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THE SUSTAINED RELEASE COATING OF SOLID DOSAGE FORMS: A HISTORICAL REVIEW

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ABSTRACT

The continued development of sustained release technology over the past forty years has provided countless ways of producing long acting dosage forms. Of all the methods proposed, coating has proven to be one of the most enduring. Although many have attempted to introduce new sustained release coatings to the marketplace, only three have been widely accepted. This paper seeks to provide the reader with a historical review of sustained release coating and examine the reasons why three materials, cellulose acetate, ethylcellulose and methacrylic acid copolymer have dominated this technology.

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INTRODUCTION

The coating of tablets, granules, and other dosage forms has provided manufacturers with a means to extend the utility of an active ingredient which may have physical or biopharmaceutical shortcomings. Usually, great changes in the invivo performance of a problematic, yet effective drug can be imparted by applying the proper coating to it. Some of these changes, hiding an unpleasant odor for example, may seem insignificant when looked at from a biopharmaceutical standpoint. However, it is rather easy to comprehend the benefits of applying a thin, acid resistant coating to protect an acid labile drug from the low pH of the stomach.

Several authors (1,2,3) have published reviews of pharmaceutical coating which pay close attention to the techniques and equipment employed for solid dosage forms. These reviews are an invaluable tool to the formulator as they contain in depth descriptions of the most common coating processes, including individual advantages and disadvantages. An added benefit to these reviews is their near timelessness. While it is true that the science of coating has evolved over the years, it is also true that the coating equipment which we employ today is not much different than that which was used twenty or even forty years ago.

The evolution of coating equipment has not proceeded rapidly, largely due to the limited ways in which large amounts of material can be handled efficiently. A similar evolutionary trend is evident for coating

materials. Although progresses in polymer chemistry have allowed the development of specialized polymer systems which provide any number of desired properties, the conservative nature of the pharmaceutical industry has, until recently, allowed for the widespread usage of only a few. Yet the introduction and popularity of these engineered materials is largely responsible for transforming pharmaceutical coating from an artform, guarded by a few skilled individuals, to a science which can be readily duplicated, tailored to specific needs and transferred between manufacturing sites.

Many contemporary sustained release coatings are really the direct descendants of those that were first introduced in the 1950's. While many attempts have been made to introduce new coatings to the industry, those systems which applied new technologies to extant polymers have proven most successful. This paper seeks to provide the reader with a concise overview of the coatings employed for sustained release, providing a brief history of the most popular coating techniques, an examination of the reasons why products are coated, and provide a historical review of sustained release coatings in the pharmaceutical industry.

REASONS FOR COATING SOLID DOSAGE FORMS

To the layman, tablet coatings may appear as mere decoration added to make tablets more attractive to the eye and pleasing to the palate. However, just as the sugar coating on some chocolate candies keeps the chocolate from melting in your hand, coatings on tablets

provide a means to improve the stability and performance of the drugs held within them. Of course coatings are not just a cosmetic placed on tablets to make them more inviting, although they may be used as such. Sometimes an opaque coating is used to mask a mottled or discolored tablet but, more frequently, coatings are used to modify the biopharmaceutical properties of a drug or to compensate for physico-chemical shortcomings which it may possess.

It is possible to remedy certain problems encountered in tabletting by applying a some type of coating. The nature of the problem is what ultimately determines which type of coating is applied. Therefore, coatings can be loosely placed into one of three categories, grouped by the shortcomings which they are intended to overcome. There are coatings which can alter the biopharmaceutical profile of a drug and others which help counteract the physical incompatibilities of some drugs. Lastly, there are coatings which are used for purely cosmetic purposes.

Many authors have posed many reasons for coating tablets. The remainder of this section shall present those reasons which are still relevant today and some others which are of historical interest.

