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Aqueous pseudolatex of zein for film coating of solid dosage forms

Patrick B. O'Donnell[a,*], Chuanbin Wu[a], Jijun Wang[a], Lisa Wang[a], Benjamin Oshlack[b], Mark Chasin[b], Roland Bodmeier[c], James W. McGinity[a]

[a]*College of Pharmacy, University of Texas at Austin, Austin, Texas 78712-1074, USA*
[b]*Purdue Fredrick Research Center, 99 Saw Mill River Road, Yonkers, New York 10701, USA*
[c]*Institut für Pharmazie, Freie Universität Berlin, Kelchstr. 31, D-12169 Berlin, Germany*

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Abstract

A surfactant-free aqueous based pseudolatex of 6% w/v zein was prepared by spontaneous dispersion of a hydro-alcoholic solution containing 15% zein. Formulation parameters investigated included the type and amount of plasticizer and preservative required in the final dispersion. The pseudolatex was applied to acetaminophen (APAP) tablets in a hi-coater, and to placebo sugar spheres using a uniglatt fluid-bed coater. The dissolution properties of the tablets were investigated in a USP dissolution apparatus, method II. The release media investigated included purified water, 0.1 N HCl, simulated gastric fluid, and phosphate buffer pH 6.0, 6.8 and 7.4. After 12 h, only 35% of the drug was released in purified water from tablets coated with a 5% zein coating. Drug release in purified water could be modified by the application of varied amounts of the zein pseudolatex. Slower dissolution occurred as the pH increased, indicating a relationship between the pH of the dissolution media and the permeability of the zein coating. Simulated gastric fluid containing pepsin caused an increase in the release of APAP due to an interaction of pepsin with the protein based coating. An external coating of Eudragit® L30 D-55 was found to prevent this interaction and sustained release profiles prevailed at pH 6.8. Thermal analysis and X-ray diffraction analysis of the films indicated that the parabens present in the pseudolatex acted as plasticizers.

Keywords: Aqueous film coating; Controlled release; Glass transition temperature; Plasticizers; Preservatives; Pseudolatex; Zein

1. Introduction

Zein is a long chain prolamine of molecular weight 38 000. It has the ability to form films when cast from solution. Zein is isolated from maize gluten by an alcoholic extraction process. It has been used to a limited extent in solid dosage forms as an organic-based granulating agent [1], a pH-sensitive binding solution [2,3], and as an organic solution containing a color concentrated dispersion to be used as a tablet pigment coating [4]. Solutions of zein and drug have been spray dried and the granules have been compressed to produce delayed release tablets [5]. Matrix tablets comprised of zein and methyl cellulose have also been investigated [6]. Other applications of zein have been found in the food industry, primarily as an edible coating for food products [7–9]. A structural model for zein has been proposed by Argos and coworkers [10].

Zein protein displays significant hydrophobic properties and is insoluble in water. It is, however, soluble in a hydro-alcoholic solution. Due to health and environmental concerns with organic solvents, there has been an increased need to develop aqueous coating systems. Existing aqueous-based coating materials include cellulosic and acrylic derivatives. The focus of the current paper was to prepare a pseudolatex of zein and to explore applications of the zein pseudolatex as a coating material for placebo pellet and tablet formulations containing acetaminophen (APAP) as the model drug. In addition, the influence of additives on the thermal

* Corresponding author.

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properties of films prepared from the zein pseudolatex was investigated.

2. Materials and methods

2.1. Materials

Zein regular grade F4000 was used as supplied by Freeman, Tuckahoe, NY. Ethyl Alcohol USP, McCormick Distilling, Weston, MO. Methyl Paraben USP/NF, Propyl Paraben USP/NF, Pepsin USP, and Propylene Glycol USP, Spectrum Chemical, Gardena, CA. Compap L (Acetaminophen) Mallinckrodt Chemical, Greenville, IL. Nu-Core Sugar Spheres NF, size 18 mesh, Crompton and Knowles, Mahwah, NJ. Eudragit® L30 D-55, Rohm Tech, Malden, Massachusetts. Avicel PH-101, FMC, Newark, DE. Cab-O-Sil M5P, Cabot Corporation, Tuscola, IL. Magnesium Stearate NF, Whittaker, Clark, and Daniels, South Plainfield, NJ.

