preliminary testing of potentially active compounds. In this case a twofold increase in absorption was observed by administering a polysorbate 80 solution rather than a tragacanth suspension of SK&F 33134-A.

SUMMARY

The aqueous solubility of SK&F 33134-A is increased in the presence of sodium lauryl sulfate, cetyldimethylbenzylammonium chloride, and polysorbate 80, the effect being proportional with concentration.

Sodium chloride depresses the solubility of SK&F 33134-A. However, when polysorbate 80 is present in solutions containing chloride ions the solubility of SK&F 33134-A increases.

SK&F 33134-A is excreted mainly by the biliary route.

Urinary excretion is very low and remains relatively constant regardless of the dosage form used. The data suggest that urinary excretion measurements should not be used to indicate the degree of absorption of this compound.

The selection of the proper dosage form is essential during the evaluation of potentially active compounds. A twofold increase in availability was observed for SK&F 33134-A when the compound was administered in polysorbate 80 solution compared to a tragacanth suspension.

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Effect of Colorants on the Solubility of Modified Cellulose Polymers

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Abstract □ The effect of colorants on the solubility characteristics of cellulose polymers was studied. The work was conducted because of earlier findings that FD & C Red No. 3 dye altered the solubility of hydroxypropyl methylcellulose to the extent that dried films were insoluble in media below approximately pH 5.5. A total of 28 dyes was screened in combination with hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium ethylcellulose sulfate. Free film solubility disclosed that six dyes significantly altered the solubility of the polymers tested. Coatings containing FD & C Red No. 3, FD & C Red No. 4, D & C Red No. 17, D & C Red No. 18, D & C Red No. 21, and D & C Red No. 22 dyes were shown to have a retardation effect on tablet disintegration and riboflavin dissolution rate. Riboflavin urine excretion studies confirmed that these dyes may adversely affect *in vivo* product performance. The effects of the insoluble films on *in vitro* and *in vivo* product performance will depend upon the thickness and strength of the film as well as the disintegrating characteristics of the tablet.

Keyphrases □ Cellulose polymers, solubility—colorant effect □ Film coated tablets—colorant effect on dissolution □ Colorant effect—tablet dissolution, absorption □ Polymer film dissolution viscosity—colorant effect

The use of modified cellulose polymers in pharmaceutical products is extensive. These materials are of considerable value in gels, suspensions, tablet core formulations, and tablet coatings. Within the last few years, particular attention has been focused on interaction studies of drug-adjuvant and adjuvant-adjuvant combinations with concern for stability, toxicity, and *in vivo* performance of the dosage form. The literature cites numerous examples of interactions between cellulose polymers and drugs or adjuvants. Tillman and Kuramoto (1) concluded that methylcellulose forms complexes with a number of preservatives including methylparaben and related compounds, *p*-aminobenzoic acid and *p*-hydroxybenzoic acid. Other investigators (2) confirmed and established the extent of such interactions with regard to the effect on solubility of the preservatives in the presence of some cellulose derivatives. Deluca and Kostenbauder (3) established the degree of binding of several quaternary ammonium compounds by methylcellulose. Kabadi and Hammarlund (4) recognized the interaction effects of phenols on the solubilizing and stabilizing properties of some nonionic hydrophilic polymers. Likewise, dyes have been implicated with interaction and stability problems (5, 6). Bornstein *et al.* (7) discussed dye-adjuvant interactions as they apply to color fading. However, little data have been presented on dye-polymer combinations and the effects which some dyes have on the solubility characteristics of cellulose polymers. This study was conducted because of findings that FD & C Red No. 3 dye altered the solubility of hydroxypropyl methylcellulose to the extent that dried films were insoluble in media below approximately pH 5.5. It was therefore desirable to establish if such effects could be expected with other cellulose derivatives and commonly used

Table I—Solubility of Sodium Ethylcellulose Sulfate Films[a]

