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DESIGN AND FORMULATION OF SUSTAINED RELEASE THEOPHYLLINE DOSAGE FORMS

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INTRODUCTION

During the past decade the application of kinetics to drug therapy has become highly sophisticated. Certainly, in the area of theophylline, it has become a standard practice to utilize pharmacokinetic data in treating many patients. Often, these patients are taking long-acting or sustained release products in which drug availability and thus pharmacological effect depends upon the physical release of the chemical substance from a rate limiting matrix or coating. In the past decade, such long-acting products have gone from T.I.D. to B.I.D. and now once-a-day dosing. The object of this paper is to explore the problems involved in the design, formulation and manufacture of such products and to speculate as to whether or not the treatment of pharmacokinetic data

may have surpassed the ability to accurately and precisely deliver the drug.

HISTORY

It has been just over 30 years since the introduction of the first modern oral sustained release products by Smith Kline and French Laboratories under the trade name "Spansule". This product consisted of hundreds of beads containing a drug and coated with varying thicknesses of a natural wax such as beeswax and glyceryl monostearate. This concept proved a tremendous success in its time and truly represented one of the milestones of pharmaceutical technology.

It is somewhat ironic that the design of "Spansule" products was modeled after the "friable pill" marketed by Upjohn in the late 1800's in the first attempt to promote the concept of rapid bioavailability.

Prior to the introduction of Spansules, there were a number of enteric coated products on the market-notably "Enseals" of Lilly, which were based on coatings of wax and elm bark to delay release of a drug until emptying from the stomach had occurred. Unfortunately, some of these products did not function in the manner designed and the dose of the drug was not always released.

The Spansule was almost an overnight success and it prompted many other companies to come out with sustained release products of their own. However, there were a number of problems.

1. There was little concept of biological half-life and thus all products were designed to contain two or three "regular" doses. In addition, it was not possible to analyze drug levels in the blood and therefore effectiveness could only be measured by sometimes inexact pharmacologic parameters.
2. The whole area of biopharmaceutics and pharmacokinetics was in its infancy and the concept of the role of dissolution in drug absorption had not been postulated. It was not until 1957 that Eino Nelson noted that there were marked differences in the intrinsic dissolution rate of theophylline salts and hypothesized that these differences could explain differences in peak blood levels (1). "Other factors remaining constant, solution rate determines blood levels and rate of build-up of blood levels with time."

3. Compared to today's standards, manufacturing facilities and quality control were relatively primitive and Good Manufacturing Practices were solely the responsibility of the individual company.

Regardless of these shortcomings, literally hundreds of "sustained release" products were marketed by a wide variety of companies under numerous catchy names such as "continuous release", "delayed action", "extended action", "long-play", "prolonged action", "slow acting", "controlled release", "gradual release", "timed release", "spaced release", etc.

As the science of biopharmaceutics and pharmacokinetics gradually developed, it was soon obvious that many of these old products were not well designated or formulated and for many years the whole area of sustained release oral preparations stagnated and many products were actually removed from the market. However, with the gradual decline in the number of new drug entities, and a better understanding of pharmacokinetics, the concept of sustained release was reborn and today it is a highly important component of many drug company's product lines. We even have a new name for such products-oral drug delivery systems.

THEOPHYLLINE

Probably no drug better epitomizes the success story of sustained release products than does theophylline.

Theophylline has challenged the pharmaceutical formulator since its first use as a drug. For a time it was thought that rectal administration was the preferred route. As a matter of fact one of the first scientific publications reporting the effects of dosage form on drug blood levels used theophylline as the test drug and promoted the use of a rectal solution of theophylline (2).

The first modern "sustained" release theophylline was marketed by Fleming and Co. in 1972-73. The product - Aerolate^{R}" is still marketed today and is composed of enteric coated beads designed to simply bypass the stomach. Shortly thereafter another small company, Dooner, introduced the first truly sustained release theophylline product under the name Slophylline Gyrocaps^{R}.

Slophylline was and is today manufactured by Cord Laboratories and consists of inert sugar seeds coated with various combinations of drug and shellac but is now marketed by William H. Rorer, Inc.

In 1977, Key Pharmaceuticals, Inc. introduced Theo-Dur^{R} and promoted it on pharmacokinetic principles -

zero order release. This product quickly captured the major share of the marketplace and maintains that position today.

It is interesting to note that Key had possessed a patent for sustained release theophylline since 1961 (16 years previously) but had never commercialized the concept (3). Today's product in fact employs much of the technology described in that patent.

Theophylline is a dimethylated xanthine that is similar in action to caffeine and theobromine. It forms salts at high pH, i.e. theophylline diamine or aminophylline. At a physiologic pH it is a weak base Pk_a = 8.8 and incapable of existing as a salt. Solubility is relatively little affected by pH in the normal physiological range.

For many years the monohydrate was often used in formulations, but the dissolution of the anhydrous form is faster and more reproducible. Thus, the anhydrous form is the one which is uniformly used in formulating all theophylline products today, both rapid acting and prolonged release.