2.2. Methods

The zein pseudolatex was prepared by first dissolving 15% (w/v) zein in a 70:30 mixture of ethanol and purified water. The resulting solution was then poured into an equal volume of purified water and mechanically agitated with a magnetic stirrer at 300 rpm. Spontaneous dispersion occurred and a zein pseudolatex was formed. The reaction vessel was exposed to controlled air flow with continued agitation to allow the ethyl alcohol and a portion of the water to evaporate until a solids content of 6.1% (w/v) zein was achieved.

2.2.1. Coating parameters

Acetaminophen tablets comprised of 65% Compap L, 34% Avicel PH-101, 0.5% magnesium stearate, and 0.5% Cab-O-Sil M5P were made to contain 325 mg APAP using a Stokes B2 rotary tablet press (F.J. Stokes Machine, PA). The average tablet weight was 560 mg and hardness was 9.5 kp. Acetaminophen tablets, 300 g, or approximately 536 tablets, were coated with up to 10% zein (based on tablet weight) in a Freund mini hi-coater (Vector, Marion NJ). The inlet temperature was maintained at 45°C and the outlet temperature was 30°C. The pan speed was set at 20 rpm. The pseudolatex was applied at a rate of 3 ml/min with a 1.5 mm spray nozzle positioned 11 cm above the pan bed. The atomization pressure was 1.0 kg/cm^2, and the air volume was 35 l/min. The coated tablets were allowed to cure in an oven at 45°C for 24 h. These parameters were controlled for each coating run.

Nu-Core sugar spheres, 300 g, were coated with up to 10% zein in a fluid bed coater (Uniglatt Laboratory Unit, Glatt Air Technique, Ramsey, NJ) equipped with a bottom spray head with a 1.0 mm nozzle and a Wurster column. Inlet and outlet temperatures were set at 40°C and 30°C, respectively. The atomization pressure was 1.8 kp/cm^3, and the spray rate was 3 ml/min. The coated beads were allowed to cure in an oven at 45°C for 24 h.

2.2.2. Drug release

Dissolution tests were performed with the USP dissolution method II (paddle method) in a Van-Kel model 6010 dissolution apparatus (Van-Kel Industries, Edison, NJ). Tests were performed at a temperature of 37°C and a paddle speed of 50 rpm on 6 tablets from each batch. Distilled-deionized water was used as the dissolution medium, unless otherwise specified. The samples were analyzed for APAP with a Beckman DU-65 Spectrophotometer (Beckman Instruments, Fullerton, CA) at 250 nm.

2.2.3. Scanning electron microscopy

Samples were mounted on brass stages and coated with gold-palladium for 60 s under an argon atmosphere using a Pelco Model 3 cold sputter module (TED Pella, Tustin, CA) in a high vacuum evaporator equipped with an omni-rotary stage. Scanning electron microscopy was performed using a Jeol model 35 scanning electron microscope (Jeol, Peabody, MA) at 25 kV.

2.2.4. Differential scanning calorimetry

Films were cast from the zein pseudolatex by placing 10 g of the pseudolatex in a 44 mm diameter aluminum pan. The sample was then placed in a 45°C oven for 48 h. Samples of zein film which was formed were accurately weighed and sealed in aluminum DSC sample pans. Differential scanning calorimetry was performed using a TA instruments DSC2920 modulated differential scanning calorimeter (TA Instruments, New Castle, DE). Samples were flash cooled to −20°C followed by heating at a rate of 10°C/min to 230°C.

Table 1
Compatibility of plasticizers (10% polymer weight) with a zein solution or pseudolatex

Plasticizer	Zein solution	Zein pseudolatex
Dibutyl sebacate	Precipitate	Immiscible
Dibutyl phthalate	Precipitate	Precipitates on drying
Triacetin	Gel/precipitate	Cloudy/precipitates on drying
Propylene glycol	Miscible	Miscible
Triethyl citrate	Miscible	Miscible
PED 8000	Miscible	Miscible

