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THE DEVELOPMENT OF A UNIQUE BUFFERED MATRIX ASPIRIN TABLET

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ABSTRACT

Aspirin is used widely as an analgetic, antipyretic, and antirheumatic agent. The major disadvantage of aspirin therapy is gastrointestinal irritation caused by direct contact of the solid aspirin crystals and the gastric mucosa which causes gastrointestinal bleeding. Buffered aspirin tablets have been developed to reduce gastrointestinal bleeding. However, these multilayer tablets have proven to be, at times, ineffective.

A compressed buffered aspirin tablet was formulated which was composed of aqueous-based polymer coated aspirin crystals, a buffering system, a hydrophilic gel-forming matrix material, a binder, and a hydrophobic lubricant. The aspirin crystals were

[2] Correspondence

coated with an aqueous-based polymer to reduce aspirin degradation caused by the tablet components. The Glatt GPCG5 fluid bed with a top spray apparatus was used to coat 3 to 6 percent wt./wt. polymer onto aspirin crystals.

The coated aspirin crystals were incorporated with the tablet components and directly compressed using conventional tablet technology and equipment. Aspirin was released rapidly from the eroding matrix. Erosion was achieved due to the gel formation of Methocel K100LV which protects the tablet interior from dissolving and disintegrating upon initial wetting and hydration. The buffering system created a microenvironment of pH 5 within and around the eroding tablet matrix to aid in increasing aspirin solubility. The prototype formulation was scaled-up to large processing equipment and tablet stability was evaluated.

INTRODUCTION

Since the introduction of acetylsalicylic acid as an analgesic and antirheumatic agent, its effectiveness in controlling mild pain and its infrequency of side reactions have made it the most widely used drug in the world (1). However, it has been well documented that aspirin causes damage to the gastric mucosa which can lead to bleeding from the gastrointestinal tract. Buffering agents have been incorporated into aspirin

tablet formulations to increase the dissolution and absorption of aspirin as well as to decrease gastric irritation (2). Numerous conflicting reports about the relative efficacy of aspirin in combination with buffering agents have appeared in the literature (3). Some investigators have reported that the buffered form was more rapidly absorbed and causes less gastric irritation than plain aspirin (4-10). Other workers could find no difference between aspirin administered alone and in combination with buffering agents (1, 11-13).

Buffered aspirin tablets are formulated as a layered tablet system. Layered tablets are more expensive and difficult to produce than compressed tablets (14). The purpose of the layers is to separate the incompatibility between aspirin and the tablet components, especially the buffers (15). Some researchers have postulated that the buffered tablet inefficacy may be due to layer cohesion problems. Upon tablet ingestion, the layers laminate at their interface so that the aspirin and buffer are no longer in a close proximity of each other. The amount of buffer present is insufficient to affect the gastric fluid pH and therefore is ineffective in increasing aspirin solubility (16).

The objective of this research was to produce a unique buffered aspirin tablet, in which the aspirin

and buffer were uniformly mixed throughout the entire tablet matrix. Aspirin crystals were coated with 3 to 6 percent wt./wt. of an aqueous-based polymeric coating system using a Glatt GPCG5 fluid bed. The coating served as a protective barrier against any aspirin and tablet component incompatibilities. The coated aspirin crystals were incorporated into a tablet matrix system which was evaluated using dissolution, micro-pH, and stability studies. The goals set for the system were:

1. To achieve tablet erosion rather than tablet disintegration into individual particles using a gel-forming matrix material to maintain the tablet intact until completely eroded.
2. To create a microenvironment of increased pH within and around the tablet as gastric fluid penetrates the tablet matrix due to buffer dissolution, which aids in increasing aspirin solubility.
3. To produce a tablet exhibiting a fast aspirin release rate and acceptable stability.
4. To produce an economical system by formulating a directly compressed tablet using conventional tablet and aqueous film coating technology and equipment.