Dye	Classification	Simulated Gastric Fluid, pH 1.2[b]	Simulated Intestinal Fluid, pH 7.4[b]	Deionized Water, pH 6.5[b]
Control film		S	S	S
FD & C Red No. 1	Monoazo	S	S	S
FD & C Red No. 2	Monoazo	S	S	S
FD & C Red No. 3	Xanthene	I[c]	S	S
FD & C Red No. 4	Monoazo	S	S	S
D & C Red No. 17	Disazo	S	S	S
D & C Red No. 18	Disazo	I[d]	I[d]	I[d]
D & C Red No. 19	Xanthene	I	S	S
D & C Red No. 21	Fluoran	I	S	S
D & C Red No. 22	Xanthene	I	S	S
D & C Red No. 33	Monoazo	S	S	S
D & C Red No. 36	Monoazo	S	S	S
Ponceau 4 R	Monoazo	S	S	S
FD & C Yellow No. 5	Pyrazolone	S	S	S
FD & C Yellow No. 6	Monoazo	S	S	S
D & C Yellow No. 7	Fluoran	S	S	S
D & C Yellow No. 10	Quinoline	S	S	S
D & C Yellow No. 11	Quinoline	Ss	Ss	Ss
FD & C Blue No. 1	Triphenylmethane	S	S	S
FD & C Blue No. 2	Indigoid	S	S	S
D & C Blue No. 6	Indigoid	S	S	S
D & C Blue No. 9	Anthraquinone	S	S	S
FD & C Green No. 1	Triphenylmethane	S	S	S
FD & C Green No. 2	Triphenylmethane	S	S	S
FD & C Green No. 3	Triphenylmethane	S	S	S
D & C Green No. 5	Anthraquinone	S	S	S
D & C Green No. 6	Anthraquinone	Ss	Ss	Ss
D & C Green No. 8	Pyrene	S	S	S
FD & C Violet No. 1	Triphenylmethane	S	S	S

[a] Average film thickness: 0.10 mm. [b] S = soluble, Ss = slowly soluble, I = insoluble. [c] Film disintegrates into large pieces. [d] Film disintegrates into small pieces.

dyes. It was also of interest to determine if these effects influenced *in vitro* and *in vivo* product performance.

EXPERIMENTAL

Materials and Preparation—Tests were conducted on low viscosity grade hydroxypropyl methylcellulose NF XII, hydroxypropyl cellulose[1] and sodium ethyl cellulose sulfate.[2] These polymers were selected because of their application to tablet core formulations and tablet coatings. Free films were prepared by casting mixtures of dye and polymer in solvent onto glass plates with an applicator.[3] The dried films were removed from the casting plates and cut to uniform size disks with a No. 15 (21-mm. i.d.) cork borer. The thickness of each disk was then measured with a micrometer prior to testing.

A total of 28 dyes was screened in this study. Although some are presently not approved for use in pharmaceutical dosage forms, they were included so that a wide selection of colorants within various chemical classes would be represented. These dyes were dissolved or dispersed in either aqueous or organic solvent systems along with the polymers reviewed.

In vitro testing on both free films and coated tablets was performed in deionized water, simulated gastric fluid, and simulated intestinal fluid. The simulated test fluids were prepared according to USP XVII but without the enzymes.

Tablet coating was accomplished in an air suspension coater (8) with a 15.24-cm. diameter coating column. Coating materials were applied from organic solvent mixtures with a pneumatic atomizing system.

TESTING

Film Solubility—The solubility of each film was established by attempting to dissolve a disk in 150 ml. of test media at 37°. A magnetic stirring device was used to provide gentle agitation. Slight agitation was found necessary to prevent the disk from sticking to the walls of the beaker or from curling into a wet globular mass. The test was repeated if the sticking or curling occurred or if the solubility of the film was affected by direct contact with the stirring bar.

Tablet Coating Thickness—Tablet coating thickness was determined by sectioning a representative sample and measuring the film on each tablet with a projector (Scherr Tumico Micro) at 20 × magnification.

Tablet Disintegration and Dissolution Rate Studies—Tablet disintegration tests were performed in simulated gastric and intestinal fluids using the USP XVII disintegration apparatus without plastic disks at 37°. Dissolution rates were established in the same test fluids on multivitamin tablets by withdrawing liquid samples at 10-min. intervals during the disintegration test and assaying for riboflavin by measuring fluorescence. The riboflavin dissolution rates are reported as the time required for 50% of the drug to dissolve in the test fluids.

In Vivo Studies—*In vivo* testing was conducted by establishing riboflavin urine excretion levels. Ten adult subjects on restricted diets were administered two multivitamin tablets containing 6 mg. each of riboflavin. Urine samples were collected and assayed over a 24-hr. period. Excretion levels for these subjects had previously been established after administration of a 10-mg. riboflavin tablet which had a rapid dissolution rate.

