Drug Release from Acrylic-Based Opadry® Enteric (94 Series) Coated Tablets

INTRODUCTION

The commonly accepted view is that the pH of the human gastrointestinal (GI) tract increases progressively from the stomach to the colon. Enteric coatings are pH-dependent to exploit this pH progression in the GI tract in order to prevent gastric irritation or delay the release of drugs that are inactivated by the gastric acid in the stomach. In addition, such coatings may be applied to facilitate delivery of a drug to its optimal absorption site in the intestine, provide delayed action, or for delivering the drug to its local site of action in the intestine.[1] Enteric coatings may be applied to serve one or more of these purposes.

Commonly used pH-dependent coating systems include the methacrylic acid copolymers (MAC). Dissolution pH of these polymers primarily depends on their content of carboxylic groups. These products are described in the USP/ NF under the monograph for MAC and distinguished by their methacrylic acid content and viscosity as types A, B, and C.[2]

Opadry® Enteric (94 Series), enteric coating system, is a fully formulated, delayed release coating system for solid oral dosage forms. It is based on MAC, specifically the poly [methacrylic acid, methyl methacrylate (1:1) type A]. This system may be applied using organic or hydro-alcoholic processing techniques. The objective of this study was to evaluate the coating application process, enteric performance and drug release characteristics from coatings of Opadry Enteric (94 Series) applied by hydro-alcoholic solvent techniques, in various buffer (pH) media on placebo tablets or using aspirin as a model drug.

MATERIALS AND METHODS

Opadry Enteric (94 Series) evaluations were conducted using placebo and aspirin tablets. Placebo tablets comprised of a mixture of lactose, cellulose powder, partially pregelatinized starch (Starch 1500®) and a lubricant. Aspirin tablets comprised of Aspirin USP (81mg), partially pregelatinized starch (Starch 1500), microcrystalline cellulose, and stearic acid.

TABLET MANUFACTURE

Three hundred and fifty milligram (350 mg) placebo tablets were manufactured using a 16-station Rimek single side press (Karnavati Engineering) fitted with 10 mm standard concave tooling. One hundred and sixty two milligram (162 mg) aspirin tablets were manufactured using an 8-station Rimek Mini-Press-II SF (Karnavati Engineering) fitted with 7mm standard concave tooling.

TABLET COATING

Seal Coating

Aspirin tablets were seal-coated at a 2% weight gain in a 12 inch conventional coating pan (Bectochem Consultants and Engineers Pvt. Ltd.) using Opadry 03K19229 (reconstituted at 6% solids) in a hydro-alcoholic solvent system (88:12, isopropanol: water).

Enteric Coating

Seal-coated aspirin tablets were then coated using Opadry Enteric 94O white. Coating dispersions were reconstituted at 10% solids in a hydro-alcoholic solvent system (88:12, isopropanol: water) and applied to either a 5 or 12 % weight gain.

Enteric coating of placebo tablets was carried out without the preceding seal coating step. Samples were drawn at 5, 6, 7, 8, 10 and 12% weight gains.

TABLET TESTING

Assessment of Fluid Uptake

Placebo tablets (n=6) of each of the enteric coating weight gains were individually weighed and reciprocated for 2 hours in the test media [0.1 N HCl; USP standard acetate buffer solutions (pH 4.5, 5.1 and 5.5) and USP standard phosphate buffer solution (pH 5.8)] in a USP 31 disintegration apparatus at 37 ± 2^{o}C. At the end of this time interval, the tablets were removed from the disintegration bath and inspected for any defects (bloating or swelling). Any excess surface moisture was gently blotted dry using a paper towel, and the tablets reweighed individually. The percent fluid uptake for a tablet was calculated according to Equation 1. Historically, less than 10% fluid uptake has shown to correlate to acceptable enteric protection and dissolution performance for tablets.

Equation 1 $FA\ (\%) = (T_f - T_1/T_1) \times 100$

FA (%): Percent fluid uptake

T_f: Final tablet weight (mg)

T_1: Initial tablet weight (mg)

Disintegration Testing

Placebo tablets that were observed to be physically intact following the fluid uptake test were then reciprocated in the disintegration apparatus using pH 6.8 phosphate buffer maintained at 37 ± 2^{o}C as the immersion fluid. The time taken for all of the tablets to disintegrate completely was noted.