Tablets and other solid dosage forms may be coated to:

* Mask unpleasant tastes and odors
* Hide mottled or discolored tablet surfaces
* Prevent freshly prepared pills and troches from adhering to one another (4)
* Protect from gastric fluids those drugs which are destroyed by acid i.e. erythromycin (5)

- Prevent nausea , vomiting, or ulceration due to irritation (6)
- Impart a delayed action component for repeat action tablets (4)
- Protect a drug from oxygen, carbon dioxide, water, and light (5)
- Prevent incompatibilities between medicaments in a combination tablet (6)
- Provide a semipermeable membrane which limits the release of a drug from it's respective dosage form

TABLET COATING: A HISTORICAL PERSPECTIVE

Modern coating can be traced to rather humble origins in the kitchens of 19th century confectioners who had perfected the "art" of pan coating (4). In the confectioner's kitchen, methods were developed to cover sticky, sweet candies with a bright layer of colored, sometimes flavored sugar, thus rendering them non-sticking, easily transportable, and as pleasing to the eye as they are to the palate. One might speculate that pharmacists, often faced with preparations that were difficult to handle, would welcome such a novel and useful tool to their trade. Unfortunately, during most of the 19th century, nearly all prescriptions were prepared by extemporaneous compounding. A considerable amount of the pharmacist's time was spent preparing the individual prescription so little could be devoted to a process as time consuming as sugar coating. In fact, when necessary, most pill coating was performed by simple techniques which provided a suitable means of keeping the pills from sticking together or hiding their bad taste. Large batches of pills (and later, tablets) were uncommon.

However, the 19th century pharmacist did find it necessary to apply some sort of coating to many of his products especially massed pills, troches, lozenges, and tablets. The methods employed may seem quite primitive today, but were an effective means of resolving some problems and had the advantage of being easy and efficient to use with small amounts of material.

Perhaps the simplest of these coating methods was the application of a small amount of finely divided chalk or confectioner's sugar to the moistened surface of pills (4). This was accomplished with two pilling tiles, one sprinkled with finely divided dusting powder, the other with a thin layer of gum arabic or tragacanth mucilage through which the pills could be continually rolled until a thin white coating was obtained. Color could be added by incorporating a small amount of dye into the dusting powder. A variation of this method suggests that the pills be moistened with an etherial solution of tolu balsam. The principle advantage to this variation is that the pills would dry much more quickly due to the rapid evaporation of the ether (4). Yet another adaptation of "dusting" was Furley's process, which was quite popular in 19th century England. The principal difference between the two was the ingredients of the coating. Tragacanth and sugar were used in place of dusting powder as the solid portion while albumen, obtained from a fresh egg replaced gum arabic as the binder. Other coating methods employed at the time varied in complexity ranging from the simple (i.e. "gilding") to more complex methods including gelatin and sugar coating. In most cases "complexity" meant the need for specialized equipment.

Of all the early coating methods "gilding" has been subject to the most scrutiny. Today it seems somewhat absurd to cover a medicament with a metal which could severely retard or completely prevent it's release in invivo. However, at the time it was one of the most elegant and readily available methods to coat small quantities of pills. Another advantage to this method is the excellent compatibility of gold with other chemicals. Detailed instructions for gilding pills are published in many of the earlier all inclusive pharmaceutical texts. Parrishes, 4th ed. 1874, describes several methods for gilding and cautions the pharmacist to use only pure gold and limit the amount applied. A point of interest in this nearly 120 year old work is the concern about dosage form's "solubility" (a reference to bioavailability). It states "The former belief that a coating with metallic leaf, if sufficient to hide the taste and smell of the pills, would interfere with their solubility, has been very much modified by recent experience" (4). Indicating, if only on the most rudimentary level, that pills coated with gold leaf could effectively release their medication in the gastrointestinal tract.

While successful in their own right, "dusting" and "gilding" were gradually replaced by "dipping" and pan coating. Dipping, a process once nearly forgotten, but recently resurrected in a refined form for several OTC preparations (Tylenol Gelcaps), is mentioned briefly in Parrishes and is discussed at great length in Remington's 3rd ed. 1894 (7). Similar coverage of sugar coating a technique whose popularity was ever growing at the turn of the century, can also be found in these works.

