# PHARMACEUTICAL TECHNOLOGY

VOLUME 7 NUMBER 9 SEPT 1983 $4.00



## Pharm Tech Conference '83
## Interphex '83

# The forgotten dosage form: enteric-coated tablets

WALTER G. CHAMBLISS

THE RECENT INTRODUCTION of transdermal delivery systems and other controlled-release dosage forms has demonstrated the ingenuity of the pharmaceutical development scientist. The number of potential dosage forms available for a new drug has never been higher. There is, however, one dosage form that appears to have been forgotten: the enteric-coated tablet.

An enteric-coated tablet is designed to resist the destructive action of the gastric fluid and to disintegrate in the intestinal tract.[1] Reasons for applying an enteric coat to a drug product include:[1-4]

- preventing the drug's destruction by gastric enzymes or by the acidity of gastric fluid
- preventing nausea and vomiting caused by the drug's irritation of the gastric mucosa
- delivering the drug to its local site of action in the intestine
- providing delayed action
- delivering a drug primarily absorbed in the intestine to that site at the highest possible concentration.

This presentation will review the history of this dosage form and examine the reasons for its apparent demise.

## Basic Studies

In 1965, Schroeter published a review of over 60 materials that have been used as enteric coating materials,[4] referring to studies that found both favorable and unfavorable in vivo performances for tablets coated with those materials. The four basic types of enteric coating materials are water-resistant films, pH-sensitive films, materials digested by intestinal fluid, and materials that slowly swell and dissolve after exposure to moisture.[2] The pH-sensitive films have received the most attention in the literature. Indeed, enteric products introduced recently seem to be manufactured exclusively with this type of coating.[5]

## pH-Sensitive Films

As the name implies, pH-sensitive film is directly affected by the pH of the GI tract. The film must be insoluble in gastric fluid but dissolve rapidly in intestinal fluid. Table I lists pH values found in the GI tract.[6] The usual pH of gastric fluid ranges from 1.0 to 3.5. Fasting generally reduces the pH value to a level between 1.2 and 1.8, and GI diseases and drugs such as histamine H-2 antagonists, anticholinergics, and antacids are also known to affect pH.[7]

Enteric films that are pH-sensitive consist of a long-chain polymer with ionizable carboxyl groups. In the low-pH environment of the gastric fluid, the acid groups are un-ionized and are therefore poorly water soluble. When the tablet empties from the stomach into the small intestine, a dramatic change in pH occurs: ionization of the acid groups and, therefore, increased water solubility occurs in the intestinal tract as shown in the following equation:

$$R - COOH + OH^- \leftrightarrow R - COO^- + H_2O$$

The equilibrium constant for the reaction is a function of the pH of the medium and the apparent $pK_a$ of the film.[1] The Henderson-Hasselbach equation may be used to predict the ratio of the concentration of the ionized to un-ionized acid groups based upon the pH of the medium and the $pK_a$ of the film:[7]

$$pH - pK_a = \log \frac{\text{concentration (ionized)}}{\text{concentration (un-ionized)}}$$

Enteric films that are pH-sensitive should have a $pK_a$ between 4 and 6. At a pH level two units below the $pK_a$ of the acid groups, for instance, only 1% of the acid groups on the polymer will be ionized — which explains the low solubility of the enteric material in the gastric fluid. As pH is increased, the equilibrium of the reaction shifts to the right, and the percentage of ionized acid groups increases.

*Table I: Range of pH values in the GI tract.*

| GI Area | pH Value |
|---|---|
| Stomach | 1.0–3.5 |
| Duodenum | 6.5–7.6 |
| Jejunum | 6.3–7.3 |
| Ileum | 7.6 |
| Colon | 7.9–8.0 |
| Rectum | 7.8 |

In the intestine, pH exceeds the $pK_a$ of the acid group by two to four units, the percentage of ionized groups approaches 100% and the polymer making up the film becomes water soluble.[2] Ionization of the acid groups causes a charge repulsion within the polymer, leading to a stretching of the polymer chain.[8] Stretching the chain allows water to penetrate to the tablet core, resulting in tablet disintegration.[1]

The pH-sensitive films that have been studied include shellac,[9] cellulose acetate phthalate,[10-16] cellulose acetate succinate,[17] half-esters of the copolymer polyvinyl methyl ether/maleic anhydride,[18] methacrylic acid/methyl methacrylate copolymer,[19] polyvinyl acetate phthalate,[20] and hydroxypropyl methylcellulose phthalate.[2] Two of these polymers — shellac and cellulose acetate phthalate — will be discussed in detail in the following sections.