EXPERIMENTAL

Materials

The formulation of the buffered matrix aspirin tablet developed in this study contained five

components: 50% polymer coated aspirin crytals[a] (100-200 mesh); 25% buffer system, 5% or 10% of a gel-forming hydrophilic matrix material, HPMC K100LV[b]; 19.5% or 14.5% microcrystalline cellulose[c] (Avicel PH 101) as the binder/disintegrant/flow promoter/diluent; and 0.5% stearic acid[d] as the hydrophobic lubricant. All materials were used as supplied. The buffering system and the aspirin crystal polymeric coating material will not be revealed due to their proprietary nature.

Methods

The components of the tablet formulation were weighed and mixed. Six hundred fifty mg samples were compressed on a Carver Laboratory Press[e] using 1/2" punches and dies at a compression pressure of 5000 lbs.

An in vitro drug dissolution method was used to evaluate the aspirin release from the buffered matrix tablets. The standard U.S.P. dissolution Method II, the paddle method, was used for the experimental dosage forms. The equipment consisted of a six station dissolution apparatus. Standard paddles (Method II) were used at 50 rpm. The dissolution media was 900 ml of 37°C pH 1.2 simulated gastric fluid. Triplicate samples were withdrawn at appropriate time intervals and analyzed for aspirin and salicylic acid content using High Performance Liquid Chromatography (HPLC).

The HPLC assay that was utilized consisted of a Waters M-45 solvent delivery system, a Rheodyne

injector with a 20 ul fixed volume sample loop, a Waters Resolve C-18 5 u HPLC column, a Waters model 441 variable wavelength UV detector, and an HP-3390A integrator. The mobile phase consisted of 75% 0.1M phosphate buffer pH 2.5, and 25% acetonitrile. The aspirin and salicylic content of all samples was determined at 274 nm, and m-hydroxybenzoic acid was used as the internal standard.

The formulation was scaled-up and run on a sixteen station Stokes B-2 tablet press[f]. The tablet characteristics of the formulations were evaluated. Weight variation was performed on twenty tablets using a Mettler balance[g]. Tablet hardness was performed on 10 tablets using a suitable tablet hardness tester[h]. Tablet friability was evaluated using a friabillator[i] containing 20 tablets that were rotated for 10 minutes at 30 rpm. The tablets were subject to dissolution testing using the U.S.P. Method II, the paddle method.

An experiment was conducted to evaluate the hypothesis that a microenvironment of increased pH was created within and around the buffered matrix tablet due to the buffer and the gel-forming matrix material that maintained the tablet intact until completely eroded. A 7.8 gm tablet size was used due to the limitations of the micro-pH apparatus. Several tablet formulations, listed on Table 1, were compressed on the Carver Press at 5000 lbs. using 1" punches and 1" deep

TABLE 1

Micro-pH Tablet Formulation Modifications

Matrix Former Concentration	5% HPMC K100LV
	10% HPMC K100LV
	15% HPMC K100LV
Buffer Concentration	15% Buffer System
	25% Buffer System
	35% Buffer System
Buffer Substitutes	25% $Mg(OH)_2$
	25% $Al(OH)_3$
	25% $MgCO_3$
	25% Corn Starch
	25% Lactose
Tablet Size Variation	7.8 gm
	3.3 gm
	1.5 gm
	650 mg

dies. The center of the tablets was drilled out by hand with a 13/72" drill bit to a depth of 4.5 mm. A micro-pH probe[j] was inserted into the drilled out hole in the tablet. The micro-pH probe was a combined miniature glass/reference electrode designed for stomach pH measurements. The tablet and probe were inserted into a specially designed 1 cm^2 40 mesh basket. The probe was attached to the basket to insure that it remained motionless during the experiment. The basket was placed in a 1000 ml water-jacketed beaker containing 900 ml of 37°C dissolution medium. The probe was connected to a pH meter and the recording of tablet micro-pH vs. elapsed time was obtained using a

strip chart recorder. The pH of the bulk dissolution medium was also monitored using a separate pH meter.

