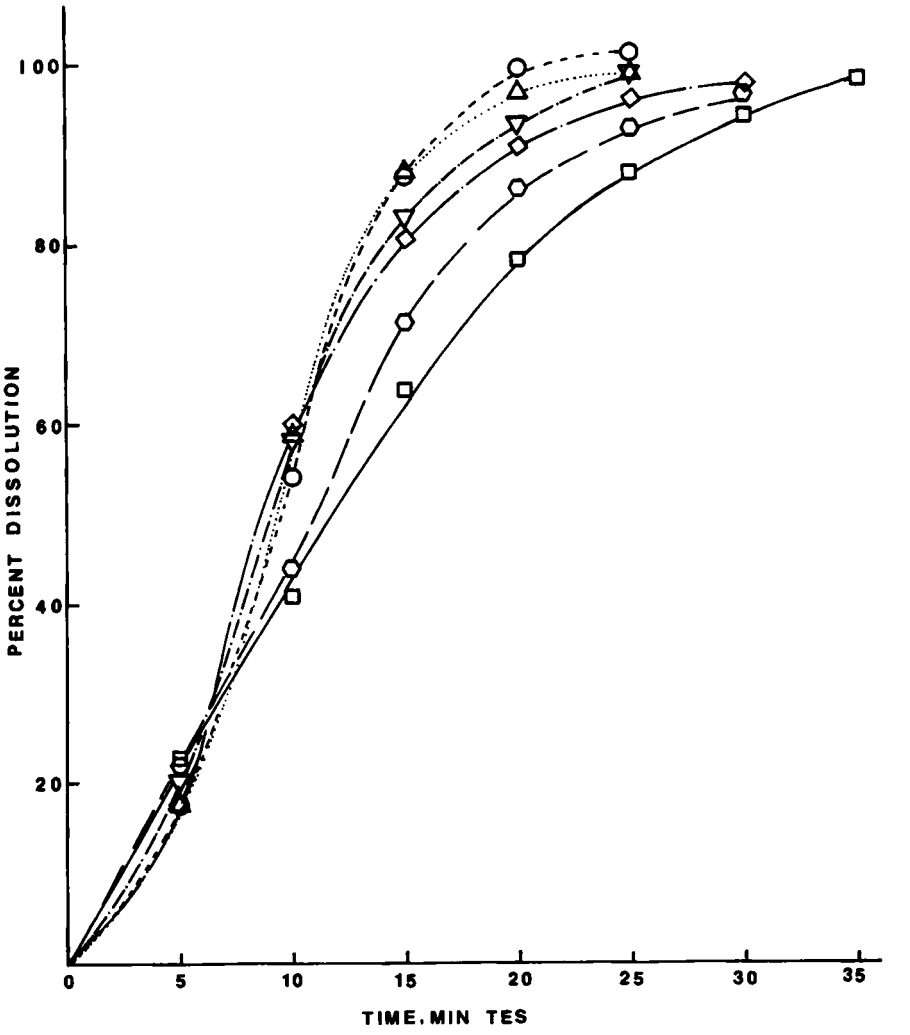

Fig 1:

Effect of aging under 95% relative humidity at 23° on dissolution-time profiles of aqueous film coated ticlopidine hydrochloride tablets (formulation I). Key: ○ , initial; △ , 2 weeks; ▽ , 4 weeks; □ , 8 weeks; ◇ , 12 weeks; ⬡ , 15 weeks.