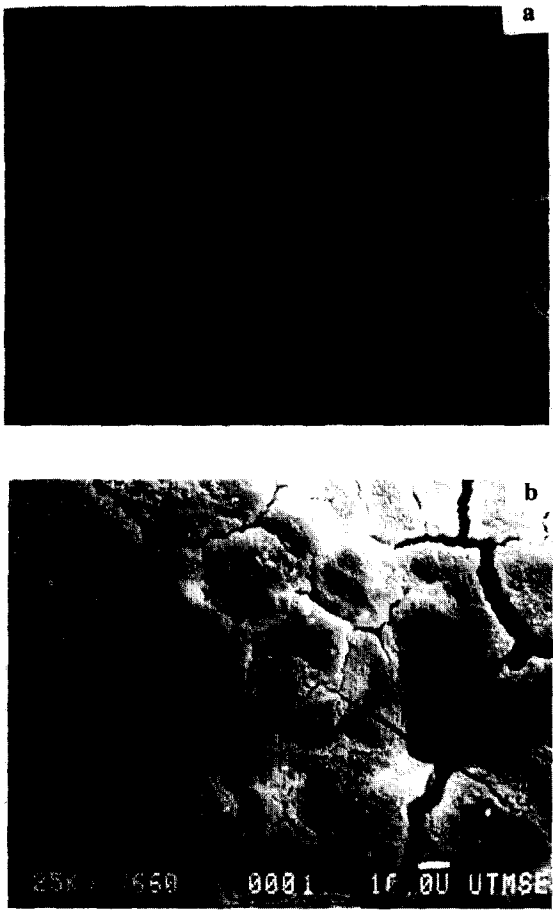

Fig. 1. Scanning electron micrograph of: (a) tablet; and (b) bead coating comprised of zein pseudolatex without methyl or propyl paraben.

2.2.5. X-ray diffraction

The zein pseudolatex was freeze-dried in a Lacoumb lyophilizer (Labconco, Kansas City, MO), and the resultant powder was analyzed using a Philips vertical scanning diffractometer, type 422273 X-ray diffraction apparatus (Philips Electronic Instruments, Mount Vernon, NY). The step increment was set at 0.05 and the time per step was set at 1 s. Freeze drying was necessary to obtain the fine powder necessary for use in X-ray diffraction studies. The powder is spread on a plate and bombarded with high energy electrons. Randomly oriented crystallites will have the correct angle to diffract the incident beam, producing a recognizable diffraction pattern.

3. Results and discussion

3.1. Plasticizer selection

Zein pseudolatexes containing 6.1% solids were produced by the procedure described in the methods section. The pseudolatexes were pale yellow in color and when filtered through a # 200 US standard screen were found to be free of aggregates. Cast films from the zein pseudolatex exhibited severe brittleness and cracking, which demonstrated the need for a plasticizer. Six different plasticizers for both a zein solution and a zein pseudolatex were investigated (Table 1). Propylene glycol, triethyl citrate, and PEG 8000 were all found to be compatible with the zein pseudolatex, however upon drying, both the PEG 8000 and the triethyl citrate separated from the film. Propylene glycol remained incorporated in the film, due to the solubility of zein in propylene glycol. Cast films from a zein pseudolatex plasticized with propylene glycol (35% based on protein weight) were found to be initially flexible and very sticky, however these films became brittle with aging. Due to the tackiness of the zein film formed with 35% propylene glycol as plasticizer, a 25% propylene glycol level was selected for film coating studies.

Table 2
Effect of humidity on the flexibility of zein films cast from a pseudolatex

Time	0% RH	33% RH	50% RH	75% RH
1 Day	Brittle	Flexible	Flexible	Flexible*
3 Day	Brittle	Flexible	Flexible	Flexible*
5 Day	Brittle	Flexible	Flexible	Flexible*
8 Day	Brittle	Brittle	Flexible	Flexible*
17 Day	Brittle	Brittle	Brittle	Flexible*

* Film remained tacky.
RH, relative humidity.