An evaluation was made of the buffered matrix aspirin tablet stability to investigate the effects of temperature, relative humidity, and time on aspirin degradation from tablets produced with 0 to 6 percent wt./wt. polymer coated aspirin crystals. Tablets containing the uncoated aspirin, 3% polymer coated aspirin, and 6% polymer coated aspirin were placed in into 4 dessicators. Two dessicators contained saturated solutions of magnesium chloride (33% R.H.) and the remaining two dessicators contained saturated solutions of sodium chloride (75% R.H.). One dessicator of each relative humidity condition was placed into two temperature conditions of 20°C and 50°C. Duplicate samples of tablets produced with the three coated aspirin levels were randomly selected from the four temperature/relative humidity conditions every few days for a period of two weeks. A three month time point was also taken. The aspirin and salicylic acid content of each tablet at each time point was determined using HPLC. The data were calculated and the storage time, temperature, relative humidity, and coated aspirin level effects were tested for statistical significance using analysis of variance.

RESULTS

Tablet dissolution profiles were obtained for the buffered matrix tablets produced with 0 to 6 percent wt./wt. polymer coated aspirin crystals. The tablet formulation consisted of 50% coated aspirin crystals, 25% buffering system, 5% HPMC K100LV, and 20% Avicel PH 101. The aspirin release profiles are shown in Figure 1 and the data were analyzed using analysis of variance. The results showed that the main effect of the polymer coating level applied to the aspirin crystals was statistically significant (alpha = 0.05). The Student Newman-Keuls comparison of the means for the significant main effect coating level on aspirin release rate indicated that as the level of coating applied to the aspirin crystals increased, the tablet dissolution rate decreased. The data illustrated that the higher levels of polymer coated aspirin crystals (3-6% wt./wt.) had significantly slower aspirin release rates than the crystals coated with 0-2% wt./wt. polymer. Upon visual observation, it was noted that the tablets eroded rather than disintegrated into individual particles.

The aspirin release rate was evaluated at levels of the buffering system between 0 to 40 percent of the tablet formulation. Tablet dissolution was performed to analyze the effect of the buffer level on aspirin

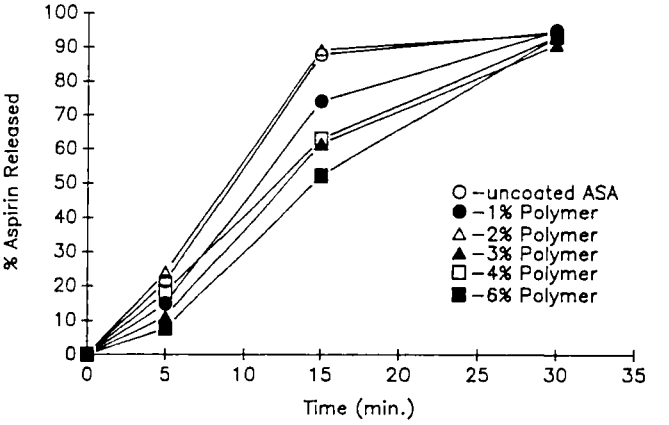

FIGURE 1

The Effect of the Level of Polymer Coated onto the Aspirin Crystals on Aspirin Tablet Release in Simulated Gastric Fluid.

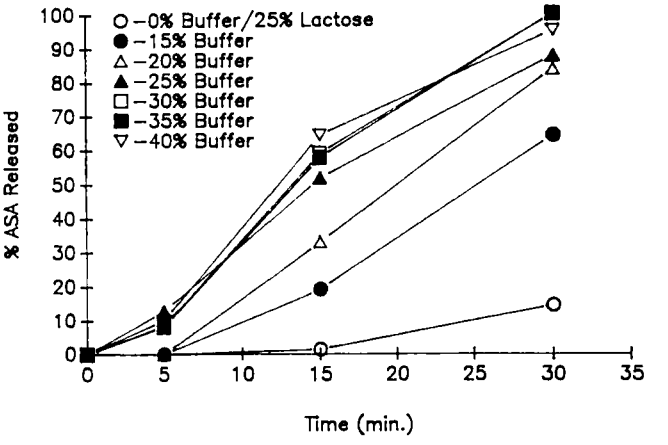

FIGURE 2

The Effect of the Buffer Concentration on Aspirin Tablet Release in Simulated Gastric Fluid.

release. Figure 2 depicts the aspirin release profiles for the various buffer system levels. From this figure, it is evident that at least 25% buffering system is required to produce a rapid aspirin release rate from the eroding tablet matrix. Statistical analysis of the data indicated that the main effect of the buffer system concentration was significant (alpha = 0.05). The comparison of the means analysis of the buffer concentration main effect revealed that the 30-40% buffer system levels were not significantly different in their effect on aspirin release rates. At these high levels of buffer system, the tablet formulation could not be altered to any great extent. Therefore, the 25% level was determined to be the most suitable for this buffered matrix aspirin tablet system.