DESIGN OF SUSTAINED RELEASE PRODUCTS

There are many different mechanisms by which the release of a drug can be physically slowed down from a tablet or bead type matrix. However, in the case of

theophylline products this can be reduced to three basic mechanisms or combinations of those containing the drug.

1. Erosion of a matrix (either tablet or bead)
2. Erosion of a coat surrounding a drug product (either tablet or bead)
3. Diffusion of the drug through a semi-permeable membrane or coating which remains intact

The materials to retard the release of a drug substance fall into the following categories. These substances with their mechanism of release are listed in Table I.

1. Lipid substances
2. Water soluble or dispersable acidic polymers (pH dependent)
3. Water insoluble polymers (pH independent)
4. Water soluble hydrophilic polymers

Lipid substances may be mixed in or coated around the drug substance. Release is due primarily to emulsification of the lipid by bile salts and/or gradual erosion along with enzyme (lipase) hydrolysis of any esters (i.e. glyceryl monostearate). This mechanism was the basis for the original Spansule® capsule. The acidic polymers release drug mainly

TABLE I

SUBSTANCES UTILIZED FOR RETARDING RELEASE OF THEOPHYLLINE FROM TABLETS OR CAPSULES

Lipids	Release Mechanism
Castor Wax White Wax Beeswax Glyceryl Monostearate Stearyl Alcohol Carnauba Wax Glyceryl Palmito Stearate Myristyl Alcohol Hydrogenated Castor Oil	1. Emulsification by Bile Salts 2. Erosion 3. Lipase Hydrolysis (Glyceryl Esters)
Acidic Polymers	**Release Mechanism**
Cellulose Acetate Phthalate Shellac (Aleuritic and Shellolic Acids) Methacrylic Acid Copolymers (Not in U.S.) Carbomer (Carboxyvinyl Polymer)	1. pH Dependent Erosion and Some Enzymatic Hydrolysis 2. Diffusion at Low pH
Insoluble Polymers	**Release Mechanism**
Ethyl Cellulose Cellulose Acetate (Not in U.S.)	1. Diffusion and Dialysis
Water Soluble Polymers	**Release Mechanism**
HPMC (Hydroxy Propyl Methyl Cellulose)*	1. Gradual Solution and Swelling with Erosion

*May also be used to modify permeability of insoluble polymers.

through erosion brought about by ionization and partial solubility caused by increases in pH. Polyners can be modified to release drug at a variety of pH's ranging from 4.5 up to greater than 7.0. At a low pH (4.0), these polymers form insoluble films which can release drug only by diffusion. The first acidic polymer used for this purpose was shellac and in spite of its natural origin and variations in chemical composition, it is still widely used today. However, many newer products use synthetic polymers such as cellulose acetate phthalate and hydroxy propylmethyl cellulose phthalate.

One of the most reliable forms of drug release involves coating the drug (in a bead or tablet) with a film of polymer which is totally insoluble regardless of pH. The most widely used polymer for this purpose is ethyl cellulose. Water diffuses through the polymer coating, dissolves the drug and the solution then passes back through the membrane. The porosity of the membrane and thus the rate of release of the drug can be modified by adding substances to the insoluble ethylcellulose film which makes it more water permeable. These include hydroxypropyl methyl-cellulose (HPMC) or the more pH dependent cellulose acetate phythalate.

Most bead-type products contain cores consisting of sucrose/starch. As this core material dissolves, it increases the positive pressure within the coated particle and assists in diffusion of the drug out of the system.

Finally, the drug can be compressed into a mesh of specially treated hydroxypropyl methylcellulose fibers. Upon exposure to body fluids, the hydrophilic polymer dissolves and swells into a gelatinous mass which gradually erodes away releasing the drug.

COMMERCIAL THEOPHYLLINE PRODUCTS

Many of the sustained release products in the marketplace today use the mechanisms, materials and manufacturing processes first utilized in the 1950's and 60's. Others employ more modern materials and technology. However, all systems are subject to one or more of patient variables such as pH of the gastrointestinal tract, presence or absence of enzymes or variations in transit times. Following is a discussion of the composition and release mechanism of a wide variety of products found in the marketplace today.

1. Elixophyllin^{R} (Berlex Lab Inc.), Theovent^{R} (Schering Corp.) and Theobid^{R} (Glaxo, Inc): All of these products are made by KV Laboratories and appear

to be identical in composition and release pattern. They are manufactured by a process and utilize materials described by a patent issued in 1961 (4). This includes the use of coatings of shellac, stearic acid and castor oil to slow down dissolution of the theophylline.

2. Bronkodyl-SR^R (Winthrop-Breon Lab.) and Theophyll SR^R (McNeil Pharmaceutical). These also appear to be identical products made by Cord Laboratories and primarily involve the use of shellac as the rate delaying coating material.

3. Theolair SR^R (Riker Laboratories, Inc.) and Respid (Boehringer Ingelheim) are identical sustained release tablets in which the theophylline is granulated with cellulose acetate phthalate and compressed into a non-disintegrating tablet.