The zein pseudolatex plasticized with 25% propylene glycol was applied to tablet and bead formulations as described in Section 2.2.1. Examination of the tablet coating by scanning electron microscopy revealed numerous surface defects and cracking in the film structure as shown in Fig. 1(a). Likewise, S.E.M. examination of beads coated with the zein pseudolatex (Fig. 1b) displayed a poor coating comprised of numerous cracks and surface defects. Loss of propylene glycol during aqueous film coating has been investigated by

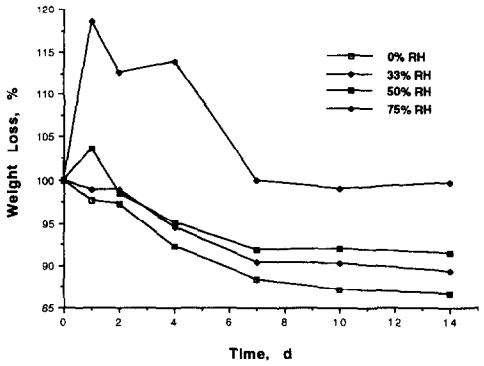

Fig. 2. Change in sample weight as a function of time of cast films stored at different relative humidities.

Table 3
Effect of preservative on zein pseudolatex dispersions

Preservative	Amount (%w/v)	Initial	5 days	15 days	30 days
Benzalkonium chloride	0.25	Stable	Slight sediment	Unchanged	10% sediment
Benzoic acid	0.5	Stable	Slight sediment	Unchanged	2.5% sediment
Benzyl alcohol	1	Stable	Slight sediment	Unchanged	1.0% sediment
Methyl paraben	0.2	Stable	Slight sediment	Unchanged	Unchanged
Propyl paraben	0.02	Stable	Slight sediment	Unchanged	Unchanged
Control	0	Stable	Slight sediment	All sediment	Foul odor

other researchers [11]. The failure of the plasticizer and the loss of moisture from the zein film as the tablets or beads dried in the coating device promoted the formation of cracks in the film, similar to the cracks that were observed with cast film studies.

3.2. Cast film studies

3.2.1. Effect of relative humidity

Zein films were cast as described in the methods Section 2.2.4. Cast films containing 35% propylene glycol were placed in desiccators at 25°C and stored at relative humidities of 0, 33, 50, and 75%, respectively. Films stored at 0% relative humidity became brittle after one day, whereas films stored at 75% relative humidity remained flexible over a 17 day period (Table 2). Films stored at 33% relative humidity remained flexible for only 5 days. Cast films were accurately weighed using a Sartorius MP8-1 electronic balance (Sartorius, Germany), and then placed in humidity chambers set at 0, 33, 50 and 75% relative humidity. The change in moisture of the sample was determined by the change in sample weight over a 14 day period. The change in weight of each sample was expressed as a percentage, with the initial weight designated as 100%. Films stored at 75% relative humidity initially adsorbed moisture, but returned to the original weight after 7 days as shown in Fig. 2. However, films stored at 0% relative humidity lost moisture rapidly after a seven day period, and experienced a net loss in weight of 13.4%. The loss of moisture correlated with the change in flexibility of the films stored under the same conditions. The loss of moisture, and possibly the inability of the plasticizer to soften and extend the polymeric matrix propagated the formation of cracks in the cast films.

3.2.2. Preservation of dispersion

It was noted that the zein pseudolatex began to display aggregation due to the formation of mold colonies several days after production. Zein particles adhered to the mold colonies until the aggregates were large enough to settle to the bottom of the reaction vessel. It was also observed that the pseudolatex produced an odor which suggested the presence of microbial growth. Table 3 outlines the effect of several common preservative systems which were investigated with the zein pseudolatex. The recommended level of preservatives as suggested from the literature was used for the study [12,13]. Of the preservatives tested, methyl paraben and propyl paraben were found to be the most effective in stabilizing the formulation, and after a 30 day period the zein pseudolatex did not show any sign of sedimentation caused by the formation of aggregates. The control sample, however, displayed complete sedimentation and a foul odor. Films cast from the zein pseudolatex without the addition of propylene glycol or methyl paraben was found to be brittle after equilibration for 24 h at 45°C. Free films cast from the zein pseudolatex without propylene glycol

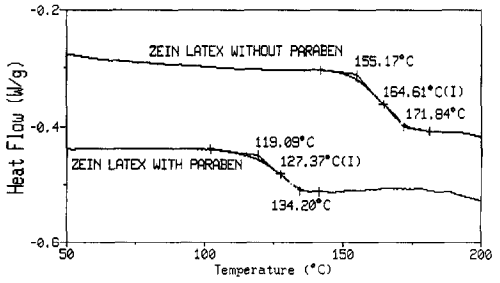

Fig. 3. Thermograms of cast films of zein pseudolatex with and without methyl paraben (12% protein weight) and propyl paraben (1.2% protein weight).

