Constant Potassium Chloride Release from Microporous Membrane-Coated Tablets Prepared with Aqueous Colloidal Polymer Dispersions

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To achieve constant drug release and to avoid the use of organic solvents, potassium chloride tablets were coated with aqueous latexes containing dispersed pore-formers with pH-dependent solubility characteristics. The pore-forming agent, dibasic calcium phosphate, was insoluble in the latex but soluble at low pH. Upon contact with simulated gastric fluids, it leached out rapidly to form a rate-controlling, microporous membrane. The release of potassium chloride was linear with time up to 75–80% drug released. It increased with increasing level of pore-former and decreasing membrane thickness but was independent of the degree of agitation and the pH of the dissolution medium after leaching of the pigments. Upon storage at different relative humidities, moisture uptake of the film coat and variations in the release profiles over time were minimal.

KEY WORDS: aqueous latexes; controlled drug release; zero-order drug release; microporous membranes; pore-forming agent; potassium chloride; tablet coating.

INTRODUCTION

Oral drug delivery systems with constant drug release include osmotic devices (1), tablets coated with multiporous membranes (2,3), and matrix systems which balance an increase in the diffusional path length over time with an increase in the surface area available for drug release (4,5).

With osmotic tablets, the presence of a single orifice could result in a nonconstant drug release as a result of clogging of the orifice and, with irritating drugs, in serious side effects in the gastrointestinal tract. To overcome the drawbacks of a single orifice, soluble tablet cores were coated with an organic solution of impermeable or semipermeable polymers (polyvinyl chloride or cellulose acetate) containing dispersed, water-soluble pore-formers such as micronized sucrose or sorbitol (2,3). Upon contact with dissolution fluids, the pore-formers leached out rapidly to form a multiporous rate-controlling membrane through which the drug diffused in a zero-order fashion. Potassium chloride, a highly water-soluble and irritating drug, was used in both systems.

The disadvantages of the multiporous systems are the use of organic solvents necessary to dissolve the polymers and stability problems resulting from the sensitivity of the membrane to moisture because of the hygroscopicity of the pore-formers. Safety hazards, toxicity, and high costs prompted the development of aqueous latexes or colloidal polymer dispersions to replace organic solvents in the coating of solid dosage forms with water-insoluble polymers (6). The objective of this study was to prepare microporous membrane-coated potassium chloride tablets in a completely aqueous environment by using aqueous latexes.

MATERIALS AND METHODS

Materials. Materials included chlorpheniramine maleate (Sigma Chemical Co., St Louis, MO), potassium chloride crystals, U.S.P. (J. T. Baker Chemical Co., Phillipsburg, NJ); calcium phosphate, dibasic, dihydrate U.S.P. ($CaHPO_4$; particle size, <10 μm; Spectrum Chemical Mfg. Corp., Gardena, CA); lactose (Fast-Flo, hydrous, N.F.; Foremost Whey Products, Baraboo, WI); magnesium stearate (Mallinckrodt, Inc., Paris, KY); poly(ethylacrylate-methylmethacrylate) latex (Röhm Pharma, West Germany); styrene butadiene latex (Dow Chemical Co., Midland, MI); and ethylene-vinyl chloride emulsion (Air Products and Chemicals, Inc., Allentown, PA).

Preparation of Core Tablets. Potassium chloride crystals (sieved through a No. 40-mesh screen) were blended with magnesium stearate (0.5%, w/w; sieved through a No. 80-mesh screen) for 5 min in a twin-shell blender (The Patterson-Kelley Co., East Stroudsburg, PA). Chlorpheniramine maleate and lactose (sieved separately through a No. 40-mesh screen) were blended for 20 min, followed by the addition of magnesium stearate (0.5%, w/w; sieved through No. 80-mesh screen) and blending for an additional 5 min before compression. The potassium chloride tablets (weight, 700 mg; hardness, 6 kp) and the chlorpheniramine maleate tablets (12 mg drug; weight, 500 mg; hardness, 7 kp) were prepared by direct compression on a Stokes F single-punch tableting press using 3/8-in.-deep cup punches.