Viscosity—The reported viscosity for each mixture of dye and hydroxypropyl methylcellulose was determined at 25° with a viscometer (Brookfield) using a No. 1 spindle at 60 r.p.m.

RESULTS AND DISCUSSION

Sodium Ethylcellulose Sulfate—Results of solubility studies on free films of sodium ethylcellulose sulfate prepared from mixtures of 3% w/v polymer, 0.25% w/v dye in 30% v/v methanol, 20% v/v ethanol, and 50% v/v methylene chloride are summarized in Table I.

[1] Klucel 2LF, Hercules Powder, Co., Wilmington, Del.
[2] Distillation Products Industries, Div. of Eastman Kodak Co., Rochester, N. Y.
[3] Gardner Laboratory, Inc., Bethesda, Md.

Table II—Solubility of Hydroxypropyl Cellulose Films[a]

Dye	Classification	Simulated Gastric Fluid, pH 1.2[b]	Simulated Intestinal Fluid, pH 7.4[b]	Deionized Water, pH 6.5[b]
Control film		S	S	S
FD & C Red No. 1	Monoazo	S	S	S
FD & C Red No. 2	Monoazo	S	S	S
FD & C Red No. 3	Xanthene	I	S	S
FD & C Red No. 4	Monoazo	I	S	S
D & C Red No. 17	Disazo	S[c]	S[c]	S[c]
D & C Red No. 18	Disazo	S[c]	S[c]	S
D & C Red No. 19	Xanthene	S	S	S
D & C Red No. 21	Fluoran	I[d]	S	S
D & C Red No. 22	Xanthene	I	S	S
D & C Red No. 33	Monoazo	S	S	S
D & C Red No. 36	Monoazo	S	S	S
Ponceau 4 R	Monoazo	S	S	S
F D & C Yellow No. 5	Pyrazolone	S	S	S
F D & C Yellow No. 6	Monoazo	S	S	S
D & C Yellow No. 7	Fluoran	S	S	S
D & C Yellow No. 10	Quinoline	S	S	S
D & C Yellow No. 11	Quinoline	S	S	S
F D & C Blue No. 1	Triphenylmethane	S	S	S
F D & C Blue No. 2	Indigoid	S	S	S
D & C Blue No. 6	Indigoid	S	S	S
D & C Blue No. 9	Anthraquinone	S	S	S
F D & C Green No. 1	Triphenylmethane	S	S	S
F D & C Green No. 2	Triphenylmethane	S	S	S
F D & C Green No. 3	Triphenylmethane	S	S	S
D & C Green No. 5	Anthraquinone	S	S	S
D & C Green No. 6	Anthraquinone	S	S	S
D & C Green No. 8	Pyrene	S	S	S
F D & C Violet No. 1	Triphenylmethane	S	S	S

[a] Average film thickness: 0.06 mm. [b] S = soluble, I = insoluble. [c] Film disintegrates into fine pieces. [d] Film disintegrates into large pieces.

Table III—Solubility of Hydroxypropyl Methylcellulose Films[a]

Dye	Classification	Simulated Gastric Fluid, pH 1.2[b]	Simulated Intestinal Fluid, pH 7.4[b]	Deionized Water, pH 6.5[b]
Control film		S	S	S
FD & C Red No. 1	Monoazo	S	S	S
FD & C Red No. 2	Monoazo	S	S	S
FD & C Red No. 3	Xanthene	I	S	S
FD & C Red No. 4	Monoazo	I	S	S
D & C Red No. 17	Disazo	S	S	S
D & C Red No. 18	Disazo	P[c]	P[c]	P[c]
D & C Red No. 19	Xanthene	S	S	S
D & C Red No. 21	Fluoran	I	S	I
D & C Red No. 22	Xanthene	I	S	S
D & C Red No. 33	Monoazo	S	S	S
D & C Red No. 36	Monoazo	S	S	S
Ponceau 4 R	Monoazo	S	S	S
FD & C Yellow No. 5	Pyrazolone	S	S	S
FD & C Yellow No. 6	Monoazo	S	S	S
D & C Yellow No. 7	Fluoran	S	S	S
D & C Yellow No. 10	Quinoline	S	S	S
D & C Yellow No. 11	Quinoline	P[c]	P[c]	P[c]
FD & C Blue No. 1	Triphenylmethane	S	S	S
FD & C Blue No. 2	Indigoid	S	S	S
D & C Blue No. 6	Indigoid	S	S	S
D & C Blue No. 9	Anthraquinone	S	S	S
FD & C Green No. 1	Triphenylmethane	S	S	S
FD & C Green No. 2	Triphenylmethane	S	S	S
FD & C Green No. 3	Triphenylmethane	S	S	S
D & C Green No. 5	Anthraquinone	S	S	S
D & C Green No. 6	Anthraquinone	S	S	S
D & C Green No. 8	Pyrene	S	S	S
FD & C Violet No. 1	Triphenylmethane	S	S	S

