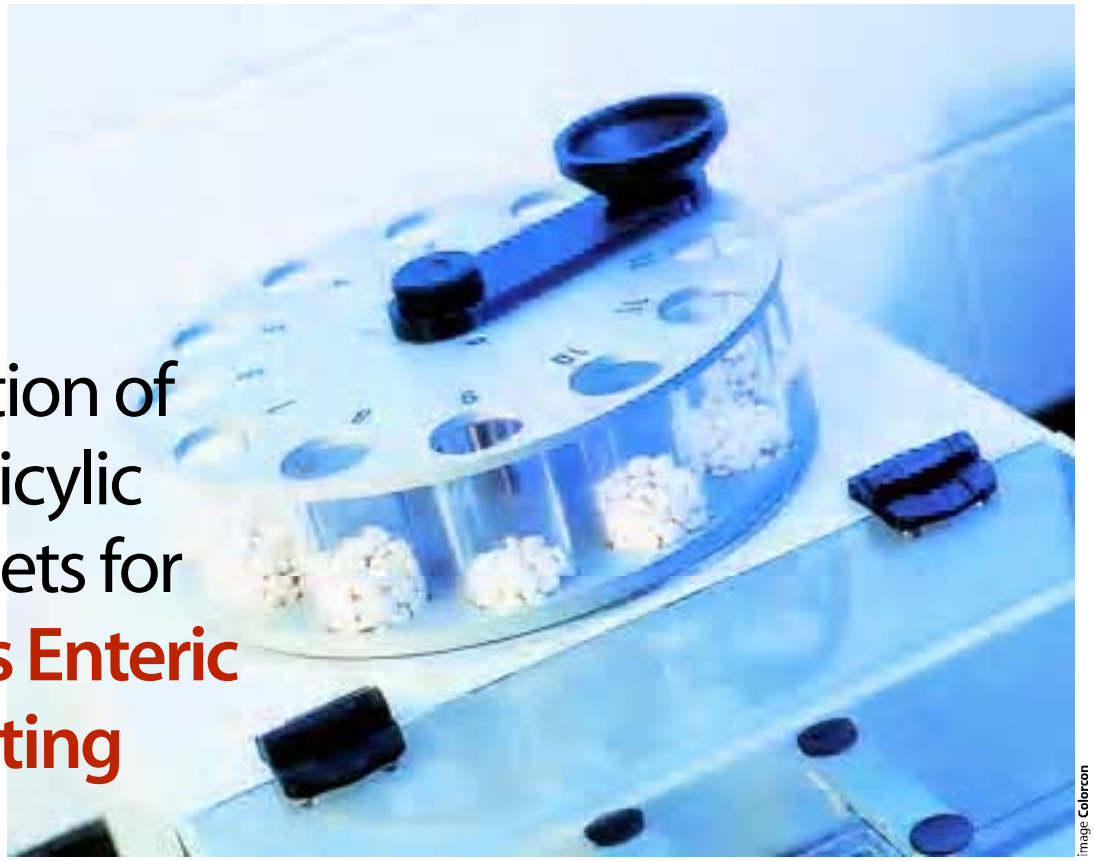
Formulation of Acetylsalicylic Acid Tablets for Aqueous Enteric Film Coating



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The goal of this study was to determine which combination of excipients would result in a tablet core that would be suitable for use in an aqueous enteric film-coating process. A relatively simple formulation of microcrystalline cellulose (MCC) and partially pregelatinized starch (P-PGS) was found to provide the necessary properties. MCC in the formulation provides the compactability needed to produce a tablet that will withstand the mechanical stresses of the film-coating process. P-PGS provides the dissolution characteristics and is responsible for the stability characteristics in this moisture sensitive, enteric film-coated application. It was also found that P-PGS could be used to reduce the deleterious effects of superdisintegrants in formulations.

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In recent years, acetylsalicylic acid (ASA; also well known as aspirin) has been prescribed for a host of indications. In addition to its uses as an analgesic, anti-inflammatory and antipyretic agent, ASA is now indicated for use in the prevention and treatment of heart disease and stroke. Further studies are currently under way investigating the potential of ASA for bolstering the immune system, treating cognitive decline and lowering the risk of colon and ovarian cancer. A low daily dose, 75–81 mg, is commonly used in preventive ASA therapy. Historically, ASA has been regarded as a potential gastric irritant[1] and studies have shown that the incidence of gastric intestinal side-effects may increase with regular use.[2] Enteric coating of the tablets is therefore desirable for preventing stomach upset or irritation in those taking daily ASA therapy.