Tablet Coating. The tablet cores were coated in a Hi-Coater (Model HCT-20, Vector Corporation, Marion, IA; coating conditions—300 g charge; inlet temperature, 70–75°C; outlet temperature, 35–40°C; nozzle air pressure, 1.0–1.5 kg/cm^2; pan speed, 20–25 rpm; spray rate, 3–5 ml/min). The pore-former, $CaHPO_4$, was dispersed into water to obtain a slurry which was then added into the latex in various proportions (65–80%, w/w, on a solid basis). The tablets were coated slowly (1 ml/min) during the first 15 min to prevent dissolution of the drug into the film coat. The spray rate was then gradually increased to 3–5 ml/min. The coated tablets were oven-cured at 40°C for 16 hr and stored for further experiments. The membrane thickness was determined from the difference between the thickness of uncoated and that of coated tablets (micrometer, Paul N. Gardner Company, Inc., Pompano Beach, FL; $n = 6$). The density of calcium phosphate was 3.257 g/cm^3 (helium pycnometer, Micromeritics Instrument Corp., Norcross, GA) and was used to calculate the volume fraction of the pore-former in the film coat.

Dissolution Study. The USP XXI rotating paddle method (dissolution test station, Hanson Research Corp., Northridge, CA; 37°C, 50 rpm, 500 ml 0.1 *M* HCl or 0.1 *M* pH 7.4 citric acid–Na_2HPO_4 buffer to simulate gastric juice and intestinal fluid; $n = 3$; coefficient of variation, <5%) was used to study the drug release from the coated tablets.

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The samples were assayed, after appropriate dilution with double-distilled water and ionic strength adjustor (5 *M* NaCl), by a potassium ion selective electrode (Orion Model 93-19, Orion Research Inc., Cambridge, MA) equipped with double-junction reference electrode (Orion Model 90-02) and a microprocessor pH/millivolt meter (Orion Model 811). Interference from other ions present in the dissolution medium was negligible within the concentration range assayed. Unless otherwise mentioned, all dissolution studies were performed in 0.1 *M* HCl. The release rate and lag time were obtained by plotting the cumulative amount of drug released versus time. The linear portion of the curve was determined statistically by linear regression analysis.

Determination of Calcium Phosphate. A colorimetric molybdovanadophosphate method (7) was used to determine the concentration of the pore-former, $CaHPO_4$, in the film coat and in the dissolution medium.

Scanning Electron Microscopy. The cross sections of the coating before and after dissolution studies were examined by scanning electron microscopy (SEM). The dried films were coated for 70 sec under an argon atmosphere with gold–palladium (Pelco Model 3 Sputter Coater) and then observed with a scanning electron microscope (Jeol JSM 35C).

Storage Humidity Study. The tablets were stored in desiccators containing saturated solutions of $MgCl_2$, $Mg(NO_3)_2$, and NaCl for maintaining relative humidities of 33, 54, and 75%, respectively, at 22°C (8). The moisture uptake and drug release characteristics were measured over a 6-month period.

RESULTS AND DISCUSSION

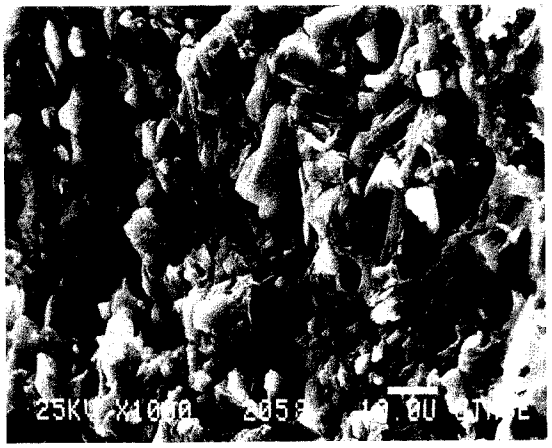
The aim of this study, to prepare multiporous membrane-coated potassium chloride tablets with constant drug release in an organic solvent-free environment, was achieved by coating the tablets with an aqueous colloidal polymer dispersion containing dispersed pore-formers. Sucrose or sorbitol, which have been used as pore-formers in the coating of potassium chloride tablets with organic polymer solutions, could not be used because they dissolved in the latex. Most latexes have a neutral or alkaline pH as a result of the presence of anionic or nonionic surfactants used to stabilize the colloidal polymer particles. A pore-former had to be found which was insoluble and could be dispersed in the latex but was soluble in gastric fluids. Calcium phosphate had the required solubility characteristics by being insoluble in the latex but rapidly soluble in simulated gastric juice. The calcium salt is widely used as a tablet filler and is physiologically inert (9).