Generally, pills were dip coated in one of three materials gelatin, keratin and salol. Of these three, gelatin was the most popular and versatile, while keratin and salol were reserved for enteric coatings (8). This fairly simple and effective process for coating involved the placement of freshly prepared pills onto long pins which were then dipped, several times, into a hot solution of gelatin. After hardening, the pins were removed and the hole which they left behind was filled with additional gelatin. This efficient process was well suited for the extemporaneous compounding of pills and many machines which improved the process were patented.

"Dip Coating" of pills was quite effective, regardless of the few shortcomings of the method, however it was impossible to coat compressed tablets in this manner because they could not be easily pierced with a needle. A remedy to this problem and a better way to coat pills was invented by J.B. Russell and later adopted by Parke, Davis & Co (7). This apparatus replaced the pins, previously used to hold pills, with a suction device which covered one half of the tablet. Tablets were still dipped in the gelatin solution and allowed to cool. Once cool, another set of tubes with vacuum was applied to the opposite side of the tablet while the first set was removed. Again the tablets were dipped and allowed to cool. The result was a gelatin coated tablet or pill that did not require further processing.

As the turn of the century approached, sugar coating in rotating pans was becoming the coating standard in large pharmaceutical houses.

In a large company, product batches were of sufficient size to warrant the use of pan coating. Many thousand pills or tablets could be economically coated by relatively few employees. The era of modern pharmaceutical coating had begun.

During the first half of this century, tablet coating evolved into the processes with which we are familiar today. Sugar coating pans have changed little in the last one hundred years. Copper pans, a leftover from confections, have been replaced by stainless steel. The source of drying air has progressed from charcoal fires (4) to steam and finally, the forced hot air systems in use today. Lastly, the coater's ladle has been replaced by a spray nozzle to better control the application of coating solutions.

While the art of sugar coating had reached near perfection in the early 1950's its shortcomings (9) would lead to its overshadowing by a more efficient and versatile technology. The introduction of film coating (Abbott Laboratories, 1953) to the pharmaceutical industry allowed for great changes in the way formulators perceived tablets. No longer were they bound to the use of featureless, nearly spherical tablets as the newer polymeric coatings allowed for tablets of many shapes. Even embossed tablets could be coated in an efficient and aesthetically pleasing manner. These new coatings although versatile, were not well suited for use in existing coating equipment. At about the same time as the development of the new polymeric coatings, two advances in coating technology were introduced. Both of which have become essential to the modern pharmaceutical industry.

The addition of many small holes and it's enclosure within a sealed cabinet were modifications of the conventional coating pan which led to the "perforated" pan. Perforated pans (i.e. Thomas Engineering's Accela Coater and others) allow for the passage of great volumes of air across the tablet bed and controlled temperatures which are necessary to meet the demands of polymeric film coatings.

The second of these innovations, the air suspension coater was an entirely different approach to coating (10). Unlike coating pans, the mechanics of the suspension coater caused tablets to continually rise and fall in a stream of gas while the coating solution is sprayed onto them from below. Since it's inception, the "fluid bed" coater has undergone continual modification leading to a very versatile tool capable of coating tablets, pellets, and even very small granules in a timely fashion. While capable of many things, perhaps the greatest advantage of this apparatus lies in its ability to function in a "closed loop" thereby facilitating the recovery of organic solvents and increasing the level of occupational and environmental safety.

Further advances in coating technology have been less monumental yet have served to enhance the existing technology. After all, the coating machinery and methods most commonly employed are well suited to the types of coating that is performed in today's industry. Likewise, progress in coating machinery will most likely accompany, or follow, the development of new types of coatings. Unfortunately, this is the age of cost containment and conservative formulation strategies

within the industry. The chance of an entirely new approach to tablet coating coming into large scale usage in the near future is rather small unless it proves vastly superior to existing methods.

SUSTAINED RELEASE COATINGS: A HISTORICAL SURVEY

In the preceding section, an attempt was made to provide the reader with an overview of the methods and technologies employed in the coating of solid dosage forms during the past century. The majority of the methods described were simple, developed by pharmacists for use within the pharmacy, primarily for the purpose of making distasteful drugs more palatable. Later, coating would evolve into a science which allowed the formulator to selectively alter, or improve, the biopharmaceutical behavior of the products to which they were applied.