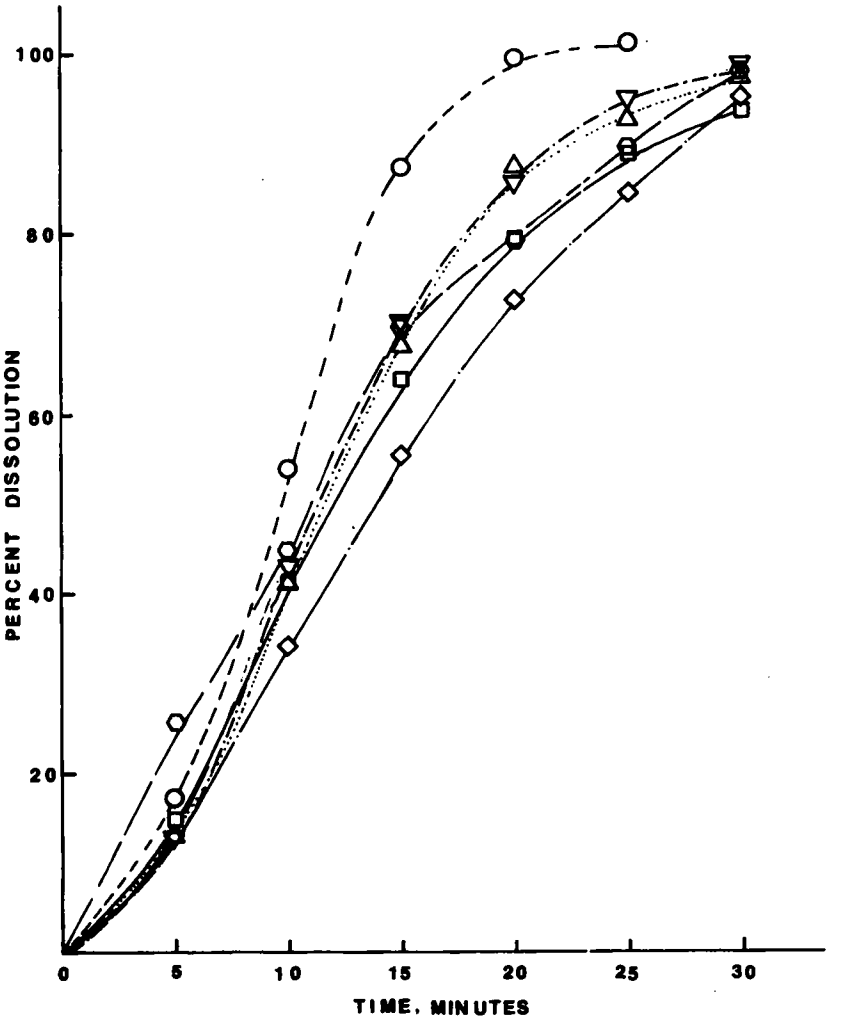

Fig. 2:

Effect of aging under 95% relative humidity at 37° on dissolution-time profiles of aqueous film coated ticlopidine hydrochloride tablets (formulation I). Key: ○, initial; △, 2 weeks; ▽, 4 weeks; □, 8 weeks; ◇, 12 weeks; ⬡, 15 weeks.

hydroxypropyl methylcellulose as film forming agents) before and after aging under 95% relative humidity at 23° are given in Fig 3. A substantial change in the drug dissolution profiles was seen as a result of aging under these conditions. The in vitro dissolution rate increased after 2 weeks storage, but on further aging there was a large decrease in the amount of drug dissolved. The dissolution profiles of these tablets after aging under 95% relative humidity at 37° (Fig 4) show very little changes in the dissolution rate compared to the 23° results.

Fig. 5-6 give the dissolution profiles of the drug from tablets coated with formulation III (polymethacrylic acid esters dispersion and hydroxypropyl methylcellulose as film forming agents) before and after aging under 95% relative humidity at 23° and 37°. The initial dissolution rate of these tablets was much slower than the tablets coated with formulation I or formulation II. After 2 and 4 weeks storage at 23° and after 2 weeks storage at 37°, the dissolution rate increased. However, on prolonged aging under these conditions, a large decrease in the dissolution rate was observed.

The plots of the percent drug dissolution at the 15 minute time point versus aging time under 95% relative humidity at 23° for uncoated and coated tablets are given in Fig. 7. The in vitro dissolution of the uncoated tablets before aging was higher than