[a] Average film thickness: 0.06 mm. [b] S = soluble, P = partially soluble, I = insoluble. [c] Film breaks into pieces.

Table IV—Viscosity of Hydroxypropyl Methylcellulose-Dye Mixtures[a]

Dye	Average Viscosity, cps.
Control (no dye present)	30
FD & C Red No. 1	46
FD & C Red No. 2	32
FD & C Red No. 3	50
FD & C Red No. 4	36
D & C Red No. 17	46
D & C Red No. 18	35
D & C Red No. 19	30
D & C Red No. 21	31
D & C Red No. 22	72
D & C Red No. 33	34
D & C Red No. 36	35
Ponceau 4 R	32
FD & C Yellow No. 5	33
FD & C Yellow No. 6	32
D & C Yellow No. 7	30
D & C Yellow No. 10	34
D & C Yellow No. 11	32
FD & C Blue No. 1	37
FD & C Blue No. 2	30
D & C Blue No. 6	30
D & C Blue No. 9	36
FD & C Green No. 1	38
FD & C Green No. 2	32
FD & C Green No. 3	31
D & C Green No. 5	31
D & C Green No. 6	31
D & C Green No. 8	31
FD & C Violet No. 1	35

[a] Viscometer (Brookfield), 25°, No. 1 spindle, 60 r.p.m.

Those films containing D & C Red No. 19, D & C Red No. 21, and D & C Red No. 22 dyes remained intact in simulated gastric fluid. An insoluble film was found with FD & C Red No. 3 dye in simulated gastric fluid but it disintegrated into relatively large pieces. An insoluble film that also disintegrated into pieces occurred with D &C Red No. 18 dye in all three test fluids. D & C Yellow No. 11 and D & C Green No. 6 dyes had an influence on the solubility of the film but to a much smaller degree than the aforementioned dyes. Films prepared with either of these two dyes became gummy when immersed in any of the three test fluids and dissolved very slowly. Dissolution times were approximately 20 min. in contrast to the soluble films that dissolved in from 3–6 min.

Hydroxypropyl Cellulose—Hydroxypropyl cellulose films were prepared as 5% w/v polymer and 0.5% w/v dye in water. Free film solubility is summarized in Table II.

FD & C Red No. 3, FD & C Red No. 4, and D & C Red No. 22 dyes produced insoluble films that remained intact in simulated gastric fluid. D & C Red No. 21 dye also produced insoluble films in simulated gastric fluid but these films disintegrated into large pieces. Films prepared with D & C Red No. 18 dye, while soluble in 3–6 min., showed some fine pieces of film remaining at the end of the testing in all dissolution fluids. Similar results were obtained with D & C Red No. 17 dye but the films were completely soluble in deionized water.

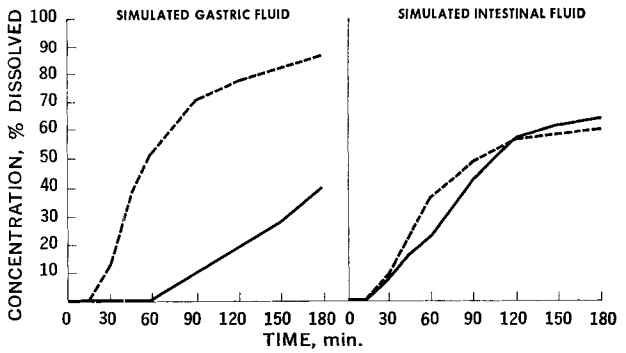

Figure 1—*Riboflavin dissolution rate study on hydroxypropyl methylcellulose coated tablets. USP XVII disintegration apparatus, 37° (without plastic disks). Key: - - -, control; —, film with FD & C Red No. 3 dye.*