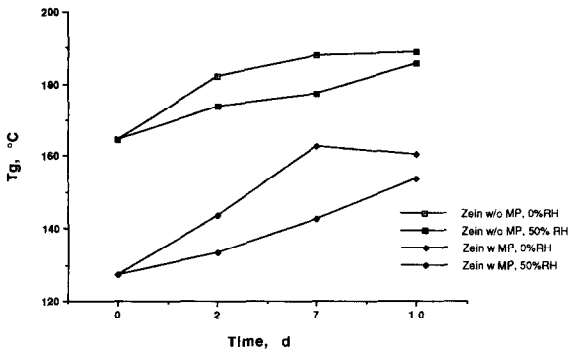

Fig. 4. Influence of relative humidity on the glass transition temperature of preserved and non preserved zein pseudolatex films as a function of time.

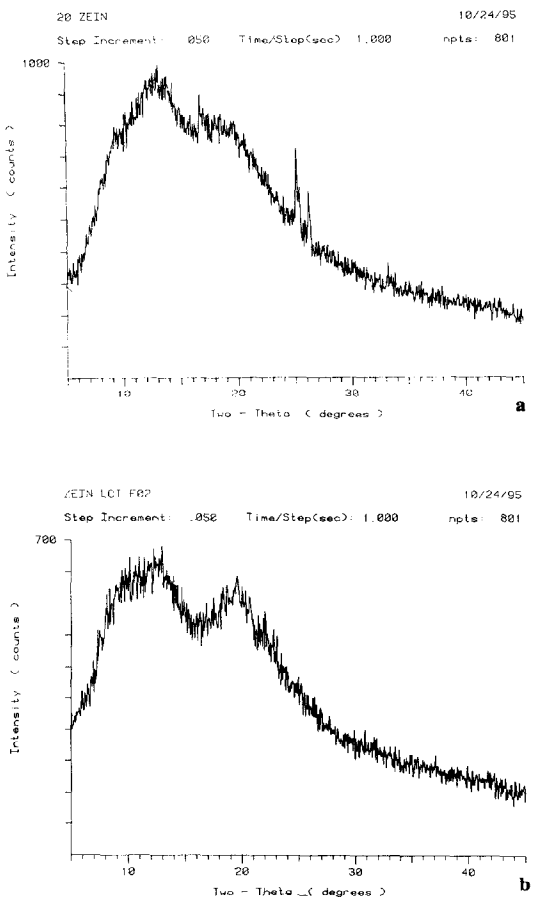

Fig. 5. X-ray diffraction patterns of: (a), a physical blend of Zein with methyl paraben (12% protein weight) and propyl paraben (1.2% protein weight); and (b), a freeze dried zein pseudolatex of zein with methyl paraben (12% protein weight) and propyl paraben (1.2% protein weight).

but containing 0.2% methyl paraben, (equivalent to 12% polymer weight) were found to be flexible after equilibration for 24 h at 45°C, which indicated that the paraben also functioned as a plasticizer.

3.2.3. Differential scanning calorimetry

To determine if the methyl and propyl paraben functioned as a plasticizer, differential scanning calorimetry was used to examine changes in the glass transition temperature of the protein. A reduction in the glass transition temperature would indicate that effective plasticization occurred. Films cast from the zein pseudolatex displayed a glass transition temperature of 164.6°C, as shown in Fig. 3. The zein pseudolatex which contained 0.2% methyl paraben had a glass transition temperature (T_g) of 127.3°C, which was more than 37°C lower than the preservative-free film. A preservative-free zein pseudolatex was stored for 2 weeks at 20°C. Films were cast and thermal analysis was performed, which showed that the T_g of the sample was 156.7°C. An aliquot of the preservative-free pseudolatex was then combined with 0.2% methyl paraben and agitated for 4 h to ensure dissolution of the preservative. Films were cast and DSC analysis revealed a T_g of 136.3°C, a reduction of 20.4°C over the preservative-free sample.