***Shellac.*** Shellac, a long-chain polymer of esters of aleuritic acid, was introduced as an enteric coating material by Wruble in 1930.[9] Although once used extensively in the industry, shellac is no longer the polymer of choice for enteric-coated tablets. Shellac has an apparent $pK_a$ between 6.9 and 7.5, and this high value leads to poor solubility of the film in the duodenum, where the pH is generally slightly acidic; delayed intestinal release of the drug may therefore occur.[2]

The stability of shellac has also been criticized. Luce reported that marked changes in disintegration times occurred in shellac-coated dicalcium phosphate tablets after storage at room temperature for one year. Before storage, tablets disintegrated in intestinal fluid within 50 min; after storage, they failed to disintegrate within 120 min. The stability of the dosage form may also be influenced by the grade of shellac; several grades are commercially available. USP recognizes two basic grades: orange shellac (wax or dewaxed), and bleached or refined

# Eastman® C-A-P™

Enteric Coating Material

# It delivers.

Eastman C-A-P—Cellulose Acetate Phthalate—as an enteric coating can give your tablets an elegant, appealing finish. But there's more to the effectiveness of this free-flowing white powder than meets the eye.

Because of their excellent enteric properties, coatings of C-A-P withstand prolonged contact with gastric juices but readily dissolve in intestinal fluids. So, one coating material delivers both elegance and protection.

Also, impressions made in the tablet are visible through the finish, thus eliminating the need for printing the coated tablets.

For more information about C-A-P for enteric coatings, contact Gunther Doerfert, 615-229-3797, or write him at Eastman Chemical Products, Inc., a subsidiary of Eastman Kodak Company, Kingsport, Tennessee 37662.

**Eastman® C-A-P™**

Kodak



Circle Reader Service Card No. 74

shellac (wax or dewaxed).[21] It has been reported that alcohol solutions of orange shellac are more stable than are corresponding solutions of bleached shellac; bleached shellac tends to esterify faster because residual chlorine lowers the pH.[22] (The tablets in the study by Luce cited earlier used bleached shellac.)

***Cellulose acetate phthalate.*** Cellulose acetate phthalate (CAP) is a white, free-flowing powder prepared by reacting a partial acetate ester of cellulose with phthalic anhydride. The cellulose polymer used in the reaction has a molecular weight between 2000 and 8000, and the final product contains 30% to 36% combined phthalyl and 19% to 23.5% combined acetyl. Approximately one-half of the available hydroxy groups in the cellulose chain are acetylated; one-fourth are esterified with one of the two phthalic acid groups.[10] Figure 1 shows the structure of cellulose and a representative structure of CAP.[23]

CAP, the most widely used enteric coating material, was introduced by Hiatt in 1940.[11] Couvreur conducted an extensive study of enteric coating of tablets and concluded that CAP combined all of the qualities required of a true enteric coating. Indeed, Couvreur found that CAP was the only material tested that responded exactly to the requirements.[12]

Zatz and Knowles studied the effect of pH on CAP monomers. From pH 2 to pH 4, the CAP monomers were observed to be in a compact form. As the pH changed from 4 to 6, however, ionization of the acid groups occurred; the greatest effect on film stability was seen at pH 6.[24]

A controversy has developed in the literature concerning the role of pancreatic esterases in the disintegration of CAP-coated tablets. Bauer and Masucci attributed disintegration of CAP-coated tablets in slightly alkaline pancreatic fluid to the hydrolytic effect of the esterases and not to a pH effect,[14] while Payne found that a pancreatin concentration of 3 g/L had no significant effect on the in vitro disintegration time of CAP-coated tablets.[25]

Long-term toxicity studies in rats and dogs performed as early as 1944 showed that CAP was very safe. Rats had depressed growth rates, but no fatalities were attributed to ingestion of CAP. Dogs fed 10 g of CAP daily showed no adverse affects after one year.[26]

Storage of CAP-coated dicalcium phosphate tablets at room temperature for 12 months caused no significant change in disintegration times.[16] Blythe et al., however, reported that the type of disintegrant incorporated into the tablet core affected the stability of the dosage form. On the one hand, they found that CAP-coated aspirin tablets containing starch as the disintegrant showed marked changes in both in vitro and in vivo disintegration times after 18 months in storage. On the other hand, no change in disintegration times was observed after storage of CAP-coated aspirin tablets containing guar gum as the disintegrant.[27]

## Methods of Coating

The oldest method of enteric coating involves manual pan coating. Conventional coating pans are constructed of stainless steel and range in diameter from 12 in. to 60 in. Pans are available in doughnut, pear, and hexagonal shapes, and most are equipped with an exhaust system and a humidity-controlled air source.[2] The angle of the axis and the rotation speed may be adjusted as needed for a particular product.[28]

The conventional pan has a single front opening through which processing air enters. Side-vented pans provide a unidirectional flow of air through the bed and the pan's perforations, increasing coating efficiency.[28]

Coating solutions may be added to the pan by either intermittent or continuous processes, and new spray systems have largely replaced the conventional ladle technique for solution addition. A dusting powder such as talc or magnesium stearate may be added to the bed to prevent tablet sticking. The thickness of the coat depends upon the nature of the coating film,[2] the physical properties of the specific tablet,[15] and the desired in vitro/in vivo release profile.