Although there are many ways to obtain the sustained release of medication (11,12), coatings applied to tablets, pellets, or granules are perhaps the most popular. According to USP XXII (13) there are three classes of coating commonly employed in the manufacture of solid dosage forms. The oldest of these, the "Plain Coatings" (USP XXII), are those used to alter the taste and appearance of tablets or to protect them from the detrimental effects light and moisture. Plain coatings, perhaps best exemplified by sugar and hydroxypropylmethylcellulose, are not intended to alter the biopharmaceutical performance of the drug contained within them. The second group of coatings, dubbed "Delayed Release" by USP, are more commonly know as "enteric". The enteric

coatings (i.e. cellulose acetate pthalate), due to their poor solubility in acidic media, serve to protect acid labile drugs from the low pH of the stomach by delaying their release until the tablet has reached the intestinal tract. Sustained release coatings ("extended-release" USP XXII), those which have been designed to meter the amount of drug released from a dosage form, complete the list.

Until this point, the discussion of sustained release film coatings has been oversimplified, implying that the coating is a single, pure entity. Rather, film coatings are a mixture of several components which result in a continuous film with desirable properties. Generally, a film coating solution will contain four basic components; film former, solvent, plasticizer, and colorant (3). These components, both alone and in conjunction with one another have been the subject of numerous studies and several lengthy reviews. While not the focus of this paper, general reviews of film coating have been presented by Banker (14), Conrad and Robinson (15), and Seitz et. al. (1).

Pharmaceutical film coatings is a broad terminology which encompasses several types of film. These films modify the release of medicaments via three basic mechanisms; erosion (polyethylene glycol), gel formation (hydroxyethylcellulose) and diffusion (ethylcellulose). Those coatings which provide release through diffusion have a reputation of being predictable, easy to apply and are probably the most common sustained release coatings employed today. Yet the majority of today's sustained release coatings are ones , or descendants of ones, first used

in the 1950's. Generally, the evolutionary path of these coatings began with polymers dissolved in organic solvents. Later, in response to many factors, attempts were made to prepare entirely or partially aqueous coating solutions. Throughout the past forty years other coating techniques have also been attempted, none of which has received the acceptance of coating from solution.

The vast body of literature published on the subject of coating would lead an investigator to believe that there are hundreds of coatings and methodologies employed today. A closer examination reveals the contrary. The current United States Pharmacopeia only lists three sustained release coatings that function as a rate controlling membrane; *cellulose acetate*, *ethylcellulose*, and *methacrylic acid copolymer*. Although other coatings exist, these three remain the most popular, undergoing continual modification to withstand the challenges of time and changing regulatory climates. As the previous sentence suggests, the evolution of sustained release coatings was not one that was purely driven by the quest for better performance. Other issues, including safety (occupational and environmental) and cost have played an equally important role in the development of suitable coatings.

At the time, film coating was introduced to the marketplace (Abbott Laboratories 1953) researchers were searching for economical and more versatile alternatives to sugar coating (9). The use of polymeric film formers in conjunction with organic solvents was perhaps the most important advance in dosage form development of that era. Their

introduction provided researchers with new avenues to explore in the quest for controlled drug delivery and has led to the invention of many of the technologies which are so important today.

Many of the early commentaries touted the benefits organo-soluble polymers as coating agents, while they remained quite apprehensive about the use of aqueous solutions (9,17). The fear of dilute aqueous solutions was largely based on experience gained from sugar coating where the high water contents of coating solutions were implicated as the cause of stability problems and long processing times. The principle benefits of solvent usage were the considerable reduction in processing times and the removal of water from the process, thereby reducing the loss of active ingredient through hydrolysis. Yet another advantage of organic solvents was their ability to completely dissolve the polymeric film formers thereby allowing for smooth, continuous coatings which were capable of protecting medicaments from environmental stresses and making tablets more distinctive.