Aspirin is a moisture sensitive drug and can hydrolyse into acetic and salicylic acids when exposed to high humidity and elevated temperatures.[3] As the coating process will subject ASA tablets to both high temperatures and humidity, it is important that the formulation is resistant to moisture interaction. Mitrevej and Hollenbeck found that a hydrophilic field is generated around ASA crystals under high humidity conditions and that upon combining the ASA with certain hydrophilic disintegrants, condensation in the vicinity of the ASA crystal can occur.[4] The disintegrants studied were sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone and colloidal silica. During the aqueous film-coating process, Faroongsarng and Peck determined that depth of water penetration into the tablet core could be directly linked to the concentration and type of disintegrant used in the formulation.[5] Further work by Bashar Al-Taani studying aqueous coating solutions for ASA tablets confirmed that moisture penetration during the coating process was not only formulation dependent but could be directly linked

to the stability of the final coated ASA tablet.[6]

A review of ingredients contained in five commercially purchased ASA products found that, in most cases, the primary listed excipients were microcrystalline cellulose (MCC) and some form of starch. The use of additional excipients including disintegrants (such as CCS and SSG), lubricants and glidants varied. All five products were packaged in foil-sealed high density polyethylene (HDPE) bottles, three of which contained carbon/silica desiccant packs.

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Materials and equipment

Aspirin 1040 (Aspirin USP 40-mesh crystals, Rhodia, Cranbury, New Jersey, USA) was used as the active material. The excipients used in the study were partially pregelatinized starch (P-PGS) (Starch 1500, Colorcon, West Point, Pennsylvania, USA); MCC (Emcocel 50M, Penwest, Patterson, New York, USA); SSG (Explotab, Penwest); CCS (Ac-Di-Sol, FMC, Princeton, New Jersey, USA) and stearic acid NF (purified vegetable grade powder, Oleotec Ltd, London, UK).

The packaging materials used were 85 mL foil-sealable HDPE bottles (Drug Plastics and Glass Co., Boyertown, Pennsylvania, USA) and desiccant packs (3964, Süd-Chemie Performance Packaging, Belen, New Mexico, USA). The coating materials used were an aqueous enteric coating system (Sureteric) and an aqueous film coating system (Opadry II), both manufactured by Colorcon.

Ingredients were dry blended in a 16-quart twin-shell blender (Patterson-Kelley Co., East Stroudsburg, Pennsylvania, USA). Tablets were compressed on an instrumented 10-station Piccola rotary press (Riva, Buenos Aires, Argentina). Tablet hardness was measured using a Multichek tester (Erweka, Milford, Connecticut, USA). A side-vented 15 in. coating pan (Labcoat II, O'Hara Technologies, Toronto, Canada) was used to apply the coatings. A dissolution test station (VK 7010, apparatus I, VanKel, Cary, North Carolina, USA) with a UV spectrophotometer (Varian, Palo Alto, California, USA) was used for drug release testing. An HPLC (high performance liquid chromatography) system (Alliance 2690, Waters Corp., Milford, Massachusetts, USA) was used to determine free salicylic acid concentration.

Table I Study formulations.

	Ingredients	Concentration (% w/w)					
		A	B	C	D	E	F
Constant	Aspirin	50.0	50.0	50.0	50.0	50.0	50.0
	Stearic acid	0.5	0.5	0.5	0.5	0.5	0.5
Study variables	Microcrystalline cellulose (MCC)	49.5	29.5	46.5	46.5	26.5	26.5
	Starch 1500 (P-PGS)	0.0	20.0	0.0	0.0	20.0	20.0
	Croscarmellose sodium (CCS)	0.0	0.0	3.0	0.0	3.0	0.0
	Sodium starch glycolate (SSG)	0.0	0.0	0.0	3.0	0.0	3.0

Methods

Blending and tablet preparation. Six formulations (see Table I), composed of constant levels of ASA and lubricant and varying levels of MCC, P-PGS, CCS and SSG, were each dry blended for 15 min in the twin-shell blender. The batch size of each blend was 5 kg.