An increase in the concentration of the HPMC K100LV in a matrix system increases the viscosity of gel that forms on the tablet surface. Therefore, an increase in the level of HPMC K100LV will yield a decrease in the aspirin release from the buffered matrix tablet. This behavior was observed for tablets produced with 5-25% HPMC K100LV in simulated gastric fluid as shown in Figure 3. The 5-12.5% levels resulted in an eroding tablet that produced a fast aspirin release rate. However, as the level of gel-forming matrix material was increased to between 13.75-25% of the total tablet

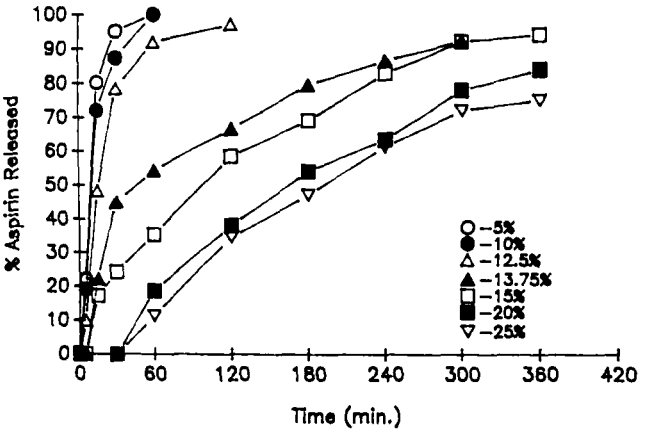

FIGURE 3

The Effect of the Level HPMC K100LV on Aspirin Tablet Release in Simulated Gastric Fluid.

weight, the aspirin release was prolonged due to the increased viscosity of the gel layer around the tablet surface which created a barrier to aspirin release from the tablet matrix.

Table 2 lists the formulations and the physical properties of the tablets which were scaled-up to 2 kg pilot lots on a Stokes B-2 16 station tablet press. The weight variation for all of the batches produced was minimal. Tablet hardness and dissolution were well within the acceptable ranges. Tablet friability was outside of the acceptable range, but could be improved by increasing the hardness, or altering the formulation to include another binder. Greater than 90 percent aspirin was released for all of the formulations indicating good content uniformity of the tablets due

TABLE 2

The Physical Properties of the Tablet Formulations Produced in the Scale-Up Study

Formulation* ASA Type HPMC K100LV Level	Weight Variation (mg)	Hardness (kp)	Friability (%)	Dissolution Rate (%ASA/30 min)
Uncoated ASA 5% HPMC K100LV	653.8	8.4	6.2	99.2
3% Coated ASA 5% HPMC K100LV	652.5	9.0	3.8	99.9
6% Coated ASA 5% HPMC K100LV	651.5	9.4	3.9	92.9
3% Coated ASA 10% HPMC K100LV	654.2	9.8	3.8	96.0

*Formulations also contained 25% buffer system, Avicel PH 101, and 0.5% stearic acid.

to proper mixing and flow of the direct compression formulation on the tablet press.

A micro-pH study was conducted to confirm the existence of a microenvironment of increased pH within and around the tablet matrix due to the buffer system and tablet erosion. The aspirin and the buffer remained in close proximity during tablet erosion. The buffer solubilized as the simulated gastric fluid penetrated the tablet core thereby producing a higher pH within and around the tablet matrix. The increased pH allowed for increased aspirin solubility versus the low pH of the simulated gastric fluid. The micro-pH profiles of the tablet formulations listed in Table 1

