HOW ARE DRUG THERAPEUTIC LEVELS MAINTAINED WHILE AVOIDING DANGEROUS SIDE EFFECTS ASSOCIATED WITH CONVENTIONAL IMMEDIATE-RELEASE DOSAGES?

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INTRODUCTION

Ever since the discovery of bacteria and their role in the disease process in the mid-1800s, scientists have been heavily involved in the discovery and development of drug therapies and their mechanism of action in the human body. Shortly after the initial discovery came the era of drug discovery of the late 1800s-early 1900s, also known as the "drug revolution" (Dash and Cudworth 1998). Although the drug revolution led to the rapid discovery of many new drugs, pharmacological factors such as dosage forms, drug delivery systems, plasma drug levels, and how all these factors contribute to the efficacy of a drug were poorly understood. It wasn't until the mid-1900s that these factors were identified (Dash and Cudworth 1998). One particular factor which, once discovered, turned into a main focus in pharmacological research and lead to improvements in drug efficacy is centered on the importance of maintaining a steady therapeutic drug concentration level in the plasma.

The most conventional method for drug administration has always been through the use of oral products, such as tablets and capsules. These conventional oral drug products are formulated to release the active drug immediately after oral administration to obtain complete and rapid drug absorption in the body and immediate therapeutic effects (Shargel et al. 2004). However, once the body fully absorbs the drug, plasma drug concentration levels decline precipitously, possibly falling below the minimum effective plasma concentration (MEC), resulting in a loss of therapeutic activity. Before falling below MEC, the patient must be administered another dosage to maintain therapeutic effects (Shargel et al. 2004). Clearly, the conventional dosage form leads to a peak-and-valley curve of drug plasma levels versus time. This peak-and-valley pattern can have adverse effects since peaks, high plasma concentration of drugs (a result of frequent dosing), can cause toxicity, and valleys, low drug concentration in the plasma, may lead to sub-therapeutic levels and a possible buildup of drug resistance by the body's immune system (Dash and Cudworth 1998). How are drug therapeutic levels maintained while avoiding dangerous peak-and-valley side effects that often occur after the administration of conventional immediate-release dosage forms?

In order to maximize the therapeutic effectiveness of a drug while avoiding potential side effects that result from large fluctuations in drug blood levels, optimal concentration of drug in blood plasma must be sustained continuously (Breimer et al. 1984). In the past, the only known way to maintain a steady concentration of a drug's level in the plasma was through intravenous (IV) administration of the drug at a constant rate. Although steady IV administration is effective, it generally requires a health care professional to monitor the plasma drug concentration and cannot be performed at home (Dash and Cudworth 1998). In recent years, continued advances in pharmaceutical sciences have given rise to modern technological processes which

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provide alternate drug delivery systems that can maintain a steady therapeutic drug-plasma level while avoiding the inconveniences of IV administration and the possible dangers of frequent oral dosing (Chen et al. 2010). "Modified-release drug products" is the general term used by the US Pharmacopeia (USP) to describe products that "alter the timing and/or rate of release of the drug product to accomplish constant therapeutic levels not offered by conventional immediate release products" (Chen et al. 2010).

A major subdivision of modified-release products includes drug products with extended-release (also referred to as controlled-release) characteristics. Examples of extended-release drug products primarily include prolonged-action drug products and sustained-release drug products. Prolonged-action drug products are designed to slowly release the active drug substance in a way that provides a continuous supply over a period of time, thereby avoiding rapid and peak drug absorption in the plasma. Sustained-release drug products are designed to deliver an initial therapeutic dose followed by a slower steady release of drug that equals the rate of drug elimination from the body, resulting in minimal plasma drug concentration fluctuations (Shargel et al. 2004). Figure 1 portrays a plasma drug concentration versus time profile for both oral and sustained release delivery systems. This graph proves the value of an extended-release drug delivery system over the conventional frequent oral dosage since the sustained-release delivery system clearly stays in the desirable therapeutic and relatively homeostatic level while the oral immediate-release pill fluctuates between toxic and ineffective levels (Dash and Cudworth 1998). Currently, extended-release drug products encompass a wide range of products ranging from extended-release oral products, transdermal patches, and even implantable drug systems.