Drug Release Testing

Aspirin release was determined using a USP compliant dissolution bath (Erweka DT 800), apparatus 1 (basket), at 100 rpm.

In the first stage, the dissolution medium was 1000 mL of 0.1 N HCl at 37°C (±0.5°C). After 2 hours of operation in this medium an aliquot was withdrawn and the aspirin content determined spectrophotometrically at 280 nm. The remaining solution was discarded and the tablets moved to the pH 5.5 buffer media (1000 mL) equilibrated to 37°C (±0.5°C). After 1 hour of operation in this medium, an aliquot was removed and the aspirin content determined spectrophotometrically at 280 nm. The remaining solution was discarded and the tablets moved to the pH 6.8 buffer media (1000 mL) equilibrated to 37°C (±0.5°C). Sample aliquots were withdrawn at 15, 30, 45, 60 and 90 minutes and the aspirin content determined spectrophotometrically at 265 nm.

All determinations of aspirin content were carried out using a dual-beam spectrophotometer (Perkin-Elmer). Tablets from each stage were moved to the subsequent stage after blotting the tablets dry using a paper towel.

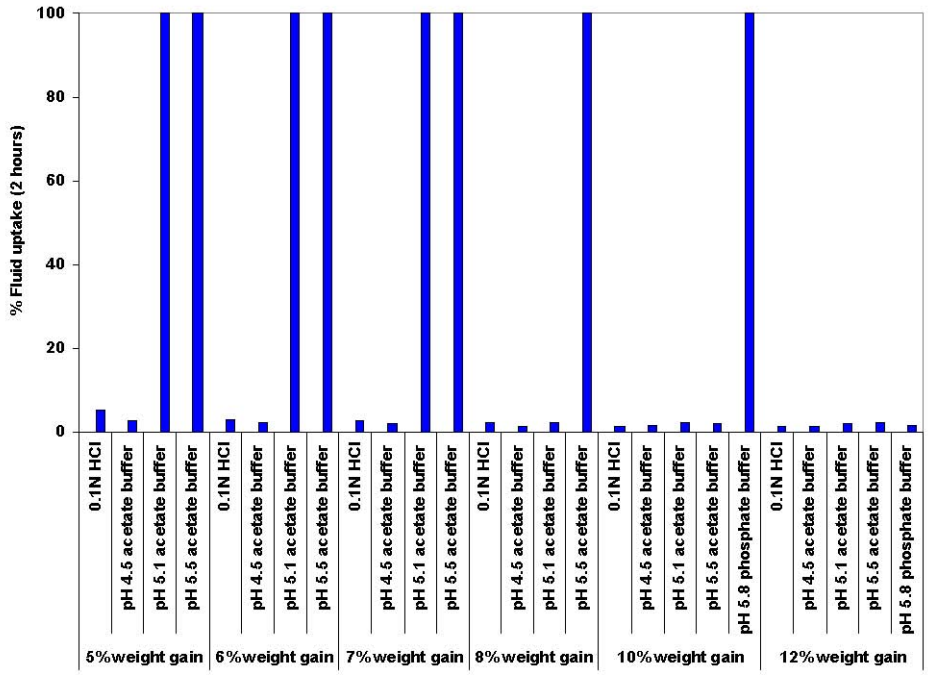
RESULTS AND DISCUSSION

Assessment of Fluid Uptake

The ability of the coating to protect the active ingredient from the effects of gastric acid was determined by measuring the percent fluid uptake of the coated tablets when reciprocated in acid media for 2 hours in a disintegration apparatus. The effect of coating weight gain (thickness) on acid resistance (fluid uptake) of placebo tablets is shown in Figure 1. At all the coating levels, tablets demonstrated very low fluid uptake (i.e., less than 6%) in 0.1 N HCl (pH 1.2). Good acid resistance was obtained in pH 5.1 acetate buffer at upwards of 8% coating weight gain (9.22 mg/cm^2). Acid resistance in pH 5.5 was obtained at 10% coating weight gain (11.53 mg/cm^2), while a 12% coating weight gain (13.83 mg/cm^2) provided acid resistance at pH 5.8. Fluid uptake of the coated tablets in all tested media decreased with increase in coating weight gain. This effect was observed until a certain minimum coating weight gain was achieved after which the effect was less pronounced. These results indicated that there was a minimum coating thickness required to delay the drug release until a specific pH target, or to effectively protect an acid-labile drug. These results are in agreement with other reports documented in literature.[3]