Cast films of zein pseudolatex with and without methyl paraben were prepared and placed in humidity chambers equilibrated to 0% and 50% relative humidity. Thermal analysis of the films was performed over a 10 day period. In all cases, the T_g of the films increased over the 10 day period, as seen in Fig. 4. The films containing methyl paraben had a lower glass transition temperature than the films without methyl paraben. The increase in the T_g was attributed to the loss of water from the films during storage, as indicated by the relative humidity study performed in Section 3.2.1.

3.2.4. X-Ray diffraction

Samples of the preserved and the preservative-free zein pseudolatex were freeze-dried to a fine powder. These powders, together with samples of methyl and

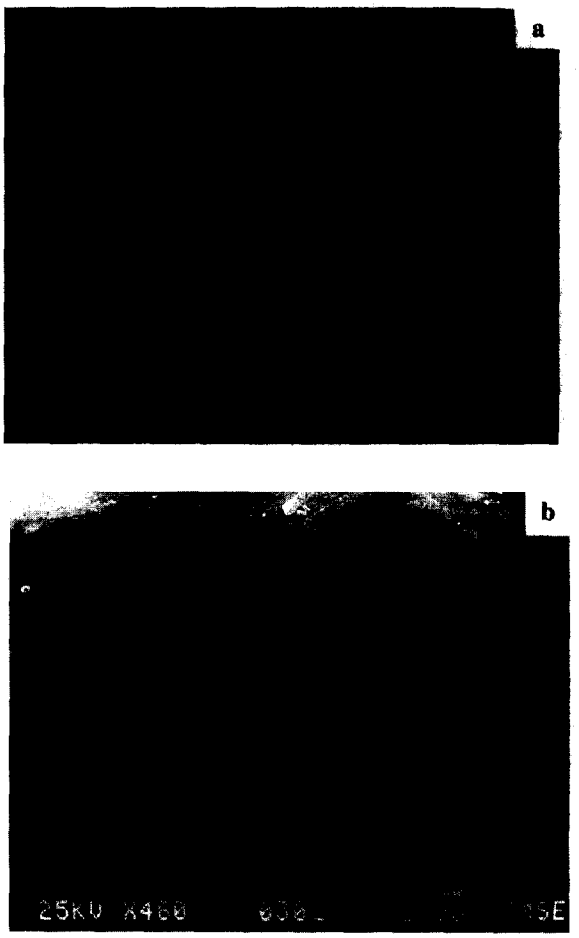

Fig. 6. (a) tablet and (b) bead coating comprised of zein pseudolatex with methyl paraben (12% protein weight) and propyl paraben (1.2% protein weight).

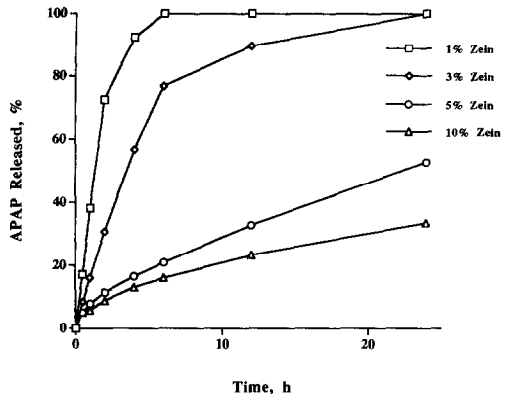

Fig. 7. Influence of coating level on the release of APAP in purified water from tablets coated with a zein pseudolatex containing methyl paraben (12% of protein weight) and propyl paraben (1.2% of protein weight) at 37°C using the USP dissolution method II.

propyl paraben, zein, and a physical blend of paraben and zein were examined by X-ray diffraction. The parabens showed characteristic peaks due to their crystalline nature. These peaks were also visible in the physical blend of the zein and parabens as shown in Fig. 5a. These crystalline peaks were not visible in the freeze dried zein pseudolatex which contained the parabens (Fig. 5b) or in the zein sample without parabens. The parabens were incorporated within the polymeric network and functioned as a plasticizer for the zein protein.

3.3. Dissolution studies

A zein pseudolatex containing 0.2% methyl paraben, 0.02% propyl paraben and 25% propylene glycol was used to coat tablet and bead formulations with 10% (weight gain) of zein. During the coating process, samples were removed a 1, 3, and 5% coating levels. APAP tablets coated in a Freund mini hi-coater were examined by S.E.M. and found to be free of cracks or other surface defects in the 5% film coating level (Fig. 6a). Placebo beads coated in a uniglatt fluid bed coater were also examined by S.E.M. and found to be free of defects (Fig. 6b).