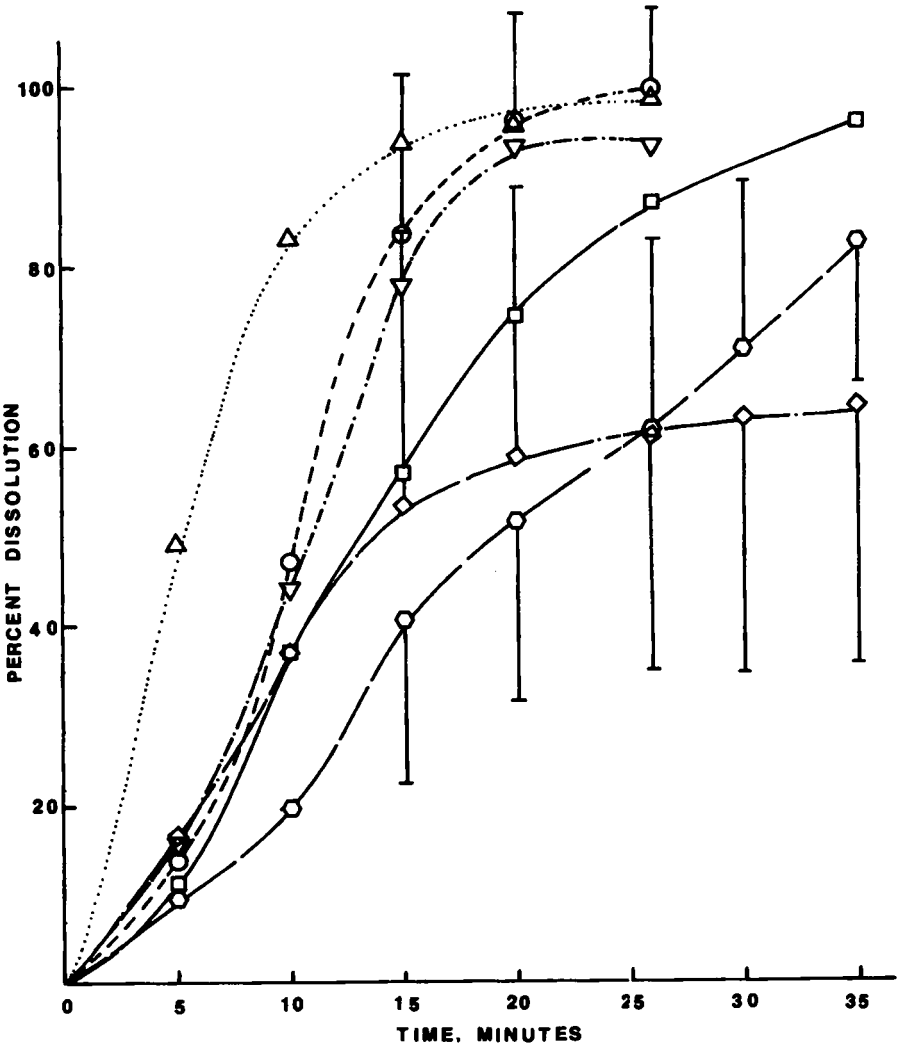

Fig. 3:

Effect of aging under 95% relative humidity at 23° on dissolution-time profiles of aqueous film coated ticlopidine hydrochloride tablets (formulation II). Key: ○, initial; △, 2 weeks; ▽, 4 weeks; □, 8 weeks; ◇, 12 weeks; ⬡, 15 weeks. Vertical lines indicate standard deviations.

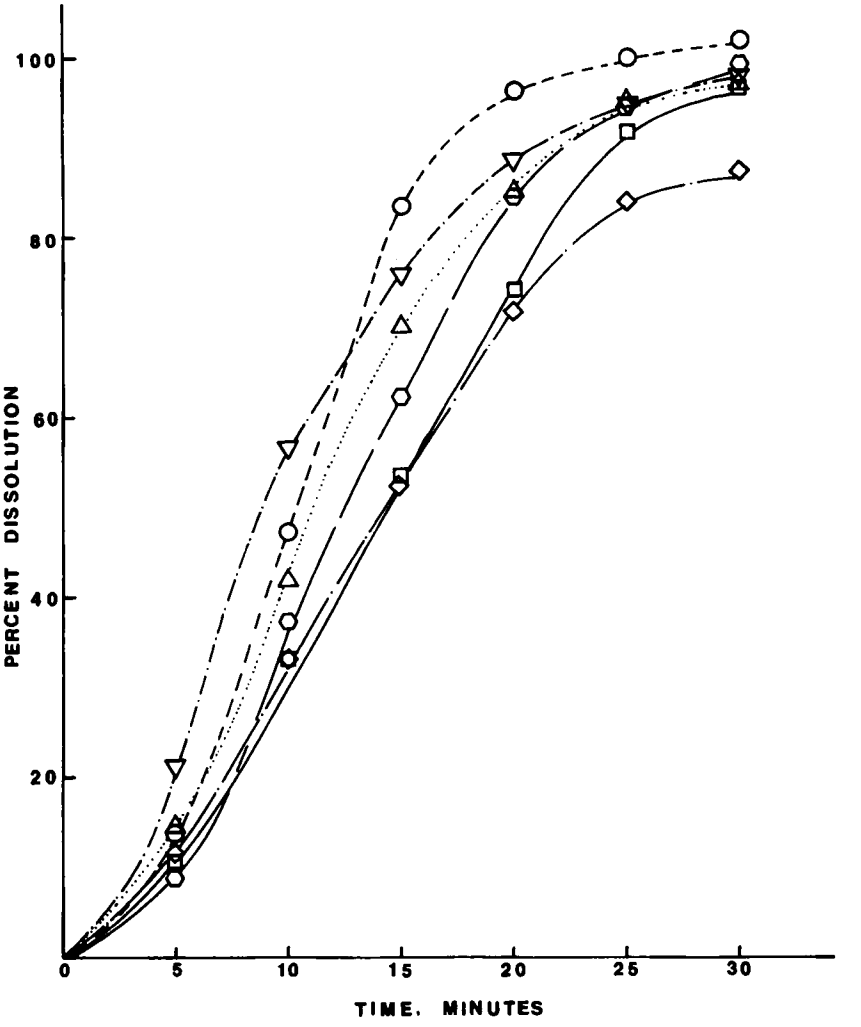

Fig 4:

Effect of aging under 95% relative humidity at 37° on dissolution-time profiles of aqueous film coated ticlopidine hydrochloride tablets (formulation II). Key: ○ , Initial; △ , 2 weeks; ▽ , 4 weeks; □ , 8 weeks; ◇ , 12 weeks; ⬡ , 15 weeks.