An early patent for a sustained release tablet is recognized as, the first to make use of a polymeric membrane to control the release rate of a drug substance. Assigned to Consolazio in 1949 (US patent # 2,478,182), this patent described the manufacture of a tablet composed of granules of sodium chloride coated with cellulose acetate or cellulose nitrate that was designed to eliminate the gastrointestinal upset caused by the localized deposition of medicaments.. Consolazio claimed that the invention delayed the solution time of sodium chloride some 60 to 80

minutes by the gradual leaching of drug through and the subsequent bursting of the cellulosic membrane (11). Unbeknownst to Consolazio at the time, was the semipermeable nature of cellulose acetate. His results might have been quite different if a larger organic molecule had been used since, due to their size, many drugs will not pass through cellulose acetate membranes. Although larger organic molecules are retained, water will still enter the tablet leading to the eventual bursting of the membrane and subsequent "dumping" of the medication within. A similar approach to sustained release was undertaken by Rosenthal (US patent # 2,895,880 issued 1959) that substituted any one of a number of prolamines for cellulose acetate. The principal difference between this approach and that of Consolazio was the digestibility of prolamines which would ensure the release of medication into the GI tract.

By 1958 ethylcellulose had joined cellulose acetate as a polymeric membrane for sustained release. A patent issued to Lowey (US patent 2,853,420) made use of granules of an inert material that were coated with a solution of ethylcellulose and drug. Once ingested, the drug entrapped within the ethylcellulose membrane would slowly diffuse out from the membrane and be absorbed. Knowledge of the mechanics of diffusion allowed the release rate to be "programmed" by blending together granules of differing film thicknesses.

It is interesting to note that the three polymers most commonly used today as sustained release membranes were introduced to the industry before 1962. Cellulose acetate and ethylcellulose, both

mentioned previously, were introduced before 1958. The third polymer (really a class of polymers) Methacrylic acid copolymer, was first used in a 1961 matrix formulation patented by Levesques (US patent # 2,987,445). Levesques designed a matrix tablet which contained drug and soluble pore formers dispersed in a matrix of polyethylmethylmethacrylate or copolymers of methylmethacrylate and alkylacrylate that allowed for the slow leaching of drug into the gastrointestinal tract.

The fact that only three polymers which provide sustained release through membrane diffusion are listed in USP should not be construed as a lack of research in this area. Several researchers of the 1960's sought to find other polymeric materials that would exhibit suitable sustained release properties (18, 19, 20, 21). Much of their work was focused on various combinations of other vinyl, acrylic, and cellulosic polymers and provided a battery of screening tests by which the suitability of a candidate polymer system could be judged. However, what these studies had failed to do was develop a new organo-soluble coating system which would be widely accepted by the industry. Possible reasons for this are many but perhaps the two most significant ones are the risks associated with organic solvent usage and the emergence of a newer hybrid technology, the pseudolatex coating.

Near the end of sixties, new, improved methacraylate derivatives had been introduced to the industry for use as diffusion controlled membranes (22). Although they performed well, these copolymer

systems represented the end of an evolutionary pathway. Stricter environmental legislation in conjunction with the high cost of controlling organic solvent emissions forced researchers to find alternative, "environmentally friendly" coating systems. An early, and now widely known, product of this search was the pseudolatex dispersion.

Research has shown that pseudolatex dispersions, finely divided colloidal dispersions of water insoluble polymers in aqueous media, can be prepared from many water insoluble polymers. These preparations possess several properties which made them the most popular possible replacements for organic solvent based coatings including; no need for organic solvents, high solids concentration with low viscosity, shorter drying times through increased solids concentration, and lower water vapor permeability than comparable films from organic solution (23).

The use of latex dispersions invivo could be traced back to their listing in the U.S. Federal Register (1961) as a food additive (23). Later, after perfecting acrylate pseudolatexes for other pharmaceutical coatings, at least two researchers had developed systems which would provide diffusion controlled drug release (24, 25). The commercial acceptance of acrylate pseudolatexes for diffusion controlled membranes (Eudragit (26)) led to the development of ethylcellulose pseudolatexes (Aquacoat (27) and Surelease (28)) and more recently, those made form cellulose acetate (FMC corporation (27)).