Table V—Disintegration Times for Multivitamin Tablets Coated with Hydroxypropyl Methylcellulose[a]

Dye	Average Disintegration Time Simulated Gastric Fluid, pH 1.2	Simulated Intestinal Fluid, pH 7.2
Uncoated	14 min.	21 min.
Control (no dye present)	18	24
FD & C Red No. 1	18	24
FD & C Red No. 2	18	24
FD & C Red No. 3	45[b]	27
FD & C Red No. 4	26[b]	25
D & C Red No. 17	33[c]	40[c]
D & C Red No. 18	20[c]	28[c]
D & C Red No. 19	22	25
D & C Red No. 21	45[b]	28[b]
D & C Red No. 22	38[b]	26
D & C Red No. 33	18	24
D & C Red No. 36	13	27
Ponceau 4 R	18	24
FD & C Yellow No. 5	18	24
FD & C Yellow No. 6	18	24
D & C Yellow No. 7	18	35
D & C Yellow No. 10	22	26
D & C Yellow No. 11	18[c]	26[c]
FD & C Blue No. 1	18	25
FD & C Blue No. 2	18	30
D & C Blue No. 6	18	24
D & C Blue No. 9	18	26
FD & C Green No. 1	21	28
FD & C Green No. 2	18	32
FD & C Green No. 3	18	24
D & C Green No. 5	18	24
D & C Green No. 6	25	35
D & C Green No. 8	19	24
FD & C Violet No. 1	18	24

[a] USP XVII disintegration apparatus, 37° (without plastic disks), average film thickness: 0.08 mm. [b] Insoluble film. [c] Coating flakes off.

Hydroxypropyl Methylcellulose NF XII—The solubility of hydroxypropyl methylcellulose films is shown in Table III.

The films were prepared from mixtures of 3.0% w/v polymer and 0.1% w/v dye in a solvent system of 50% v/v ethanol and 50% v/v methylene chloride. FD & C Red No. 3, FD & C Red No. 4, and D & C Red No. 22 dyes produced films which were completely insoluble in simulated gastric fluid. D & C Red No. 21 dye produced insoluble films in both simulated gastric fluid and deionized water. Films containing D & C Yellow No. 11 and D & C Red No. 18 dyes disintegrated into small pieces in all three test fluids and were considered only partially soluble after 20 min. All other soluble films dissolved in from 3–6 min.

When cellulose polymers interact with some materials the result is often observed by a change in the viscosity of the mixture (9). Table IV summarizes observations on the viscosity of hydroxypropyl methylcellulose-dye combinations in ethanol/methylene chloride.

While the presence of some dyes did influence the viscosity of some polymer mixtures, there was no consistent relationship with respect to film solubility. FD & C Red No. 1 and D & C Red No. 17 dyes significantly affected viscosity but did not alter the solubility of the films in the test fluids. FD & C Red No. 4, D & C Red No. 18, D & C Red No. 21, and D & C Yellow No. 11 dyes were responsible for changes in the solubility of the films but had no influence on the viscosity of the preparations. Only FD & C Red No. 3 and D & C Red No. 22 dyes were shown to have an effect

Table VI—Riboflavin Dissolution Rate Studies on Multivitamin Tablets Coated with Hydroxylpropyl Methylcellulose[a]

Dye	Average t-50%—Simulated Gastric Fluid, pH 1.2	Average t-50%—Simulated Intestinal Fluid, pH 7.4
Uncoated	9.0 min.	16.5 min.
Control (no dye present)	14.5	19.5
FD & C Red No. 1	13.0	16.5
FD & C Red No. 2	12.0	17.5
FD & C Red No. 3	23.0	19.5
FD & C Red No. 4	17.5	21.0
D & C Red No. 17	19.5	29.0
D & C Red No. 18	14.0	19.5
D & C Red No. 19	10.5	22.0
D & C Red No. 21	28.5	24.5
D & C Red No. 22	27.0	18.0
D & C Red No. 33	13.0	19.0
D & C Red No. 36	12.5	21.5
Ponceau 4R	12.0	19.0
FD & C Yellow No. 5	12.5	18.5
FD & C Yellow No. 6	12.0	18.5
D & C Yellow No. 7	13.5	26.0
D & C Yellow No. 10	13.0	18.5
D & C Yellow No. 11	14.0	19.5
FD & C Blue No. 1	13.0	18.5
FD & C Blue No. 2	13.0	22.0
D & C Blue No. 6	13.5	18.0
D & C Blue No. 9	12.0	19.0
FD & C Green No. 1	13.5	20.0
FD & C Green No. 2	13.0	25.0
FD & C Green No. 3	11.5	18.0
D & C Green No. 5	11.0	17.0
D & C Green No. 6	13.5	27.5
D & C Green No. 8	13.5	19.5
FD & C Violet No. 1	13.5	19.5