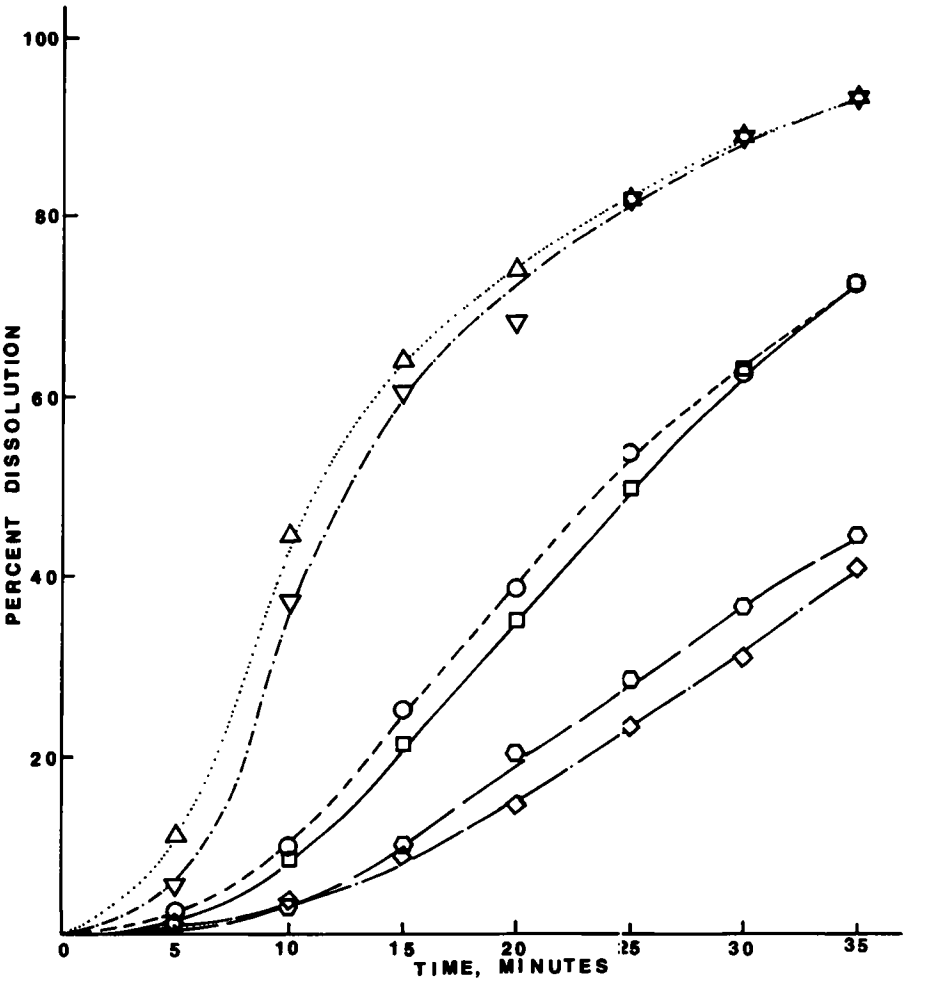

Fig. 5:

Effect of aging under 95% relative humidity at 23° on dissolution-time profiles of aqueous film coated ticlopidine hydrochloride tablets (formulation III). Key: ○, initial; △, 2 weeks; ▽, 4 weeks; □, 8 weeks; ◇, 12 weeks; ⬡, 15 weeks.