The MAC type A polymer starts to ionize and dissolve at pH of around 6.0.[4] In lower pH media, the polymer is not ionized and hence remains insoluble with low fluid uptake by the enteric coated dosage form. Low levels of fluid uptake at higher enteric coating weight gain may also be explained by the lower porosity, higher tortuosity and increased diffusion path length for the fluid.[5]

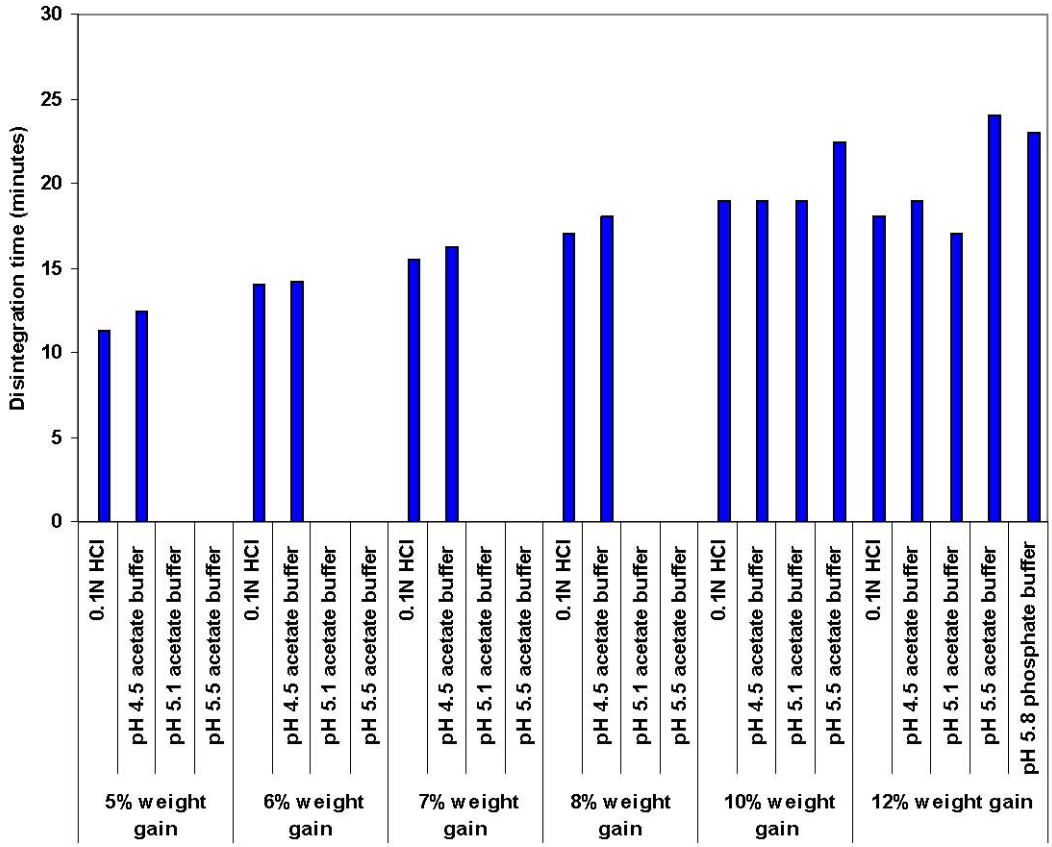
Figure 1 – Effect of Percent Coating Weight Gain (Coat Thickness) on Fluid Uptake



Disintegration Time

Changes in film permeability caused by salt formation of the carboxylic acid groups in the polymer with anions in the buffer media results in loss of integrity of the enteric film coating, causing the tablets to disintegrate.[6] Uncoated placebo tablets disintegrated in all media within 3 minutes. Results (Figure 2) indicate that disintegration time for enteric coated placebo tablets was dependent on coating thickness. Enteric coated placebo tablets with higher coating weight gains had longer disintegration times than those enteric coated at lower levels when tested in the same disintegration test medium (Figure 2). Longer disintegration times from films of higher thickness could also be attributed to a longer time taken to solubilize a thicker film.[6]

Figure 2 – Effect of Percent Coating Weight Gain (Coat Thickness) on Disintegration Time in pH 6.8 Phosphate Buffer (following acid stage).