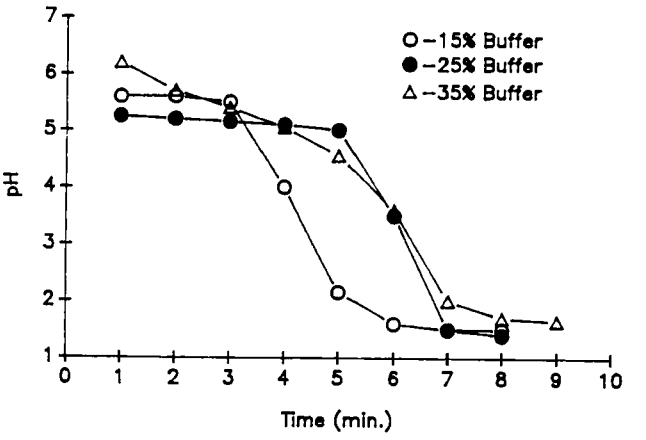

FIGURE 4

The Effect of the Buffer Level on Tablet Micro-pH in Simulated Gastric Fluid.

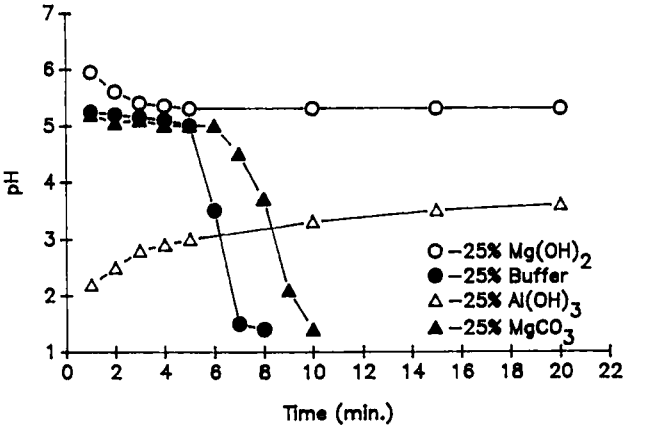

FIGURE 5

The Effect of Buffer Substitution with Other Buffers on Tablet Micro-pH in Simulated Gastric Fluid.

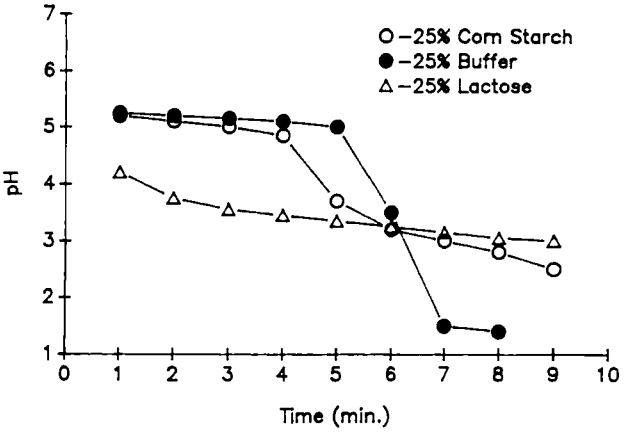

FIGURE 6

The Effect of Buffer Substitution with Inert Excipients on Tablet Micro-pH in Simulated Gastric Fluid.

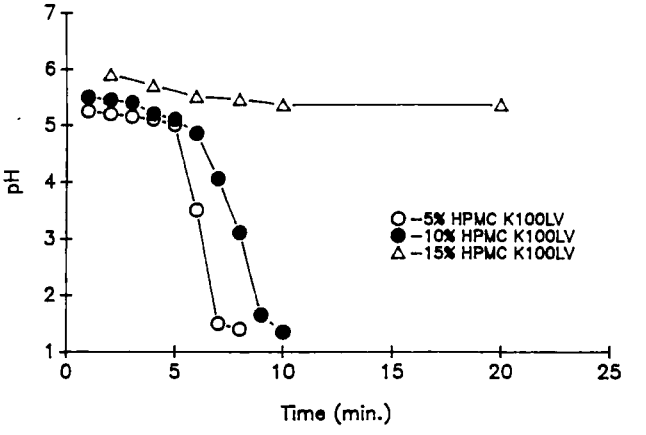

FIGURE 7

The Effect of the Level of HPMC K100LV on Tablet Micro-pH in Simulated Gastric Fluid.