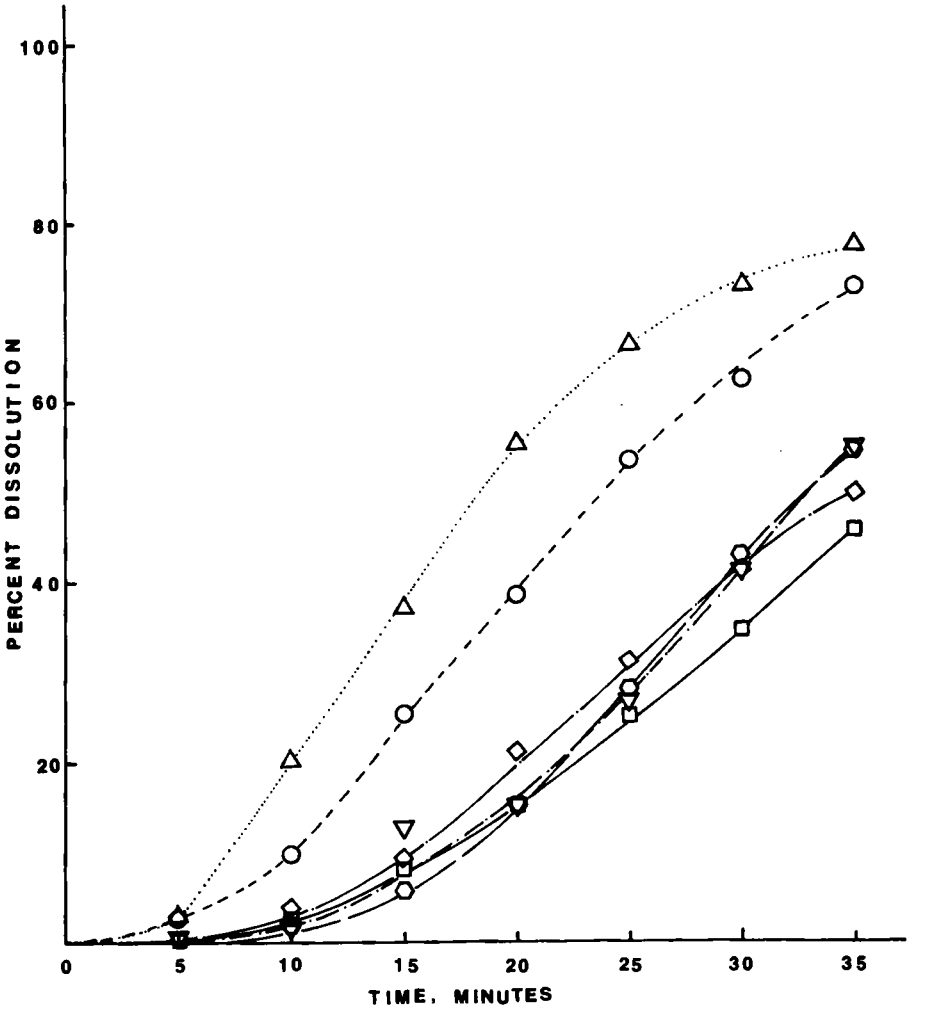

Fig 6:

Effect of aging under 95% relative humidity at 37° on dissolution-time profiles of aqueous film coated ticlopidine hydrochloride tablets (formulation III). Key: ○, initial; △, 2 weeks; ▽, 4 weeks; □, 8 weeks; ◇, 12 weeks; ⬡, 15 weeks.