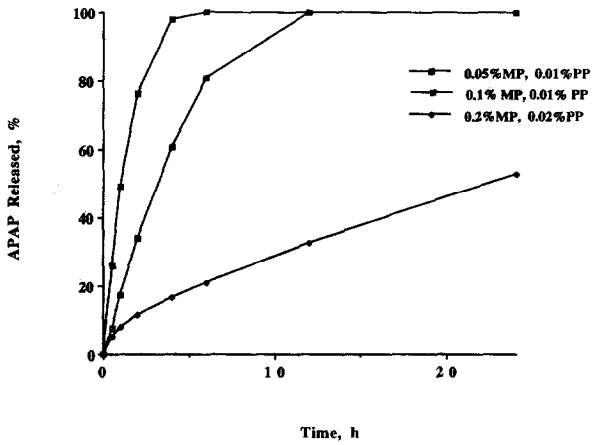

Fig. 8. Influence of paraben concentration on the release of APAP in purified water from zein coated tablets at 37°C using the USP dissolution method II.

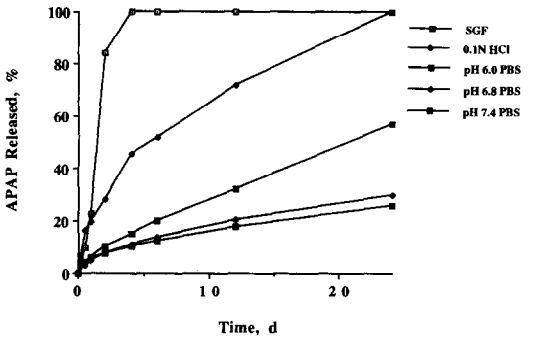

Fig. 9. Influence of dissolution media on dissolution profiles of APAP tablets coated with 10% zein pseudolatex with methyl paraben (12% protein weight) and propyl paraben (1.2% protein weight) at 37°C using the USP dissolution method II.

The percent of APAP released as a function of time correlated to the amount of zein pseudolatex applied to the tablet. Dissolution tests were performed on each batch using the USP dissolution method II and release profiles are shown in Fig. 7 which illustrates the effect of the coating level on the drug release rate. Tablets coated with 1 and 3% zein released the drug rapidly when compared to tablets coated with a 5% weight gain. Tablets coated with 10% zein released the drug slower than the tablets coated at the 5% level. A 5% coating level was selected as the maximum level of coating for the remainder of the study.

Three batches of acetaminophen (APAP) tablets were coated with 5% zein (based on tablet weight) containing varied amounts of methyl and propyl paraben and 25% propylene glycol. The APAP tablets coated with the pseudolatex formulation which contained 0.05% methyl paraben and 0.01% propyl paraben released 100% of

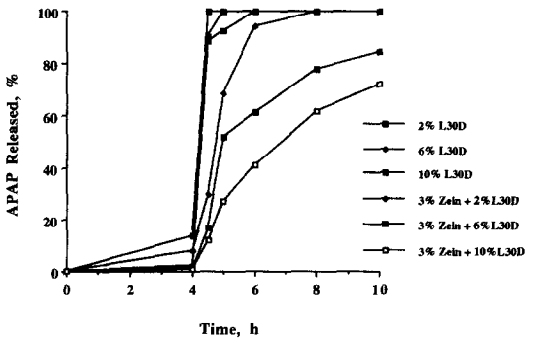

Fig. 10. Dissolution profiles in 0.1N HCl (4 h) and then pH 6.8 phosphate buffer at 37°C of APAP tablets coated with 3% zein pseudolatex with methyl paraben (12% protein weight) and propyl paraben (1.2% protein weight), and an overcoat of 2–10% Eudragit® L30 D-55, using the USP dissolution method II.

the drug within 5 h as shown in Fig. 8. The formulation containing 0.1% methyl paraben and 0.01% propyl paraben released 100% of the APAP within 12 h. However, the APAP tablets coated with the zein pseudolatex containing 0.2% methyl paraben and 0.02% propyl paraben released only 54% of the active compound within a 24 h period. The slower rate of drug release was attributed to the improved integrity of the coating produced by the plasticization effect of the parabens.