Potassium chloride tablets were coated with different latexes containing varying amounts of pore-former. Because of the dispersed state of the polymer, latexes have a high solids content without encountering excessive viscosity. The polymer can therefore be applied more rapidly when compared to organic polymer solutions, resulting in shorter processing times (10). Upon drying and water evaporation, the colloidal polymer particles are forced into a close packing, followed by deformation and coalescence of the particles into a continuous film (11,12). In order to be able to incorporate high levels of pore-former in the latex and to form mechanically strong films, the latex must have a high critical pigment volume concentration (13).

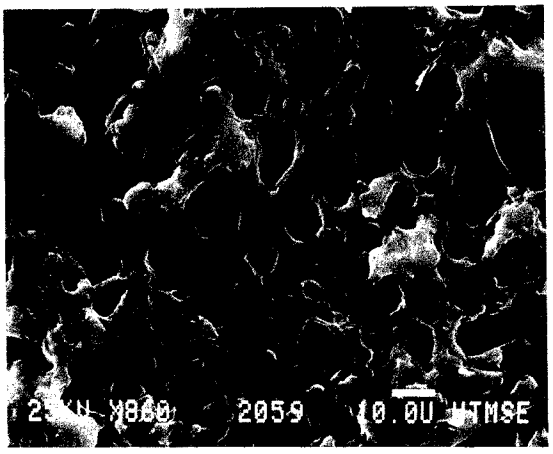
Some latexes (e.g., styrene-butadiene or ethylene-vinyl chloride latexes) formed mechanically strong films at high levels of pore-formers and performed well in simulated gastric juice. However, the coatings failed rapidly upon transfer of the tablets from simulated gastric juice into simulated intestinal fluids. The rupture of the coating was most visible at the tablet edges and could not be avoided by using deep cup punches. The lack of film integrity at higher pH, which was also seen with free latex-cast films in order to eliminate osmotic effects, was attributed to the presence and ionization at higher pH values of anionic surfactants in the film. Dialysis of the latexes and removal of the anionic surfactant improved the mechanical strength in simulated intestinal fluid, however, the coatings still failed at a later stage during dissolution studies. In addition, the selected pore-former, calcium phosphate, may react with anionic surfactants, resulting in latex flocculation prior to the coating process. The latex used in this study was based on a neutral, acrylic polymer, poly(ethylacrylate-methylmethacrylate), stabilized with a nonionic surfactant (isononylphenylpolyoxyethylene glycol). It was insoluble in gastrointestinal fluids and had a minimum film-formation temperature of less than 10°C (14), which obviated the use of a plasticizer. The pore-former could be finely dispersed in the latex without causing flocculation or coalescence of the colloidal polymer particles.

A scanning electron micrograph of a membrane cross section shows the uniform dispersion of the pore-former in the film (Fig. 1A). After exposure of the coated tablets to gastric fluid, calcium phosphate leached out, forming a multiporous, sponge-like membrane (Fig. 1B). The potassium chloride release from coated tablets was investigated as a function of the level of the pore-former, the thickness of the film coat, the pH of the dissolution medium, and the agitation rate. Uncoated tablets dissolved rapidly, and tablets coated with pure latex without pore-former did not release the drug. The weight of the pore-former in the film was varied between 65 and 80%, corresponding to a volume fraction of 0.38–0.57. As expected, increasing the level of calcium phosphate in the film coat increased the drug release (Fig. 2). High levels of pore-formers were required to form a continuous network of pores across the membrane. Below 65% (w/w) pore-former, the drug release was negligible. This might probably be explained by a discontinuous contact between the dispersed calcium phosphate particles. After leaching of calcium phosphate and formation of the multiporous membrane, the drug diffused through the medium-filled pores at a constant rate only as long as excess solid drug was present within the tablet core. The drug release was linear with time up to 75–80% drug released. The release of another water-soluble, but low-dose model drug, chlorpheniramine maleate (12 mg per tablet), was nonlinear with time (Fig. 3). Chlorpheniramine maleate dissolved completely within the medium-filled internal volume of the tablet, resulting in a nonconstant concentration gradient across the membrane and hence a nonconstant drug release.