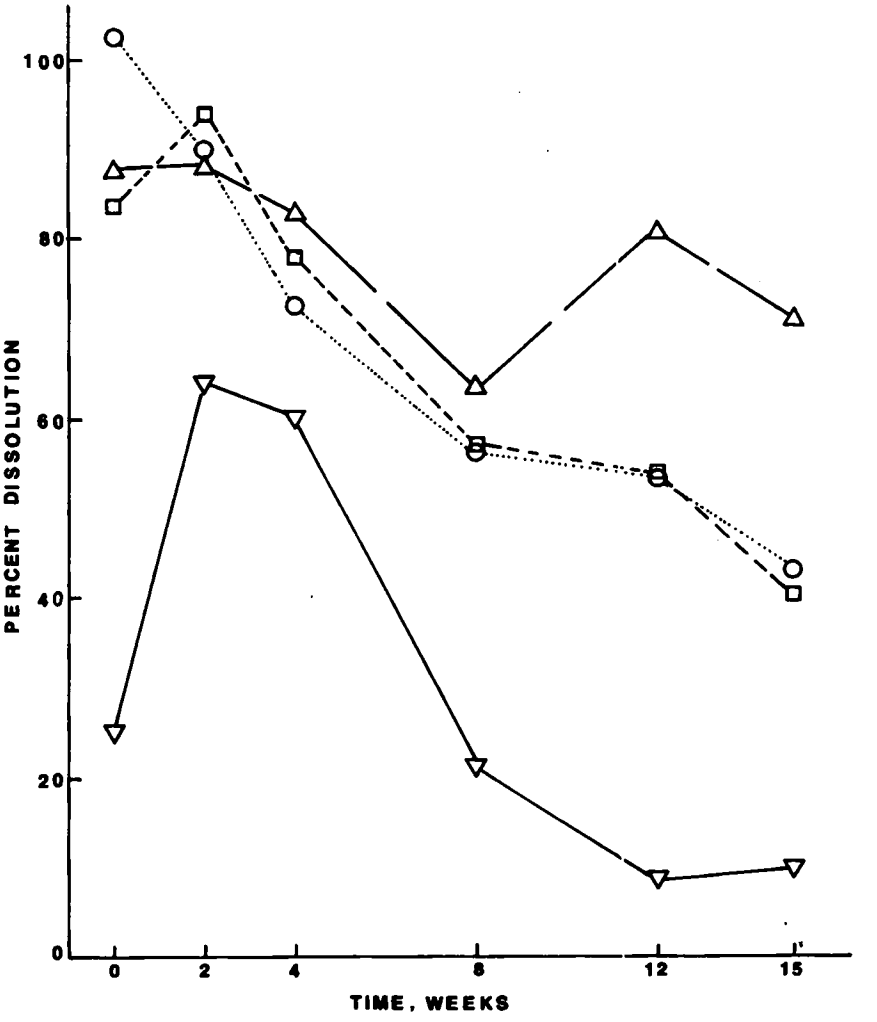

Fig 7:

Plots of the percent drug dissolution at 15 minute time point versus aging time under 95% relative humidity at 23° of uncoated and aqueous film coated ticlopidine hydrochloride tablets. Key: ○, uncoated; △, coated with formulation I; □, coated with formulation II; ▽, coatec with formulation III.

the coated tablets. Among the coated tablets, the dissolution of formula III coated tablets before aging was very slow. On aging, the uncoated tablets and the formula I and II coated tablets decreased in dissolution in a similar fashion with the exception that formula I coated tablets were much higher in dissolution after 12 and 15 weeks of aging. The tablets coated with formula III increased in the in vitro dissolution after 2 and 4 weeks of aging, but on further aging there was a large decrease in the drug dissolution.

Fig. 8 gives the plots of the percent drug dissolution at the 15 minute time point versus aging time under 95% relative humidity at 37° for the uncoated and film coated tablets. The in vitro dissolution of the uncoated tablets decreased slightly on aging under these conditions. The tablets coated with formula I and formula II were somewhat slower in dissolution after aging. The tablets coated with formula III became very slow in dissolution after aging for 15 weeks.

The moisture contents of the uncoated and film coated tablets as a function of aging time under 95% relative humidity at 23° and 37° are given in Fig. 9 At 23°, the moisture content of the tablets increased gradually with the possible exception of uncoated tablets and formula III coated tablets after 15 weeks of aging. There was no moisture gain and a possible decrease in