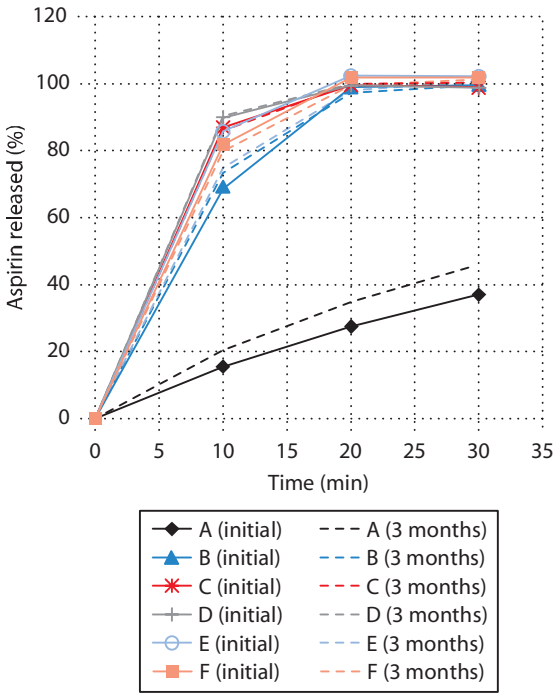
Each of the six blends was then compressed on the 10-station rotary tablet press with 7.0 mm standard concave tooling. The target tablet weight was 162.0 mg and the compaction force was adjusted to produce tablets with a breaking force of 6.0–7.0 kp. The tablet coating was performed in a 15 in. side-vented pan equipped with one spray-gun. The pan load was 3 kg. A subcoat of Opadry II dispersed in water (15% w/w) was applied to obtain a theoretical 2% tablet weight gain to tablets from all of the six batches. The subcoat application was immediately followed by an enteric coat consisting of Sureteric dispersed in water (15% w/w) and applied to obtain a theoretical 10% weight gain. A topcoat of Opadry II dispersed in water (15% w/w) was then applied to the tablets to obtain a 2% theoretical weight gain. All six coating trials were conducted using the same recommended process temperatures, spray rates and operating conditions. In general, the use of a subcoat beneath the enteric coating is optional and largely depends on the quality of the tablet core. As the six batches contained varying ingredients, a subcoat was applied to all six batches so that the enteric layer would be unaffected by minor changes in the tablet surface. The use of a topcoat is optional as well but many commercial products have a topcoat applied to colour the core.

Dissolution and free salicylic acid testing. The dissolution and free salicylic acid tests for the uncoated tablets were performed according to the USP 23 monograph for ASA tablets. The coated tablets were tested according to the USP 23 monograph for delayed-release ASA tablets.

Tablet hardness testing. The uncoated tablets were tested for diametrical breaking force before and after storage at accelerated conditions. The average result was reported from 20 tablets tested.

Packaging and stability. Samples of the uncoated tablets from each formulation were packaged in HDPE bottles (120 tablets per bottle). The coated tablets from each formulation were packaged in the same manner: one set of samples was packaged without desiccant; a second set of samples was packaged with a desiccant pack in each bottle. All bottles were induction (foil) sealed and stored under accelerated conditions — 40 °C/75% relative humidity [RH] — for 3 months.

Figure 1 Comparison of uncoated tablet dissolution profiles before and after 3 months of storage at 40 °C/75% RH.



Results and discussion

Uncoated ASA tablets. The dissolution testing conducted in acetate buffer (pH = 4.5) revealed that only batch A containing MCC alone as the excipient failed to achieve 80% drug release in less than 20 min. The dissolution results after storage under accelerated conditions showed little change from the initial tests (see Figure 1).

More significant were the results of the tablet mechanical strength after exposure to accelerated temperature and humidity conditions (see Figure 2). The tablets containing just ASA and MCC lost 8.57% in tablet hardness, whereas the tablets containing the MCC–P-PGS combination showed the least decrease in tablet hardness, with a 3.0% loss. The use of either CCS or SSG in combination with MCC resulted in a loss of more than 36.3% in tablet mechanical strength. Interestingly, when the same levels of CCS or SSG were used in the tablets that combined P-PGS and MCC, the loss in tablet hardness was less profound.

When comparing the levels of free salicylic acid in uncoated tablets, at the initial time point and after 3 months at 40 °C/75% RH, the results showed a similar trend to the tablet hardness results (see Figure 3).

The USP limit for free salicylic acid in uncoated ASA tablets is not more than 0.3%. After 3 months in accelerated conditions, the tablets containing just MCC as the excipient or MCC with either CCS or SSG exhibited significantly increased levels of free salicylic acid and failed to meet the USP requirements. The MCC–P-PGS combination showed virtually no degradation of the ASA with time in adverse storage conditions, and the increase in free salicylic acid was negligible.

It has been shown that the P-PGS used in this study has a lower propensity for moisture uptake than either CCS or SSG and will draw less moisture into a tablet under elevated humidity conditions.[7] This may account for some of the positive effects seen with its use in this formulation. The data also suggest that P-PGS may be able to trap or retain moisture within the formulation, thus retarding moisture interaction with the ASA.