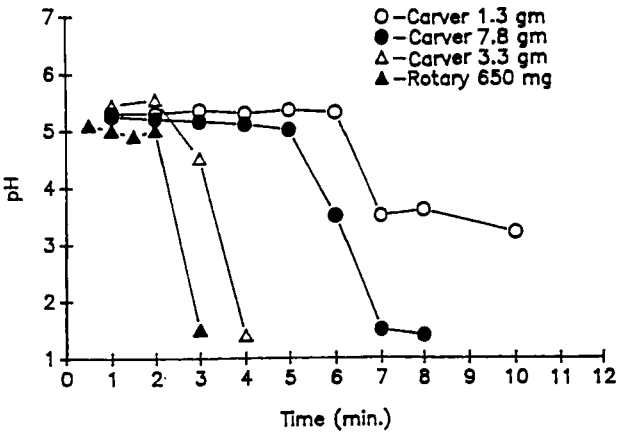

FIGURE 8

Tablet Micro-pH Profiles in Simulated Gastric Fluid for Various Sized Tablets at the 5% HPMC K100LV Level.

are shown in Figures 4-8. From the profiles, it is evident that the pH within and around the tablet matrix was maintained at approximately pH 5 for the entire tablet erosion process. After the tablets were completely eroded the pH dramatically dropped to pH 1.2 since the tablet was no longer present. The bulk pH of the dissolution medium was also monitored. The simulated gastric fluid pH varied one or two tenths of a pH unit, indicating that the buffer did not change the pH of the entire 900 mls of dissolution medium. The buffer mainly acted at the tablet surface and within the gelatinous layer around the tablet matrix. Figure 4 illustrates the micro-pH profiles of the three concentrations of buffer system. The 25% level showed

the ability of the system to maintain a pH of approximately 5 for the 5 to 6 minutes required for the tablet to completely erode, after which the micro-pH dropped to the pH of the simulated gastric fluid. The 15% level maintained the pH at 5.5 for only 3 of the 5 to 6 minutes required for the tablet to completely erode, indicating that this level of buffer was not sufficient for the tablet. The 35% level micro-pH profile did not exhibit a constant pH. The pH gradually decreased with time, indicating that this higher level of buffer was causing a disruption of the tablet matrix due to the nature of the buffer system's disintegration mechanism.

Figures 5 and 6 illustrate the effects of substituting the buffer system with either other commonly used buffers or inert excipients. The magnesium carbonate and the buffering system displayed similar profiles in which the micro-pH was maintained at pH 5 for the tablet erosion period of 5 to 6 minutes. The magnesium hydroxide also maintained a constant micro-pH for the entire erosion process. The major drawback for this buffer was the prolonged time period for the tablet to completely erode, because this buffer did not exhibit any disintegrating properties. The aluminum hydroxide was the poorest of the 4 buffers studied. It buffered around a pH of 3 to 4 and displayed no disintegrating properties. Figure 6 shows

the micro-pH profiles for tablets containing corn starch or lactose instead of the buffer system. The corn starch formulation demonstrated a brief increase and maintenance of the micro-pH at approximately 5 due to the fact that the solution of corn starch has a pH of 7. The lactose, however, demonstrated no ability to increase the tablet micro-pH and poor disintegrating properties.

Figure 7 illustrates the micro-pH profiles for tablets produced with 5, 10, or 15 percent gel-forming matrix material. The 5 and 10 percent levels of polymer exhibited very similar behavior. The micro-pH was maintained at pH 5 for the entire erosion process. The 15 percent level also maintained the micro-pH at 5, however, this level of polymer created a more viscous gel layer that caused a decrease in the tablet erosion time due to the increased time required for complete polymer hydration.

A 7.8 gm tablet size was used in these experiments due to the limitations of the micro-pH probe size. In order to determine that the micro-pH profiles of the large tablets reflected the behavior of a more realistic tablet size of 650 mg, the apparatus was modified slightly to accomodate smaller tablet sizes. The micro-pH profiles for various tablet sizes are shown in Figure 8. From these profiles it was determined that the small and large tablet samples

exhibited very similar behaviors. The only noteable difference was the time required for the tablets to completely erode, which was longer for the larger and harder (Carver compressed) tablets. Therefore, the 7.8 gm tablets, which were much easier to evaluate with greater accuracy, did reflect the behavior of the smaller tablet size.