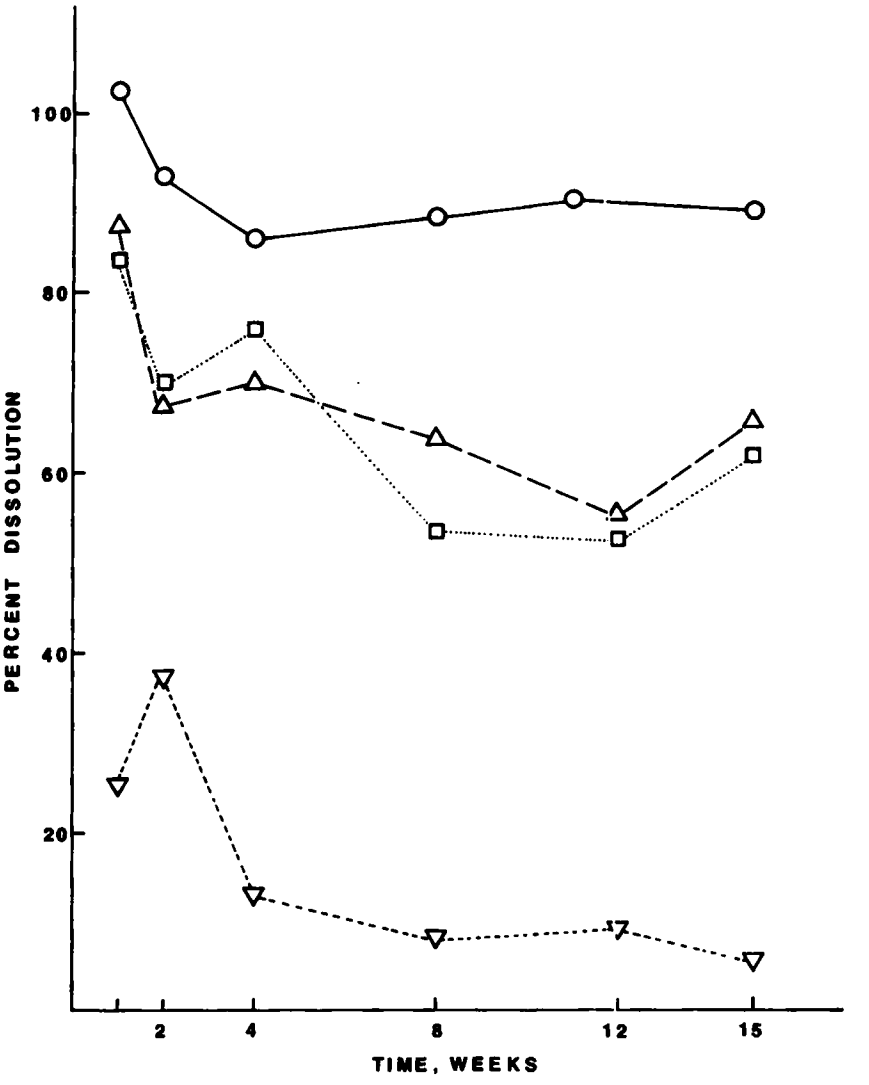

Fig 8:

Plots of the percent drug dissolution at 15 minute time point versus aging time under 95% relative humidity at 37° of uncoated and aqueous film coated ticlopidine hydrochloride tablets. Key: ○, uncoated: △, coated with formulation I; □, coated with formulation II; ▽, coated with formulation III.

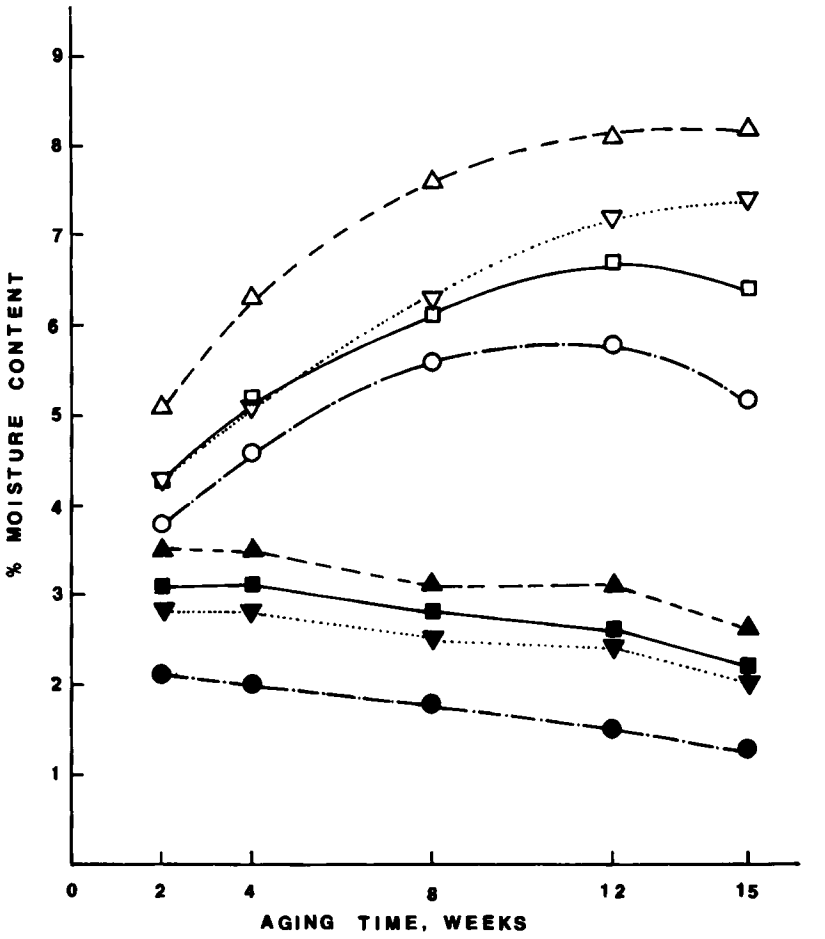

Fig 9:

Percent moisture content of aqueous film coated ticlopidine hydrochloride tablets after aging under 95% relative humidity at 23^{o} and 37^{o}C. Key: △ , ▲, formulation I, ▽ , ▼, formulation II; □ , ■ , formulation III. Open data points represent 23^{o} aging and closed data points represent 37^{o} aging.

the moisture content after 15 weeks aging at 37° under 95% relative humidity.

Fig. 10 gives the crushing strength of film coated tablets after aging under 95% relative humidity at 23° and 37°. The crushing strength of the tablets aged at 23° was lower than the crushing strength of tablets aged at 37°. The tablets coated with formulation I showed smaller decreases in the tablet crushing strength on aging under these conditions compared to the other two formulations.