Increasing the membrane thickness resulted in a decrease in drug release (Fig. 4). Plots of release rate versus the inverse of the membrane thickness at different levels of pore-formers are shown in Fig. 5. A linear relationship was



(A)



(B)

Fig. 1. Scanning electron micrographs of cross sections of film coats before (A) and after (B) dissolution study (80%, w/w, pore-former; film thickness, 116 μm).

predicted theoretically (15). At lower pore-former concentrations, the lines appear to pass through zero, however, the line for the 80% pore-former concentration intercepts at a positive value. The higher than expected drug release could

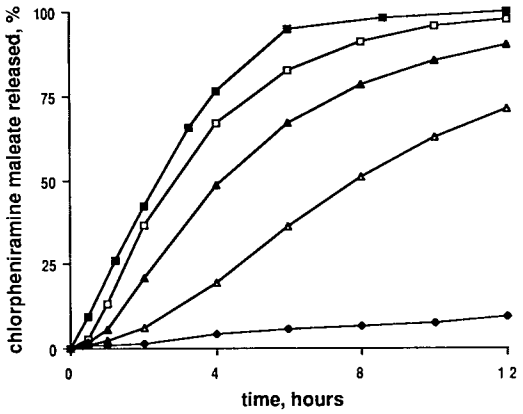


Fig. 3. Effect of the level of pore-former, $CaHPO_4$ (% w/w), in the film coat on chlorpheniramine maleate release (film thickness, 46–66 μm): (■) 80%; (□) 75%; (▲) 70%; (△) 65%; (♦) 60%.

be a result of entrapped air pockets in the coating which were observed at higher pore-former level or additional rupturing of the film through osmotic effects.

Several articles discussed the contact leaching of dispersed metal oxide pigments from antifouling paints (16,17). The rate of leaching was primarily a function of the solubility of the pigment, pigment volume concentration, temperature, and degree of agitation. In this study, rapid leaching of the pore-former was a prerequisite for a short lag time and rapid drug release. The leaching of calcium phosphate into the dissolution medium was studied as a function of film thickness at levels of 70 and 80% (w/w) pore-former by a colorimetric molybdovanadophosphate method. The rate of leaching, which corresponds to the slope of the plot, increased with decreasing membrane thickness and increasing concentration of pore-former (Figs. 6A and B). The leaching was rapid and most of the pore former was released in less than 30 min.

To study the batch-to-batch reproducibility, three batches of tablets were coated on different days and compared with respect to the concentration of pore-former in the film coat and drug release. The level of the pore-former in the film was within 3% of the theoretical value, indicating minimal loss of pigment during the coating process. The po-

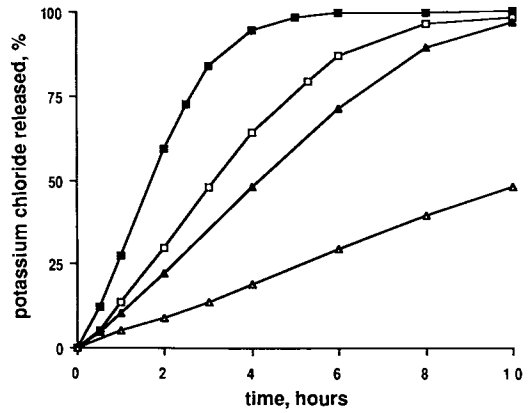


Fig. 2. Effect of the level of pore-former, $CaHPO_4$ (% w/w), in the film coat on potassium chloride release (film thickness, 116–129 μm): (■) 80%; (□) 75%; (▲) 70%; (△) 65%.

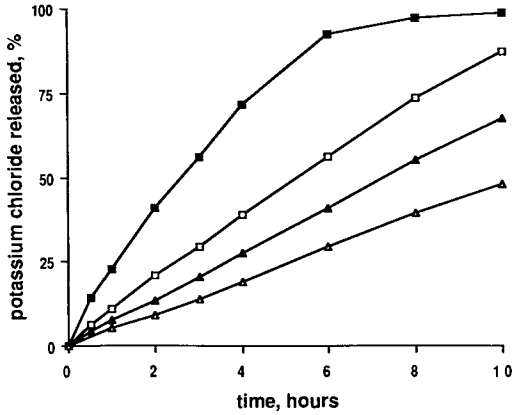


Fig. 4. Effect of the film thickness on potassium chloride release (65%, w/w pore-former): (■) 41 μm; (□) 62 μm; (▲) 71 μm; (△) 129 μm.