Initial results for the coated ASA tablets. After coating, the tablets from all of the formulations had a good appearance. None of the tablets exhibited any signs of defects either during or after the coating trials. Tablets from all the batches passed the acid phase of dissolution testing with no release of ASA after 2 h in 0.1 N HCl. During the buffer phase of testing (pH = 6.8), as with the uncoated tablet dissolution results, only the tablets containing just MCC

Figure 2 Comparison of breaking force of uncoated tablets before and after 3 months of storage at 40 °C/75% RH.

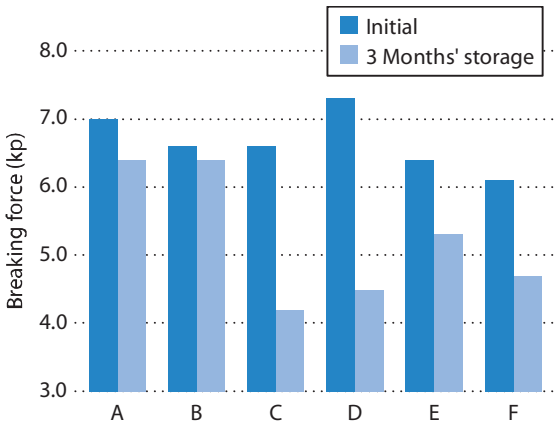
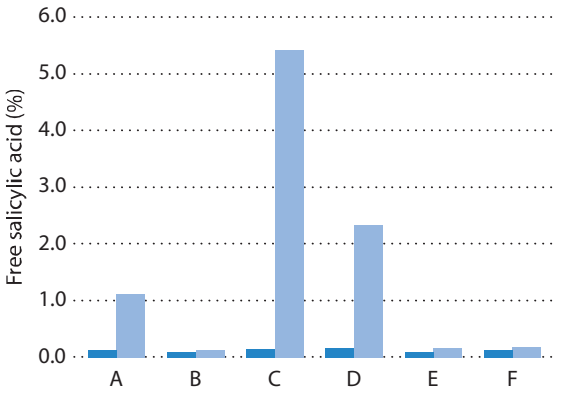


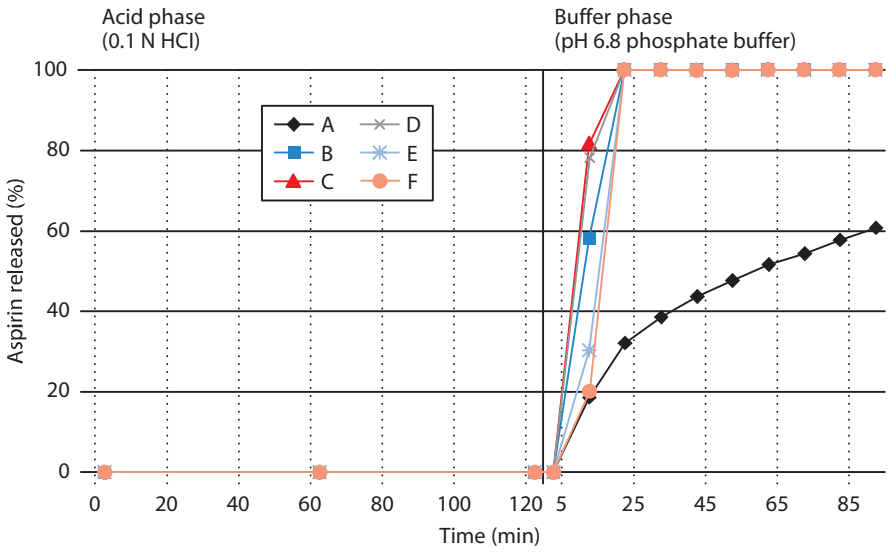
Figure 3 Comparison of free salicylic acid of uncoated tablets before and after 3 months of storage at 40 °C/75% RH (USP limit NMT 0.3%).



	A	B	C	D	E	F
Initial	0.130	0.095	0.145	0.153	0.091	0.121
3 Months' storage	1.117	0.111	5.403	2.329	0.158	0.166

After 3 months of storage … some of the tablets containing CCS or SSG exhibited softening of the film coating and sticking of the tablets to one another within the HDPE bottles.

Figure 4 Initial delayed-release dissolution profiles of enteric-coated ASA tablets.



and ASA failed to meet the USP specification of not less than 80% ASA released in 90 min (see Figure 4). In fact, the other five formulations attained 80% ASA release in less than 20 min.