A stability study was performed to evaluate the effects of storage time, relative humidity, and the level of polymer coating applied to the aspirin crystals on tablet stability. The data obtained after 3 months was analyzed using analysis of variance. Statistical analysis revealed that the main effects of storage time, relative humidity, and storage temperature were significant to tablet stability. The most interesting result was the significant main effect of polymer coating level applied to the aspirin crystals on tablet stability. A Student Newman-Keuls comparison of the means test revealed that the tablets produced with the 6% polymer coated aspirin crystals were significantly more stable than the tablets containing 3% polymer coated aspirin crystals. The tablets containing the uncoated aspirin crystals displayed the poorest stability. These results lead to the conclusion that increasing the level of polymer applied to the aspirin crystals resulted in better protection of the aspirin from the other tablet

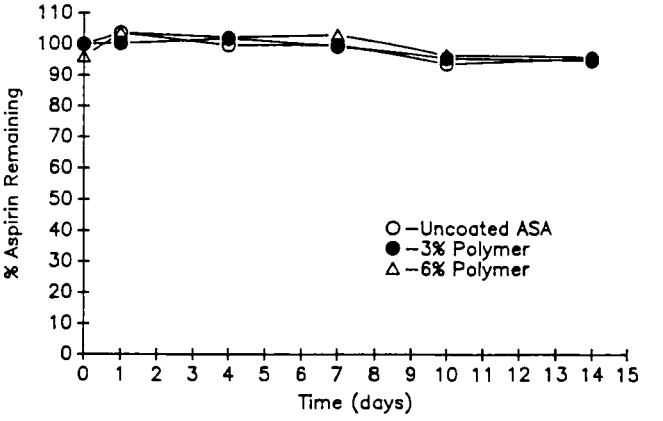

FIGURE 9

Tablet Stability Results for the Three Coated Aspirin Types at 20°C and 33% Relative Humidity.

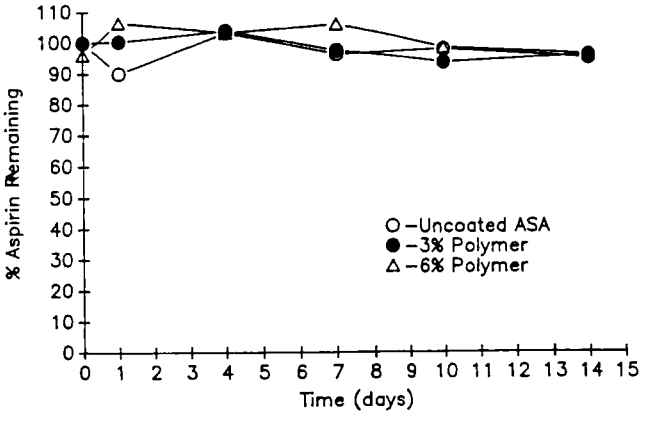

FIGURE 10

Tablet Stability Results for the Three Coated Aspirin Types at 20°C and 75% Relative Humidity.

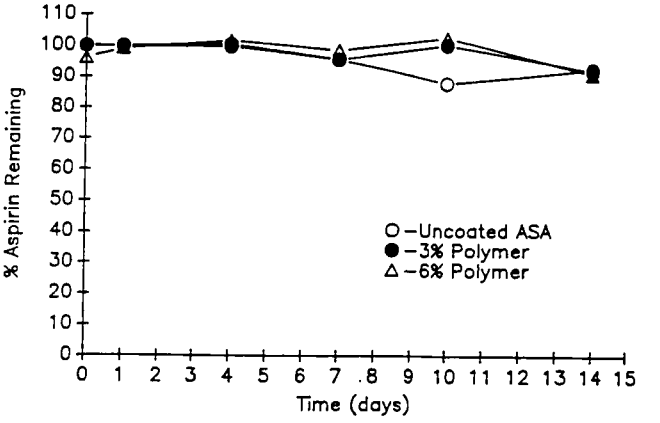

FIGURE 11

Tablet Stability Results for the Three Coated Aspirin Types at 50°C and 33% Relative Humidity.