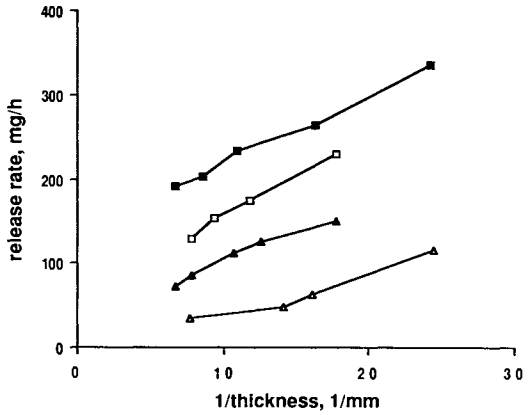


Fig. 5. Potassium chloride release rate versus the inverse of film thickness at different levels of pore-former, $CaHPO_4$ (% w/w): (■) 80%; (□) 75%; (▲) 70%; (△) 65%.

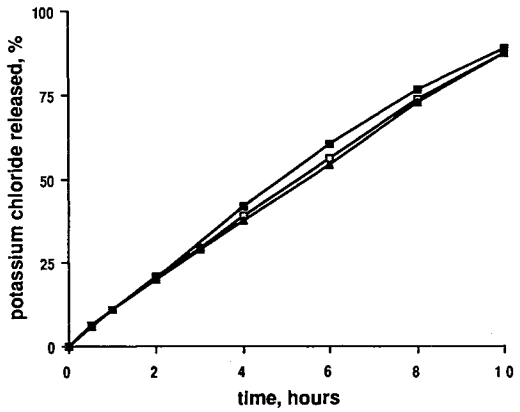


Fig. 7. Batch-to-batch reproducibility of potassium chloride release (65%, w/w, pore-former; film thickness, 62 μm): (■) batch 1; (□) batch 2; (▲) batch 3.

tassium chloride release was almost superimposable as shown in Fig. 7.

Because of the rapid leaching of the pore-former, a change in the dissolution medium from 0.1 *M* HCl to pH 7.4 buffer at different time intervals (0.5, 1, and 2 hr) had virtually no influence on the drug release (Fig. 8). After completion of $CaHPO_4$ leaching, the drug release was insensitive to pH variations. The drug release was also independent of the degree of agitation (Fig. 9).

Besides the elimination of organic solvents, another advantage of this system was its insensitivity to different humidity conditions. The tablets were stored in desiccators with relative humidities of 33, 54, and 75%. The moisture uptake of the tablets was less than 0.01% and the drug release did not vary over time as exemplified with tablets stored at 75% relative humidity (Fig. 10). $CaHPO_4$ is a moisture-insensitive pore-former when contrasted with the hygroscopic pore-formers, sucrose and sorbitol, which were present in membranes prepared from organic polymer solutions (2,3). In our studies, the hygroscopic pore-formers dissolved, formed tacky films at higher moisture levels, and recrystallized on the tablet surface under varying humidity conditions.

An important consideration for the *in vivo* use of this delivery system is the mechanical stability and resistance of the film coat to rupturing during passage through the gastrointestinal tract. None of the tablets ruptured during dissolution studies as observed visually and as indicated by the absence of a burst in drug release. The empty polymeric shells retained their original shape and floated on the disso-

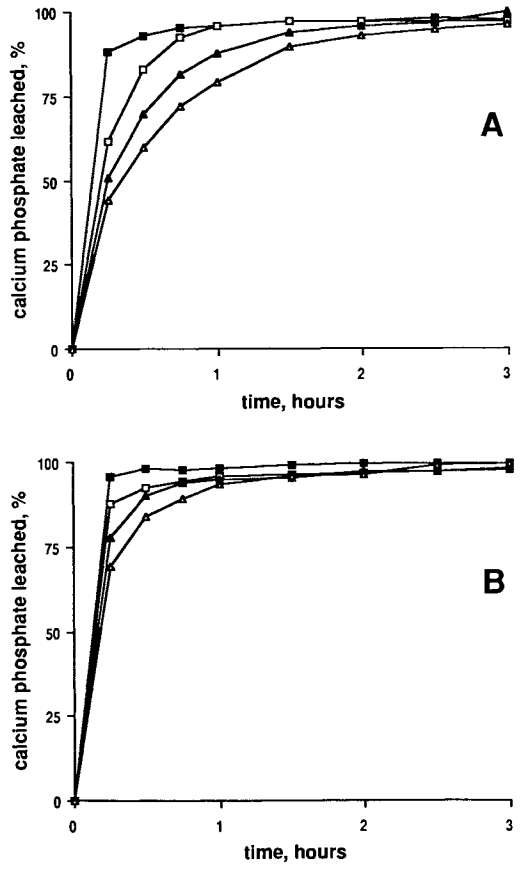


Fig. 6. Leaching of the pore-former, $CaHPO_4$, from tablets with film coats of different thicknesses at (A) 70% (w/w) pore-former—(■) 56 μm, (□) 79 μm, (▲) 94 μm, (△) 128 μm—and (B) 80% (w/w) pore-former—(■) 41 μm, (□) 61 μm, (▲) 92 μm, (△) 117 μm.