[a] USP XVII disintegration apparatus, 37° (without plastic disks) average film thickness: 0.08 mm.

on both the solubility of the films and viscosity of the preparations tested.

Table V indicates disintegration times for multivitamin tablets coated with hydroxypropyl methylcellulose films and each dye tested.

In particular, FD & C Red No. 3, D & C Red No. 21, and D & C Red No. 22 dyes showed significant retardation effects on disintegration time in gastric fluid. However, the other insoluble coatings did not have the adverse effect on disintegration time that would be expected from insoluble films. It was observed that at the film thickness level chosen, the test fluids were able to permeate through the films and cause the tablets to swell and rupture the coatings.

Riboflavin dissolution rate studies are summarized in Table VI.

Similar to the data obtained from disintegration studies, these results disclosed inconsistencies where insoluble films had little effect on dissolution rate. In all cases, the insoluble film either flaked off the tablets or ruptured when the tablets swelled permitting the riboflavin to dissolve in the test fluids. FD & C Red No. 3, D & C Red No. 21, and D & C Red No. 22 dyes do show a definite retardation effect even at the film thickness of 0.08 mm. Films containing D & C Red No. 17 dye, while soluble in the test fluids, were responsible for prolonged dissolution rates in simulated gastric fluid. The effect of this dye on the viscosity of hydroxypropyl methylcellulose mixtures may be related to film permeability. It was observed that coatings containing this dye remained on the tablets in gel form for extended periods of time after immersion in the test fluids. This would explain the retardation effects observed on both tablet disintegration and dissolution rate.

Additional studies were made on tablets coated with hydroxypropyl methylcellulose and FD & C Red No. 3 dye at a film thickness of 0.2 mm. The *in vitro* dissolution rate results are summarized in Fig. 1. It is readily apparent that at a thicker film level the insoluble coating significantly affects the riboflavin dissolution rate.

In addition, when *in vivo* product performance tests were conducted in humans with these same tablets, similar retardation effects were observed. This was evidenced by riboflavin urine excretion levels of 63% for tablets coated with hydroxypropyl methylcellulose and FD & C Red No. 3 dye. Similar tablets which were coated with only hydroxypropyl methylcellulose provided excretion levels of 96%.

CONCLUSION

From the data presented, it has been established that some dyes do influence the solubility of the cellulose polymers tested. The effects of the dyes range from partial to complete insolubility of the polymers at various pH conditions. No attempts were made to define the mechanism by which these dyes alter the polymer characteristics. The effects observed are not specific for any one particular dye classification or grouping on the dye structure. However, all xanthene and disazo dyes tested did show some effect on the solubility of the films. Mixed findings were observed with the monoazo, fluoran, quinoline, and anthroquinone dyes. A number of investigators have presented theories to explain similar results (3, 7, 10, 11). Among those discussed are: (*a*) interactions between hydrocarbon portions of the adsorbate and the linear cellulose molecules; (*b*) dipole-dipole interactions between hydroxyls of cellulose and polar groups of the dye molecule; (*c*) ionic binding to residual carboxyls or to acidic hydroxyls by ion exchange; and (*d*) ion-dipole interactions of cations with ethers or hydroxyls. However, present information suggests that individual studies are required on each dye-polymer combination to characterize the effects that were observed.

The test fluids were found to permeate the thin insoluble films and cause the tablets to swell and rupture the coatings. When thicker coatings were tested, significant adverse effects were observed which were consistent with what can be expected from an insoluble film. Therefore, retardation of tablet disintegration, drug dissolution rate, and *in vivo* product performance will depend to a large extent on the strength, permeability, and thickness of the film as well as the disintegrating characteristics of the product.

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