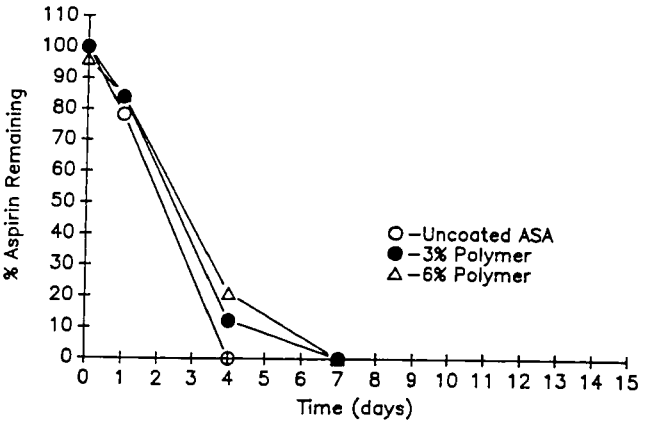

FIGURE 12

Tablet Stability Results for the Three Coated Aspirin Types at 50°C and 75% Relative Humidity.

components. At the conditions of 20°C and 33% relative humidity, the three tablets types were stable. However, at higher temperatures and humidities, the aspirin stability was adversely affected. Figures 9-12 show the percent aspirin remaining after 2 weeks for the 4 temperature/relative humidity conditions and the three tablet types. The 3 month stability data is shown in Table 3. The 3 month data confirmed the facts that the room temperature and humidity conditions are favorable for aspirin stability, higher temperatures and relative humidities can accelerate aspirin degradation, and the level of coating material applied to the aspirin crystals can reduce the formation of the degradation product, salicylic acid.

TABLE 3

	Storage Conditions		
	20°C 33% R.H.	20° 75% R.H.	50°C 33% R.H.
Tablet Type			
Uncoated ASA			
% ASA	91.5	71.1	2.8
% SA	0.0	3.2	26.8*
3% Polymer			
% ASA	88.8	78.8	27.4
% SA	0.0	2.6	18.6*
6% Polymer			
% ASA	88.8	75.4	31.0
% SA	0.0	0.8	22.9*

*Lower than the actual value due to sampling difficulties.

CONCLUSIONS

In conclusion, the Glatt GPCG5 polymer coated aspirin crystals were successfully incorporated into the tablet matrix. The HPMC K100LV produced a gel layer around the tablet matrix to achieve tablet erosion rather than disintegration into individual particles. The 5% and 10% HPMC K100LV levels allowed for fast aspirin release using 25% of the buffering system. The tablet remained intact for the entire tablet erosion process, thus maintaining a close proximity between the aspirin and the buffer. The solubility of the buffer in simulated gastric fluid caused an increase in the microenvironmental pH within and around the tablet matrix. This higher pH produced an increase in aspirin solubility, which has been shown to cause decreased gastric distress (2). As the percent polymer coated onto the aspirin crystals increased, the tablet dissolution decreased and the tablet stability increased. Tablet scale-up was very successful, producing tablets with good content uniformity and acceptable physical properties. The stability results indicated that the tablets were stable at room temperature and relative humidity. However, higher temperatures and humidities can accelerate aspirin degradation.

ACKNOWLEDGEMENTS

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FOOTNOTES

a. Acetylsalicylic acid, USP, Monsanto Company, St. Louis, Mo.

b. HPMC K100LV, Premium, Doe Chemical Company, Midland, MI.

c. Avicel PH 101, FMC Corp., Phila., PA.

d. Stearic acid, USP, Humco Laboratory, Texarkana, TX.

e. Carver Laboratory Press, Fred S. Carver, Inc., Summit, N.J.

f. Stokes B Tablet RB2 Machine, F.J. Stokes Machine Co., Phila., PA.

g. Mettler Electronic Balance AE100, Mettler Instrument Corp., Morristown, N.J.

h. Heiberlein Tablet Hardness Tester, Cherry-Burrell Corp., Cedar Rapids, IA.

i. Erweka Friabillator, Erweka-Apparatebau, West Germany.

j. Radiometer Stomach pH Electrode, GK2801C-O, Radiometer America, Inc., West Lake, OH.

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