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Hydro-Alcoholic Applications of Polyvinyl Acetate Phthalate (PVAP) for Oral Delayed Release Coating Systems

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Introduction

Despite advances in aqueous coating systems, the application of enteric or delayed release (DR) coating formulations from hydro-alcoholic systems continues for various reasons. Hydro-alcoholic systems are employed for functional reasons, i.e. with moisture-sensitive actives. They also continue to be utilized more broadly due to advances in equipment capabilities for solvent reclamation and operational safety¹ as well as “cost” reasons in certain parts of the world, i.e. the ability to achieve enteric protection at relatively low coating levels.

The objective of this study was to examine the gastro-resistance and drug release of tablets and multi-particulates (MP) coated with a DR formulated product based on polyvinyl acetate phthalate (PVAP or Phthalavin[®], marketed as Opadry[®] Enteric), using hydro-alcoholic solutions. Omeprazole and diclofenac sodium, popular drug actives formulated in MP and tablet DR dosage forms, respectively, were used as model drugs.

Methodology

10 mg Omeprazole Pellets

Drug layered omeprazole pellets (14/18 mesh, 1000 -1400 micron) were purchased from Spansules Formulations (India).

Tablet Manufacture

Diclofenac sodium (50 mg) tablets were prepared via direct compression from the composition outlined in Table 1.

Table 1. Diclofenac Sodium Tablet Composition

Material	% w/w	mg/ tablet
Diclofenac sodium (Meditech Chemicals Pvt. Limited, India)	16.67	50.0
Lactose monohydrate (Friesland Foods, Netherlands)	52.73	158.2
Microcrystalline cellulose (Avicel [®] PH 102, FMC)	15.00	45.0
Partially pre-gelatinized starch (Starch 1500 [®] , Colorcon)	15.00	45.0
Magnesium stearate (Vasa Pharma)	0.50	1.5
Fumed Silica (Aerosil [®] 200, Evonik)	0.10	0.3
TOTAL:	100.00	300.0

Tablet Compaction

Direct compression blends were compacted on an 8 station rotary press (Rimek, India).

Tablet content uniformity was determined via the USP 29/NF24 monograph for “Delayed Release Diclofenac Sodium Tablets”².

Tablet Coating

Diclofenac sodium tablets were coated in a 12” conventional coating pan (Bectochem, India) with or without an aqueous seal-coat (Opadry[®], YS-1-7027), followed by DR coating from hydro-alcoholic mixtures (isopropyl alcohol (IPA)/Water 80:20) of Opadry[®] Enteric (OY-P-7171) at 4 to 10 %w/w coating weight gains (WG).

Table 2 shows the coating parameters for the seal-coating and delayed release coating steps.

Table 2. Coating Process Parameters, Diclofenac Sodium Tablets

Parameter	Seal Layer	Enteric Layer
Pan charge (g)	500	500
Inlet temperature (°C)	52	56
Exhaust temperature (°C)	41	37
Product temperature (°C)	43	40
Fluid delivery rate (g/min.)	5	2.2
Pan speed (rpm)	10	23-24
Atomization air pressure (bar)	2	2
Coating solids content (%)	15	15
Coating weight gain (%)	3	4-10

MP Coating

Omeprazole MPs were seal-coated with Opadry® (YS-1-7027) in a fluid-bed (Glatt GPCG-1), followed by DR coating with Opadry® Enteric (OY-P-7171).

Table 3 shows the coating parameters for the seal-coating and DR coating steps. Surface and cross sectional (SEM) images were collected.

Table 3. Coating Process Parameters, Omeprazole MPs

Parameter	Seal Layer	Enteric Layer
Solvent	Water	IPA:Water (80/20)
Charge (g)	500	500
Inlet temperature (°C)	50-58	40-43
Exhaust temperature (°C)	35-37	36-37
Product temperature (°C)	40-42	36-37
Fluid delivery rate (g/min.)	8-10	5-7
Air Flow (m/s)	8-10	9-10
Atomization air pressure (bar)	1-1.7	1-1.5
Coating solids content (%)	12	15
Coating weight gain (%)	4	3-30

Disintegration Testing – Diclofenac Sodium Tablets

Enteric-coated diclofenac sodium tablets of varying coating WG were individually weighed (n=6) and reciprocated for 2 hours in 0.1N HCl, in a USP compliant disintegration apparatus. At the end of this time interval, the tablets were removed from the disintegration bath for visual inspection of any defects (bloating or swelling). In addition, any excess surface moisture was gently dabbed dry using tissue paper and the tablets were individually reweighed. The percent acid uptake for a tablet was calculated according to Equation 1.