Pseudolatex technology has received such considerable attention from both academic and industrial researchers that an in depth discussion

would be redundant and beyond the scope of this paper. If interested in the science and application of these coatings the reader should start by consulting the chapters by Lehman and Steurnagel in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms* (22,23) as they provide comprehensive reviews of the subject.

While the pseudolatex coatings mentioned previously have been proven effective in many pharmaceutical applications, one somewhat disturbing fact remains. The extensive research on, and the wide acceptance of this technology is a largely due to the fact that the same three, well accepted, polymers which had been historically used for sustained release were used in a new manner. In fact, it is only recently that another, completely different polymer has begun to gain acceptance. In 1989 Li and Peck (29) introduced sustained release tablets that were coated with a silicone elastomer latex (Dow Chemical (30)). Although it was yet another latex type coating, the use of a silicone elastomer represented a departure from the use of methacrylate and cellulosic polymers.

Unlike the existing latexes, those made of silicone are completely impermeable to water and require the use of a pore forming agent, usually polyethylene glycol, and an anti-tack agent, fumed silica. The amount of polyethylene glycol in the film ultimately determines its porosity and subsequent drug release rate. Li and Peck demonstrated the ability of silicone elastomers to provide the apparent zero order release of potassium chloride from coated tablets for greater than 12 hours with 20

percent PEG 8000 (29). Faster release could be gained by increasing the percentage of PEG. Other factors which were believed to have an effect on the release rate from silicone elastomer films include; the weight of coating applied, heat treatment and pH of the dissolution media have been confirmed by Dahl and Sue (31)

The silicone elastomer latex represents an adaptation of existing pharmaceutical technology to a new type of polymer. Although not yet approved for use in pharmaceutical formulations, silicone elastomers are used for medical applications and are a representative of a trend which has developed within the industry. The manufacturers of pharmaceutical excipients are well aware of the difficulties that are encountered when new excipients are submitted for FDA approval. The fact that only three polymers that provide diffusion controlled sustained release are listed in the Pharmacopeia is due, not to a lack of research, but due to the difficulty with which a prospective polymer would gain approval. It seems that contemporary research has taken this into consideration and has focussed it's effort on materials which are already approved for invivo usage.

Recent studies of sustained release film formers appear to be embarking on yet another major trend in pharmaceutical coating. Remember that sustained release coatings began as organic solutions and evolved to aqueous dispersions in response to changing safety and environmental regulations. Much of the sustained release film research during the 60's and 70's was centered on updating the polymers which had been used previously with a few noteworthy exceptions.

One of these attempts was is described in a patent issued to Seiyaku in 1967 (British patent #1,075,404) which described the "electrostatic" coating of tablets. In its truest form, electrostatic coating allows for the deposition of thin polymeric films without the need for any solvent. Films are formed when a charged particle is attracted to a substrate of opposite charge. Seiyaku's invention was not really a true electrostatic coating as it still required the use of a solvent which had to be removed after coating (32). Another earlier attempt by Endicott and later marketed by Abbott as "Gradumet" is a forerunner of some of the more interesting attempts of recent years (11). The Gradumet was a matrix tablet composed of drug and a plastic carrier which, after manufacture, was exposed to acetone vapors causing a the plastic to coalesce into a continuous network. The coalesced plastic provided a tortuous matrix which delayed the release of the drug held within it.

Recent studies of sustained release coatings appear to be branching out onto two pathways. While some determined researchers are experimenting with polymeric materials which have not yet gained FDA approval, others are looking at ways to modify other preapproved polymers to provide sustained release membranes.