Drug Release

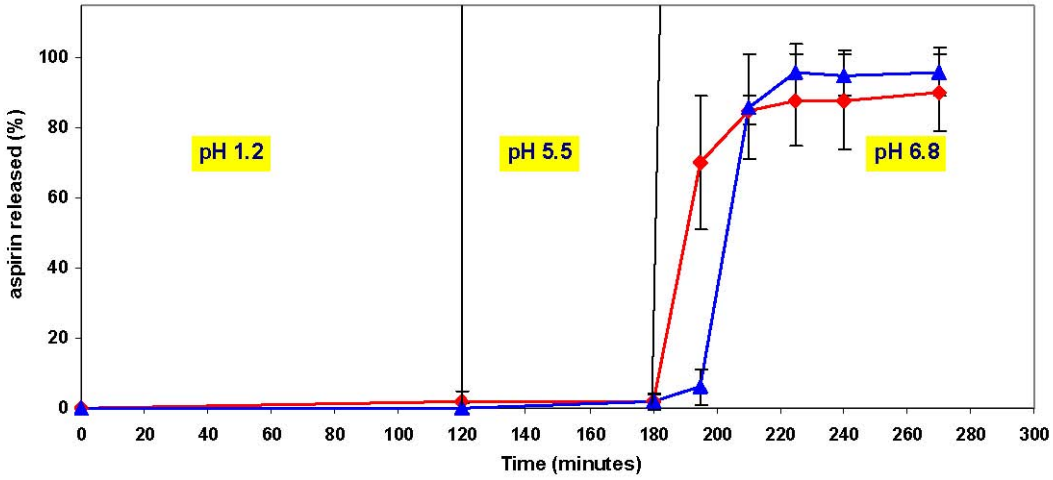
Drug release data in Figure 3 shows that no aspirin was released from enteric coated tablets (both 5% and 12% coating weight gains) after 2 hours in 0.1 N HCl, the USP acid stage dissolution medium for aspirin delayed release tablets.

No drug release was obtained in pH 5.5 buffer media for aspirin tablets coated at either 5% or a 12% enteric weight gain. Slight swelling, however, was observed in aspirin tablets coated at 5% weight gain following the dissolution test in pH 5.5 buffer media. No such swelling was observed for aspirin tablets coated at 12% weight gain. Results indicate that lower enteric coating weight gains, while meeting compendia tests, may not necessarily protect the active ingredient from the effects of gastric acid.

Slower release was obtained in the first 15 minutes in pH 6.8 buffer media for tablets coated with a 12% weight gain as compared to those with a 5% weight gain. Thereafter, rapid release of the drug in the buffer media was

obtained for enteric coated tablets at both 5% and 12% weight gains. Slower initial release could be attributed to the longer time taken to solubilize a thicker film produced at higher coating levels than a thinner film produced at lower coating weight gains. At 12% enteric weight gain, the coat is initially semi-permeable allowing limited drug release, after which it becomes sufficiently weak to allow disintegration to occur.[3] Once the enteric coat is sufficiently dissolved, rapid disintegration and release of the drug was obtained.

Figure 3 – Effect of Coating Weight Gain on the Dissolution of Aspirin Tablets



CONCLUSIONS

Enteric coating using Opadry Enteric (94 Series) provided good acid resistance in 0.1N HCl at an enteric coating of 5- 6 mg/cm^2. A higher coating thickness (12- 14 mg/cm^2) provided acid resistance in pH 5.5 buffer media. Fluid uptake data revealed that enteric and delayed release performance increased with an increase in coating weight gain. Tablets with higher Opadry Enteric coating weight gains had longer disintegration times than those coated at lower coating weight gains. Dissolution rate was dependent upon both the pH of the dissolution medium and the thickness of the applied coat.

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