Equation 1

$$\text{Percent Acid Uptake} = (T_f - T_i) / T_i \times 100$$

T_f = Tablet weight final (mg)

T_i = Tablet weight initial (mg)

Drug Release

Enteric-coated diclofenac sodium tablets with or without a seal-coat were tested for drug release according to the USP29/NF 24 monograph for “Delayed Release Diclofenac Sodium Tablets”.²

Enteric coated omeprazole pellets were tested for drug release according to the USP29/NF 24 monograph for “Delayed Release Omeprazole Capsules, Test 2”.³

Results and Discussions**Diclofenac Sodium Tablets****Tablet Physical Properties**

Tablets of low friability and good content uniformity were obtained. Table 4 shows the tablet physical properties for the uncoated diclofenac sodium cores.

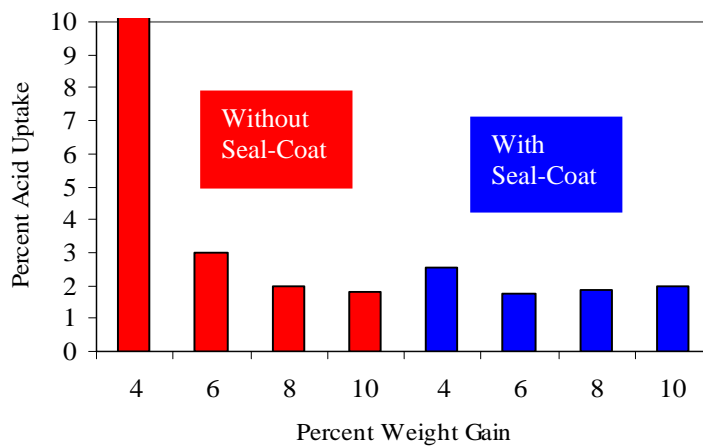
Table 4. Uncoated Diclofenac Sodium Tablet Physical Properties

Tablet diameter (mm)	10.09 ± 0.01
Mean weight (mg)	303 ± 1
Breaking force (kp)	8.0 ± 2.0
Friability (%)	0.03%
Disintegration time in pH 6.8 buffer (minutes)	5.0 ± 2.0
Thickness (mm)	4.1 ± 0.1
Content uniformity	99.2% +/- 2.4%

Percent Acid Uptake

Figure 1 shows the average acid uptake values for diclofenac sodium tablets coated with or without a seal-coat, and Opadry® Enteric at various coating WG's. It has been shown that percent acid uptake values less than 10% for tablets indicate good gastro-resistance behavior.⁴

Figure 1. Percent Acid Uptake, Diclofenac Sodium Tablets

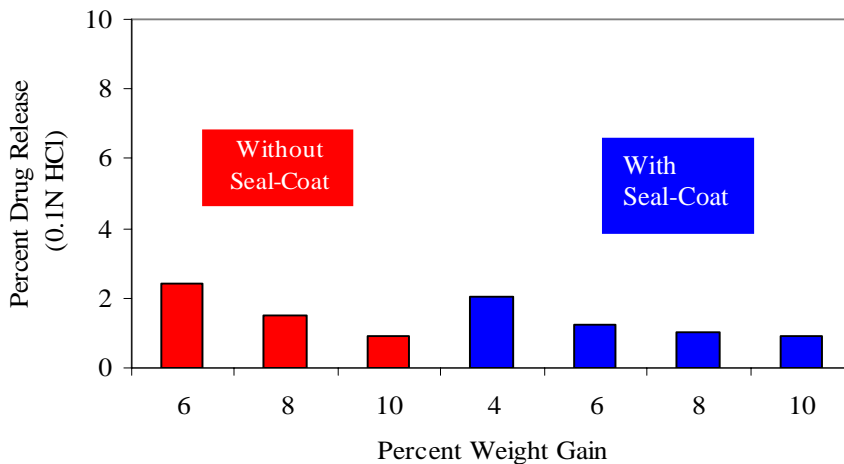


Results indicate that adequate enteric protection was achieved for all samples with a seal-coat, and for samples from 6-10% coating WG of Opadry® Enteric without a seal-coat. Application of a seal-coat has been shown to improve gastric resistance based on enhancement of the mechanical integrity of the tablet core prior to enteric coating.⁴

Drug Release

USP criteria requires less than 10% drug release after 2 hours in 0.1N HCl, followed by greater than 80% release after 45 minutes in phosphate buffer, pH 6.8. Figure 2 shows the percent drug release in 0.1N HCl for diclofenac sodium tablets with or without seal-coat, followed by application of Opadry® Enteric at various WG's. The sample without a seal-coat and 4% WG of Opadry® Enteric was not tested, as it failed the criteria for acid uptake.