The air suspension coater developed by Wurster suspends tablets in an airstream;[29] the coating solution is sprayed onto the suspended tablets and is then dried by warming the airstream. The major disadvantage of this coater is breakage and attrition of the tablets. Tablets coated in this way must therefore have sufficient hardness to withstand collision with the walls of the coating chamber and with other tablets.[2]

## Evaluation of Enteric-Coated Tablets

***In vitro tests.*** The USP disintegration test for enteric-coated tablets first appeared in 1955 in *USP XV*.[30] It was modified in the second supplement to *USP XV* and has since remained unchanged. The test specifies that the tablets must remain intact in simulated gastric fluid TS at 37 °C for 1 hr, then disintegrate in simulated intestinal fluid TS at 37 °C within a time period not to exceed the limit specified in the individual monograph for the uncoated tablet plus 2 hr.[31]

As early as 1948, investigators reported that the pH of simulated intestinal fluid should be slightly acidic to correspond to the pH of intestinal fluid in the duodenum.[14] Nonetheless, the pH of simulated intestinal fluid TS in *USP XX* (1980) is alkaline (pH 7.5).[32] A variety of alternative artificial intestinal fluids have been described in the literature, the earliest by Toplis in 1915.[33] The pH of these fluids have ranged from low values of 6.8[34] and 6.9[35] to a high of 8.5.[12] Still, the only official simulated intestinal fluid that is acidic (pH 6.8) is found in the *British Pharmacopoeia*.[34]

A large number of reports found in the literature demonstrate that good in vivo performance by an enteric-coated tablet is not ensured simply by virtue of passing the USP disintegration test.[36-40] Tablets that have passed the test have sometimes been observed to be excreted unchanged in the feces of normal human subjects.[36] Other tablets have demonstrated poor relative bioavailability as compared to the uncoated tablets.[36,38,39] Wagner and colleagues, using the USP disintegration apparatus and a pH 6.9 buffer, found no direct relationship between in vivo and in vitro disintegration times.[35,36,41] Rasmussen, however, reported a direct proportionality between in vitro and in vivo disintegration times, independent of tablet size and composition.[42]

Virtually no attention has been given to the use of a dissolution test for enteric-coated tablets; indeed, the latest *USP* does not contain an official method of evaluating the dissolution behavior of enteric-coated tablets.[32] In a study by Embil and Torosian, the USP procedure for uncoated tablets was adapted to study the dissolution of enteric-coated aspirin tablets. The authors recommended a pretreatment period of 15 min in simulated gastric fluid, followed by dissolution in simulated intestinal fluid. The study showed that longer pretreatment periods did not significantly alter the dissolution profile.[43]

In a study performed recently by the author and co-workers, the dissolution of different enteric-coated formulations was studied at pH 1.2, pH 6.0, and pH 8.0.[44] The following criteria were established to help in the selection of the best coating ma-

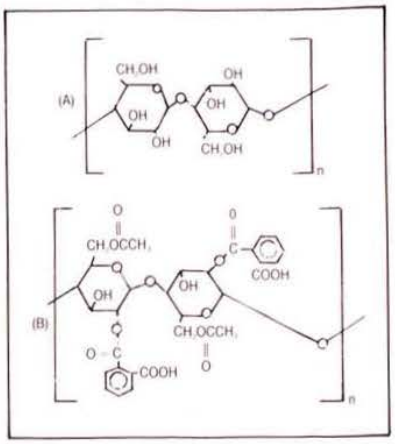


*Figure 1: Chemical structures of cellulose (A) and cellulose acetate phthalate (CAP) (B).*

# Before you put your old sterilizer out to pasture, talk to the people at SI.

**We'll custom remanufacture your old system on-site or at our plant in a fraction of the time it takes to buy a new one, plus save you up to 40% in the process.**

When it comes to sterilizers, our philosophy is simple: waste not, want not. We use pressure vessels and doors from your old sterilizer and test them to ASME specifications. All other parts are factory-new. We can also modernize your present system by adding custom features that better suit your needs.

Our expert technicians keep your design simple for greater efficiency and reliability. You get only the features you need, without costly gadgets that do little to improve processing. What's more, our systems have proven so reliable we're able to offer you the longest warranty in the industry—three full years.

**We'll update your sterilizer to meet GMP requirements and put it on a real-time basis.**

Our Steritrol microcomputer is a fail-safe system that eliminates operator/equipment error, allows complete and reliable documentation, plus provides you with many other advanced capabilities. Fully flexible and easy to program, Steritrol is able to handle jobs at all levels of sophistication, from production line to R&D applications.

For more information, call or write Scientific Industries. We'll show you how to put new life into your old system.

The sterilizer specialist.

**Scientific Industries, Inc.**

70 Orville Drive, Airport International Plaza,
Bohemia, NY 11716 (516) 567-4700

See us at INTERPHEX, Booth #3420

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.