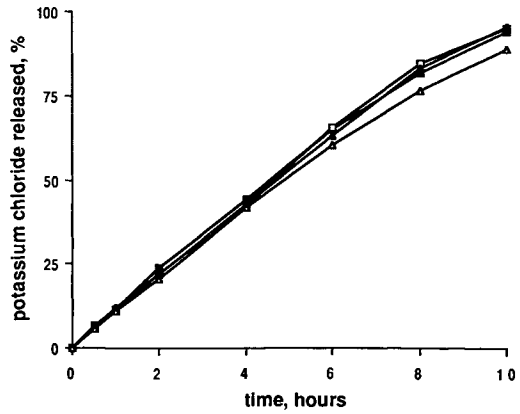


Fig. 8. Effect of pH change (from 0.1 *M* HCl to pH 7.4 buffer after the indicated time interval) on potassium chloride release (65%, w/w, pore-former; film thickness, 62 μm): (■) 0.5 hr; (□) 1 hr; (▲) 2 hr; (△) 0.1 *M* HCl—no medium change.

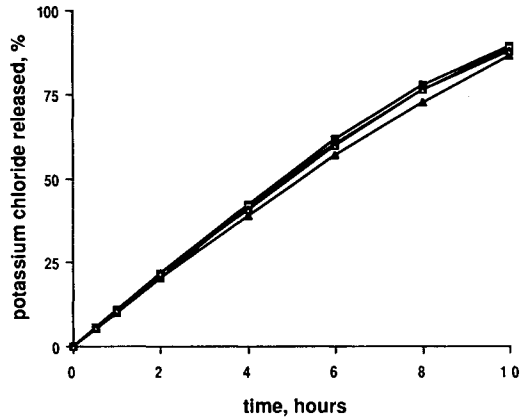


Fig. 9. Effect of agitation rate on potassium chloride release (65%, w/w, pore-former; film thickness, 62 μm): (■) 100 rpm; (□) 50 rpm; (▲) 25 rpm; (△) no agitation.

lution medium after completion of the drug release. Although the coatings did not rupture when deformed by hand, they were flexible, and fluid was pumped from the empty shell under hand pressure. This is a potential disadvantage and latexes resulting in stronger, nondeformable coatings will have to be investigated to overcome this problem.

In conclusion, potassium chloride tablets were coated with an aqueous colloidal polymer dispersion containing a dispersed pore-former to obtain constant drug-release through a multiporous polymeric film. The pore-former, dibasic calcium phosphate, was insoluble in the latex but leached out rapidly from the coating in simulated gastric juice. The drug release was linear with time as long as excess solid drug was present in the tablet core and could be controlled by varying the level of pore-former and thickness of the film coat. This delivery system may present an attractive alternative to similar devices which are prepared with organic solvents.

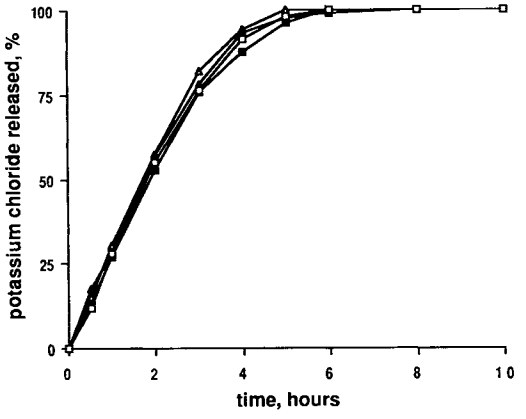


Fig. 10. Potassium chloride release from tablets stored at 75% relative humidity as a function of different storage times (75%, w/w, pore-former; film thickness, 91 μm): (■) original; (□) 1 month; (▲) 3 months; (△) 6 months.

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