4. Labid (Norwich Eaton Pharmaceuticals Inc.) is a long acting dye free tablet in which anhydrous theophylline is distributed in a blend of carbomer (polymer of acrylic acid crosslinked with a polyalkenyl polyether) and sucrose, slugged and then compressed into non-disintegrating tablets from which release is pH dependent.

5. Quibron^R Mead Johnson Lab) is one of the most unique and interesting sustained release products of

theophylline as it contains almost no excipients (95% drug). The patent describes a granulation of anhydrous theophylline with 5% hydroxypropyl methylcellulose which is blended with 0.5% magnesium stearate and compressed (5). Release depends upon the very slow dissolution rate of theophylline from a nondisintegrating surface. The geometry and scoring is also unique. The tablets are long and plate-like providing scoring in both halves and thirds (6). The plate-like geometry results in a gradual change of surface area with time, thus providing a more uniform dissolution rate.

6. Slo-Bid^R (William H. Rorer, Inc.) is a modification of an earlier sustained release product, Slophyllin^R, which is also marketed by Rorer. The shellac-theophylline matrix beads of Slophyllin^R are coated with an ethyl cellulose film which is modified slightly to assure increased permeability as residency time in the GI tract progresses. Thus the product becomes more of a diffusion controlled rather than a pH controlled release system.

7. Theo-Dur^R (Key Pharmaceuticals, Inc.) is certainly the most successful of all the sustained release theophylline products. Its relatively uniform release pattern over a 12-18 hour period of time and its commercial popularity has made it the standard

against which all other sustained release theophylline products are compared.

Theo-Dur^R however is also one of the most complicated products in terms of both formulation and method of manufacture. It is a combination of coated beads embedded in a slowly disintegrating matrix. An old patent issued to Key in 1961 provides some clues as to its probable contents (3). The theophylline is coated onto sugar beads which are then enclosed in various coatings of lipid material (glyceryl monostearate, cetyl alcohol, beeswax) and/or an acid polymer cellulose acetate phthalate. The beads are then compressed into a slowly disintegrating waxy type matrix containing additional drug. Release depends upon the type and thickness of the coatings, nature of the tablet matrix and the geometry and hardness of the tablets. In spite of its complexity, Theo-Dur^R has established a record of constant drug delivery, which is not substantially affected by food and pH. This product is identical to the Sustaire^R which is produced by Roerig under license from Key.

8. Theo-Dur^R Sprinkle (Key Pharmaceuticals, Inc.) consists of beads contained within a capsule which can be opened and the contents emptied into food for ease of administration. However, it should be noted that

the beads in the Sprinkle^{R} product are not the same beads used in the Theo-Dur^{R} tablet. Instead, Key has chosen to utilize one of the more modern diffusion controlled ethyl cellulose coatings as the release mechanism. This system is described in a recent article which depicts the partially empty and empty shells of the microspheres as the theophylline dissolves and diffuses out from them (7).

9. Theo-24 (Searle Pharmaceuticals Inc.) was the first product introduced into the marketplace for 24 hour dosing. Since its introduction there has been considerable controversy as to the appropriateness of such a dosing schedule in the regulatory agencies, the medical community and the courts. Although the promotional literature describing the sustained release beads (Probeads^{R}) is quite elaborate the company would not provide any information on the composition of the product or to explain how the beads are designed to "prolong transit time" (8). It does appear to be a diffusion controlled coated bead type product which utilizes either shellac or cellulose acetate phthalate and which is pH dependent. Subsequent studies have shown that the product does release drug at a more rapid rate when given with food than taken on an empty stomach.

10. Uniphyll Tablets (Purdue Frederick) is the most recent sustained release product to receive FDA approval for 24 hour dosing. These tablets consist of granules of theophylline which have been prepared with hydroxpropyl methylcellulose. The granules are coated with cetyl or stearyl alcohol and then compressed into non-disintegrating tablets. As the cetyl alcohol is partially digested, the hydrophilic granules are exposed to water which causes them to swell and the theophylline slowly dissolves out of the HPMC gel.

A clinical and pharmacokinetics basis for the selection and use of slow release products was recently published by Hendeles et al which documents the wide variability in blood levels obtained from a variety of commercial products (9).

CONCLUSION

The above descriptions do not include all sustained release theophylline products in the marketplace. However, hopefully they provide sufficient insight to make it obvious that their release patterns may not be nearly as sophisticated as the mathematics with which the pharmacokinetic data is treated. Furthermore, there is much still to be learned about the physiological variability to which sustained release dosage forms are exposed in the GI tract, in particular - transit time.

Twenty years ago, Lazarus and Cooper wrote the following words:

> "The development and extensive use of sustained release oral medication has created new opportunities for creative accomplishments on the part of research pharmacists and may also serve to stimulate physiological studies on the mechanism of drug absorption" (10). These authors were truly prophetic, but unfortunately much is still to be learned in the rapidly expanding science and technology of drug delivery systems.

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