Figure 2. Drug Release in 0.1N HCl, Diclofenac Sodium Tablets (n=6)



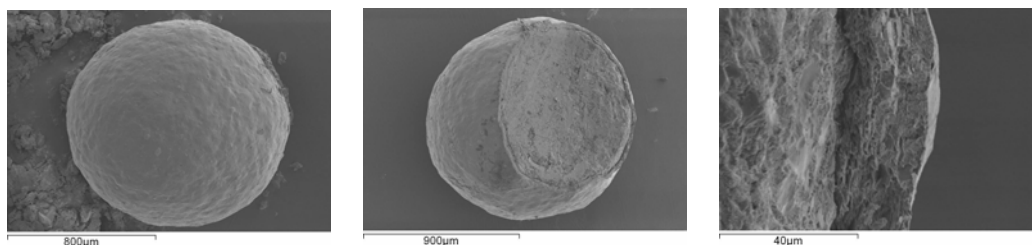
All samples met the USP specification for drug release in 0.1N HCl, and released the drug content within 45 minutes upon transfer to phosphate buffer, pH 6.8.

Omeprazole Pellets

SEM Images

Figure 3 reveals the surface and cross sectional images of a DR omeprazole pellet containing the seal-coat and 7% WG of Opadry® Enteric. The images indicate that, even at such a low coating level a uniform, low porosity film has been achieved.

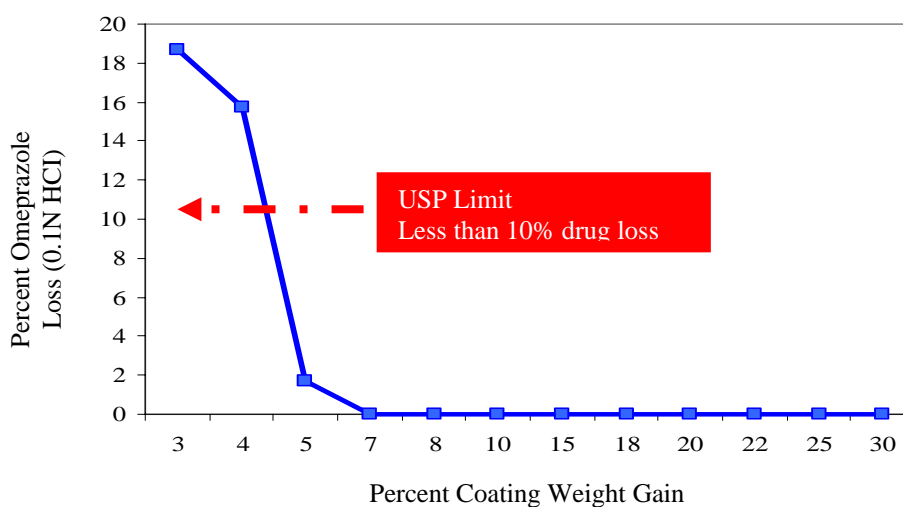
Figure 3. SEM Images, Delayed Release Omeprazole Pellet



Drug Release

USP criteria requires that less than 10% drug is released / degraded after 2 hours in 0.1N HCl, followed by greater than 80% is released after 45 minutes in phosphate buffer, pH 6.8. Figure 4 shows the percent drug loss of enteric-coated omeprazole pellets versus coating WG.

Figure 4. Drug Release in 0.1N HCl, Omeprazole Pellets (n=3)



Enteric protection in 0.1N HCl was achieved at a very low application level of Opadry® Enteric (7% WG) up to and including 30% weight gain samples. Rapid drug release (>80% in 45 minutes) was also achieved for samples ranging from 7-30% coating level in phosphate buffer, pH 6.8.

Conclusions

Hydro-alcoholic applications of Opadry® Enteric, a fully formulated delayed release coating system, yielded enteric protection at low coating WG, and complete drug release within specified monograph ranges, in phosphate buffer, pH 6.8.

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