Perhaps the most promising attempt to make use of an already approved polymer lies in the crosslinking of alginic acid salts. The sodium salt of alginic acid is a hydrophillic, water soluble polymer which has traditionally been used in tablet manufacture as a binder and disintegrant. On the other hand, the calcium salt, although hydrophillic, is

insoluble in water. Julian and colleagues studied the ability of free films of calcium alginate to control the release rate of drugs (33). Later, several researchers studied coating methods which converted sodium alginate to calcium alginate on the surface of the tablet or pellet (34,35). Bhagat et. al. describe a method in which guiafenisen tablets containing calcium chloride are dipped into a solution of sodium alginate. Immediately after immersion, insoluble calcium alginate begins to form on the tablet surface. Throughout the immersion calcium chloride, and unfortunately some drug, leach out of the calcium alginate membrane thereby maintaining the conversion of polymer at the surface. The thickness of the coating is controlled by the time of immersion in the sodium alginate solution. Through the use of this method Bhagat was able to produce tablets with an approximate film thickness of 2 mm that were able to provide the sustained release of guiafenesin for four hours. This technique, although promising, is not without its shortcomings. Perhaps the most difficult of these are the loss of drug during film formation and the rather thick films required for reasonable release rates.

Abletshauser and co-workers, dissatisfied with the immersion method used by Bhagat, adapted the sodium to calcium alginate crosslinking process for use in a fluid bed coater (35). In their study pellets of indomethcin and acetaminophen were coated in a specially modified fluid bed that contained two spray guns. One gun sprayed a sodium alginate solution, while the other sprayed calcium chloride in alternating cycles. Drug release from these pellets with a 100 micron thick coating was extended over periods of three and eight hours for

acetaminophen and indomethacin respectively. Although this method eliminated the drug loss of Bhagat's technique, it required considerable processing times due to the large amount of water in the coating solutions.

While aqueous coatings have eliminated many of the problems found in solvent coating, the removal of water remains a problem. Some recent attempts at novel sustained release coating have sought to develop systems which do not require any solvent. Yoshida and co-workers reported the sustained release of potassium chloride from beads of gamma radiation crosslinked methacrylates (36). The production of the beads was accomplished by dropping a liquid mixture of drug and monomer into an extremely cold quenching bath and then exposing the frozen globules to gamma rays. The extent of crosslinking was so complete and impermeable that the addition of PEG 600 was necessary facilitate diffusion.

A similar approach to coating is currently under study by Wang and Bogner who have been experimenting with the photocrosslinking of several siloxane prepolymers (37,38). Unlike that of Yoshida, their method employs the use of high intensity UV light in conjunction with a suitable photoinitiator (Benzoin Methyl Ether) that has been adapted for use in a fluid bed coater. Within the coater, the liquid prepolymer and photocatalyst can be sprayed onto pellets and exposed to the UV light. Upon exposure to the UV light the polymer will begin to crosslink, thereby increasing in viscosity until a solid, insoluble coating is obtained.

Radiation crosslinking offers a novel and economical way to produce sustained release coatings in the future. Unfortunately, current academic research must overcome several problems if it is to be accepted for invivo usage in the future. Firstly, both of the radiation crosslinked methods mentioned previously make use of prepolymeric monomers which pose serious health risks if they remain unpolymerized. Additionally, some of the methods require catalysts which may also prove toxic. Still another possible problem lies in use of radiation as an energy source. Remember that ultraviolet light has long been known as a cause of drug degradation. Yet, if a system can be developed which makes use of materials which are approved, or approvable, for invivo usage it will open up many new opportunities for improved pharmaceutical coatings.

CONCLUSIONS

Coating, in one form or another, remains an integral part of the pharmaceutical industry. Yet to fully understand its future, investigators must be aware of the vast body of work which precedes them and make use of the information contained within it. The past forty years have provided the pharmaceutical industry with several lessons which have been, and will remain valuable. While it is true that the equipment and materials used in the manufacture of coated, sustained release dosage forms has not changed drastically in the last forty years, it has evolved. Countless materials have been screened for use as release rate controlling membranes yet, until recently only three have been widely used. The same three polymers which were once deposited from organic

solution, have been continually updated to comply with ever changing pharmaceutical, safety, and environmental regulations.

As researchers continue to develop new types of sustained release coatings, they must remember that those which have been successful in the past have been so, not only due to their performance, but also because of their prior approval for invivo usage. Future investigators should not regard this observation as a warning to avoid new, unapproved materials. Rather, it should serve to impress upon them the realities of the pharmaceutical industry. While there have been many good ideas, greater attention should be given to those systems which are ultimately approvable.

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