All film coated tablets showed a decrease in the color intensity on aging for more than two weeks under these conditions. The color in the film coating migrated into the tablet core after 8 weeks storage under 95% relative humidity at 23°. The tablets coated with formulation I containing FD & C blue #1 lake completely discolored on prolonged storage. The tablets coated with formulation II became sticky after 4 weeks storage, chipped on the surface after 8 weeks and the film cracked after 12 and 15 weeks of aging. These physical changes in the film resulted in large variability in dissolution results (Fig. 3) and were less pronounced in tablets aged under 95% relative humidity at 37°.

CONCLUSION

On aging under high relative humidity, the uncoated and the film

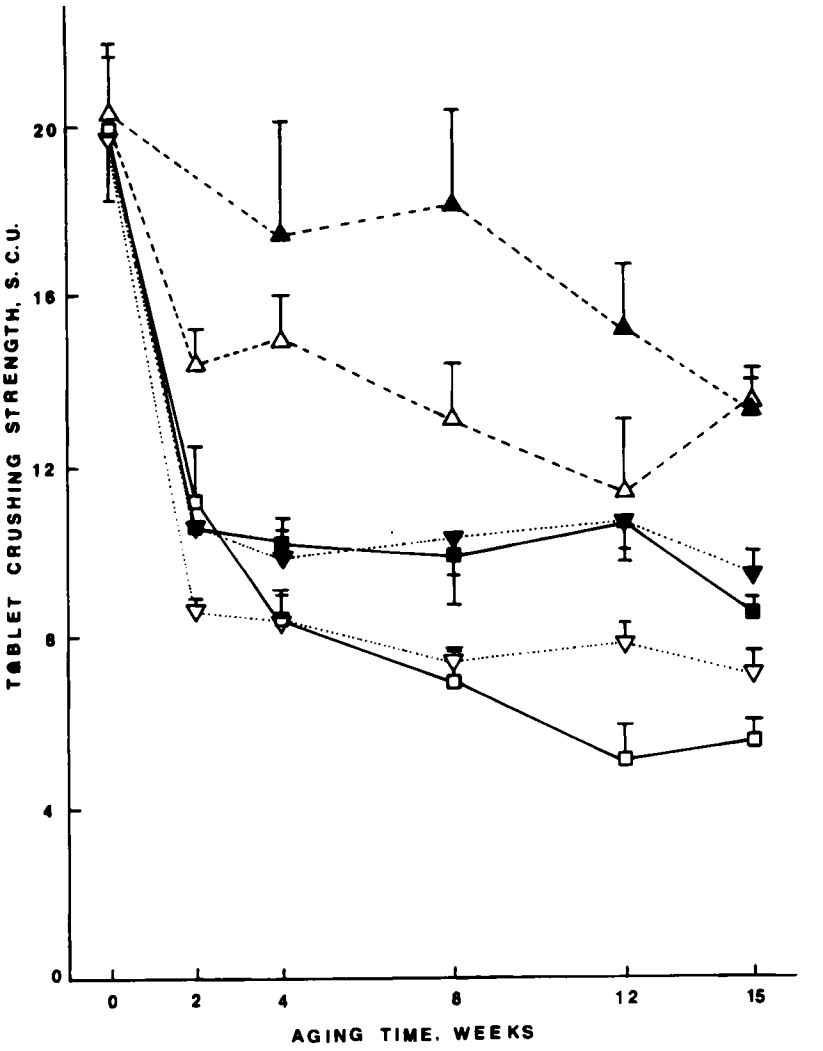

Fig 10:

Tablet crushing strength of aqueous film coated ticlopidine hydrochloride tablets and the effect of aging under 95% relative humidity at 23° and 37°C. Key: △ , ▲ , formulation I; ▽ , ▼ , formulation II; □ , ■ , formulation III. Open data points represent 23° aging and closed data points represent 37° aging. Vertical lines indicate standard deviations.

coated tablets decreased in the in vitro drug dissolution. The decrease in the dissolution rate appears to be related to the nature of the film coating formulation, temperature of aging, amount of moisture gain and the tablet core formulation. The tablets coated with the formula containing polymethacrylic acid esters were slow in dissolution before aging and became very slow after aging. The tablets coated with the formulation containing 10% hydroxypropyl methylcellulose or ethyl cellulose dispersion were similar in dissolution after aging at 23° and 37° except that the hydroxypropyl methylcellulose tablets increased in dissolution after 12 and 15 weeks storage at 23°. The tablets coated with the formulation containing ethylcellulose dispersion developed some mechanical problems, such as, cracks were seen in the film after aging. The results suggest that film coated tablets should be protected from high relative humidity in order to maintain good dissolution throughout the shelf-life of the product.

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