Coated tablet stability results. After 3 months of storage at 40 °C/75% RH, some of the tablets containing CCS or SSG exhibited softening of the film coating and sticking of the tablets to one another within the HDPE bottles (see Figure 5). This occurred in the samples that were packaged both with and without desiccant packs. Any tablets exhibiting signs of defects at this point were considered stability failures.

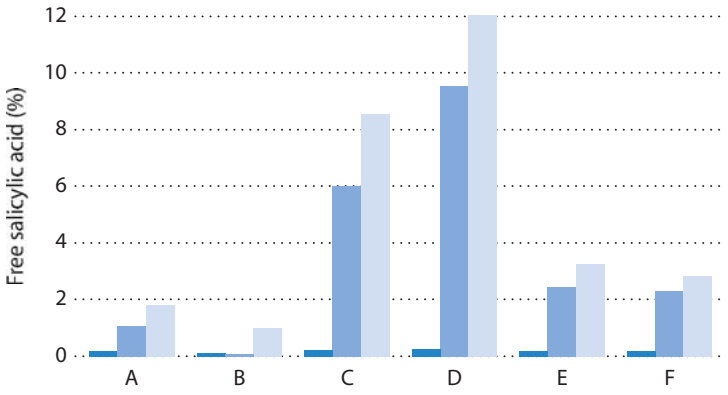
The free salicylic acid results for the coated tablets were very similar to those results obtained for the uncoated tablets. The USP limit for free salicylic acid in coated ASA tablets, 3.0%, is higher than the uncoated tablet specification. After 3 months in accelerated conditions, the tablets containing just MCC as the excipient exhibited higher, but acceptable, free salicylic acid levels (see Figure 6). The combination of the MCC with CCS or SSG resulted in substantial increases to more than 5.0% free salicylic acid overall, so failed to meet the USP requirements. Again, the most acceptable results were seen for tablets containing MCC and P-PGS as the excipients, which showed no increase in free

Figure 5 Coated tablets after 3 months of storage at 40 °C/75% RH.

MCC | MCC–P-PGS | MCC–CCS

MCC–SSG | MCC–P-PGS–CCS | MCC–P-PGS–SSG

Figure 6 Comparison of free salicylic acid levels from coated tablets before and after storage at 40 °C/75% RH (USP limit NMT 3.0%).



	A	B	C	D	E	F
Initial	0.11	0.06	0.16	0.19	0.10	0.12
3 Months with desiccant	1.01	0.04	5.97	9.52	2.38	2.26
3 Months no desiccant	1.73	0.97	8.52	12.00	3.19	2.78

salicylic acid when desiccant was used and only a 0.91% increase when packaged without desiccant. The addition of P-PGS substantially reduced the amount of ASA degradation in those tablets containing MCC combined with either SSG or CCS, which had unacceptable free salicylic acid levels.

It was interesting to note that the addition of desiccant packs to the bottles was not sufficient to eliminate, or even substantially reduce, the adverse effects of the superdisintegrants. Of the six formulations, the tablets containing MCC alone or the MCC–P-PGS excipient combination met the desired stability performance requirements of good appearance, acid resistance and acceptable free salicylic acid levels. The formulation with just MCC did not meet the delayed dissolution requirements for ASA release in buffer either initially or after 3 months of storage, in accelerated conditions. The tablets containing the MCC–P-PGS combination did exhibit excellent delayed release dissolution results initially and after 3 months at 40 °C/75% RH (see Table II).

Table II Drug dissolution results for coated tablets made from formulation B (see Table I). Tablets were stored for 3 months at 40 °C/75% RH.

	Released (%) in 0.1N HCl after 2 h	$_{80\%}$ in phosphate buffer (pH = 6.8)
Initial	0.0	<20 min
3 Months with desiccant	0.0	<20 min
3 Months no desiccant	0.0	<20 min

Conclusions

The results obtained in this study have yielded a relatively simple ASA formulation utilizing a combination of MCC and P-PGS as the primary excipients. MCC in the formulation provides the compactability needed for producing a tablet that will withstand the mechanical stresses of the film-coating process. Starch provides the necessary dissolution characteristics to the formulation and was responsible for the stability characteristics in this moisture sensitive, enteric film-coated application. This formulation without the use of additional superdisintegrants would be well suited to the aqueous film-coating process, and the final coated tablets would not require the use of any specialized packaging materials. It was also found that P-PGS could be used to reduce the deleterious effects of superdisintegrants in formulations. This would also reduce raw material costs. The next phase of this study will focus on optimization of the necessary enteric coating levels and the scale-up of the enteric coating process.

Acknowledgements

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