Dissolution tests were performed with different dissolution media on APAP tablets coated with a 5% (of tablet weight) zein pseudolatex coating containing 25% propylene glycol, 0.2% methyl paraben and 0.02% propyl paraben. It was found that drug release occurred at a faster rate in 0.1 N HCl, and as the pH increased the drug release decreased (Fig. 9). In a phosphate buffer system at pH 6.0, only 60% of the drug was released in a 24 h period. When the pH was increased to 7.4, the percent of APAP released decreased to 25% over the same time period. However, in simulated gastric fluid containing the enzyme pepsin, 100% of the drug was released within a 4 h period. This rapid release was attributed to the greater solubility of the zein in an acidic environment combined with the digestion of the protein by the enzyme. The slower release in the higher pH environment suggested a method to sustain enteric delivery of a drug compound.

Previous studies indicated that a 3% zein coating would control the release of APAP, with 78% of the drug released after 6 h. APAP tablets were first coated with a 3% coating of zein pseudolatex, followed by an overcoating of Eudragit® L30 D-55, which was varied from 2 to 10%. APAP tablets without the zein undercoat were also coated at the same levels with Eudragit® L30 D-55. The dissolution test was performed in 0.1 N HCl dissolution media for 4 h. The Eudragit® coating remained intact for 4 h in the 0.1 N HCl for all samples except the two which had the 2% coating. The dissolution medium was then changed to a pH 6.8 phosphate buffer system. The tablets without the zein undercoat released 100% of the drug within a 2 h period after the change to the high pH dissolution media (Fig. 10). The tablets with the 3% zein undercoat and 10% Eudragit® L30 D-55 overcoat displayed a controlled release of the drug, with 75% of the drug load released after 6 h in the higher pH environment.

In conclusion, a surfactant-free aqueous based pseudolatex of zein was prepared and was applied to tablet formulations containing acetaminophen. The release rates in purified water could be modified by the application of varied amounts of the zein pseudolatex. Thermal analysis of films cast from the dispersion and X-ray diffraction analysis indicated that the parabens were causing a plasticization effect in the film. Slower dissolution occurred as the pH increased, indicating a relationship between the pH of the dissolution media and the permeability of the zein pseudolatex coating.

References

[1] Leiberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets volume 1. New York: Marcel Dekker, 1989:185–186.

[2] Autant P, Cartillier A. Compositions for coating feeding stuff additives intended for ruminants and feeding stuff additives thus coated. U.S. Patent 4 876 097, 1989.

[3] Rosenthal F. Sustained release pharmaceutical product. U.S. Patent 2 895 880, 1959.

[4] Westall EB, Pimbly KC. Color concentrated base dispersion used in tablet film coating. U.S. Patent 3 802 896, 1974.

[5] Katayama H, Kanke M. Drug release from directly compressed tablets containing zein. Drug Dev. Ind. Pharm. 1992;18(20):2173–2184.

[6] Klippel KR. Sustained release pharmaceutical compositions. U.S. Patent 3 558 786, 1971.

[7] Glasser GM. Moisture resistant coating for food products, U.S. Patent 4 362 180, 1983.

[8] Ardaillon P, Bourrain D. Granules for feeding ruminants with an enzymatically degradable coating. U.S. Patent 4 983 403, 1991.

[9] Pescetti A. Coating composition and therapeutic preparation incorporating same. U.S. Patent 3 939 259, 1976.

[10] Argos P, Pederson K, Marks MD, Larkins BA. A structural model for maize zein proteins. J. Bio. Chem. 1982;257(17):9984–9990.

[11] Skultety PF, Sims SM. Evaluation of the loss of propylene glycol during aqueous film coating. Drug Dev. Ind. Pharm. 1987;13(12):2209–2219.

[12] Takruri H, Anger CB. Preservation of dispersed systems. In: Lieberman HA, Rieger MM, Banker GS, editors. Pharmaceutical Dosage Forms: Disperse Systems, volume 2. New York: Marcel Dekker, 1989:73–114.

[13] Tabibi SE, Rhodes CT. Disperse systems. In: Banker GS, Rhodes CT, editors. Modern Pharmaceutics, 3rd edition. New York: Marcel Dekker, 1996:299–332.