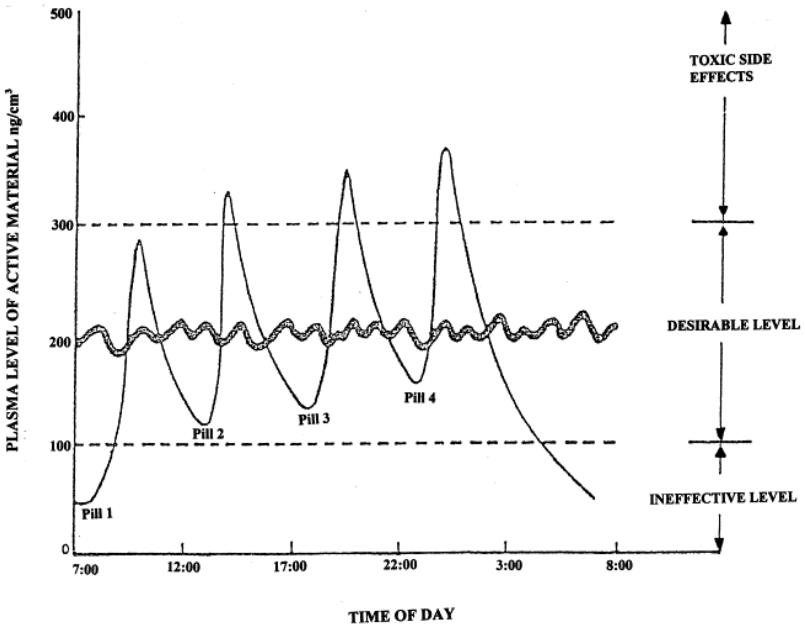

Figure 1: plasma drug concentration versus time profile for both oral and sustained release delivery systems. Source: Dash and Cudworth 1998

Before investigating the actual pharmaceutical applications used to create extended-release drug products, it is important to understand the possible biopharmaceutical factors that determine how a drug works in the gastrointestinal tract and the various pharmacokinetic properties that determine a drug's rate of absorption and release in the human body.

DRUG- ABSORPTION

As mentioned above, modified-release pharmaceutical preparations are generally designed to produce drugs with slow and uniform in-vivo absorption. In view of the fact that many of these oral modified release drugs are designed to remain intact in the gastrointestinal (GI) tract longer than the original immediate-release drugs, the anatomy and physiology of the GI tract plays a key role in the dosage and absorption of these drug products (Shargel et al. 2004). There are a number of physiological factors along the GI tract that affect drug release rate and uptake from the modified-release product. They include variations in pH, GI motility phases, presence of food, gastric emptying, presence of bacteria, enzymatic activities, varying permeability along the GI tract, volume of intestinal juice, and other factors as well (Lobenberg et al. 2000). Clearly, in-vivo behavior of modified-release oral drugs can be extremely complex considering all of the interacting mechanisms and changes occurring at every second in the gut (Varum et al. 2010). Researchers have, therefore, studied gut physiology and the mechanisms of digestion extensively with the hope that they can get a grasp on the in-vivo mechanisms and thereby produce maximally effective modified-release drugs.

The stomach is the first organ along the gastrointestinal track that a drug reaches. The general role of the stomach in the digestive system is to mix entering foodstuffs with digestive juices and then empty this mixture periodically into the small intestine (Shargel et al. 2004). Although this may seem to be a simple and predictable cycle, the movement of food and drugs through the stomach is greatly affected by the physiological state of the stomach, thereby affecting the time and location of the release of a drug from its dosage form (Shargel et al. 2004 and Varum et al. 2010). One particularly significant physiological factor which affects the ultimate time a drug is released from its dosage form depends upon the presence or absence of food in the stomach at the time of drug intake.

FACTORS THAT INFLUENCE ABSORPTION

The presence or absence of food has a major role in gastric emptying and gastric retention (Varum et al. 2010). In the presence of food, the stomach is considered to be in a digestive phase, whereas when lacking food, the stomach is considered to be in an interdigestive phase (Shargel et al. 2004). In the interdigestive phase, also known as the fasted state, gastric motility is under the control of a series of cyclical fluctuations in contractile activity commonly referred to as the migrating motility complex (MMC) (Higaki et al. 2008). The MMC is composed of four phases and can take up to about 30-40 minutes to be completed. Phase I is characterized by a total lack of activity. Phase II follows with an increase in the number and intensity of contractions. Phase III is characterized by large-amplitude peristaltic contractions that end with a strong "housekeeper contraction" which causes a massive gastric emptying of everything left in the stomach. Phase IV is an intermediate phase and acts as a transition period between the strong contractions of Phase III and Phase I of the next MMC cycle (Higaki et al. 2008 and Shargel et al. 2004). In the presence of food, on the other hand, MMC is basically abolished and low-amplitude peristaltic contractions take over, enabling gastric emptying of only small molecules into the duodenum (Higaki et al. 2008). Food particles larger than 2mm are retained in the stomach during the digestive phase (Shargel et al. 2004). Clearly, gastric emptying of

drugs (particularly tablets larger than 2mm) occurs mainly during Phases II and III of MMC in the fasted state (Higaki et al. 2008). Therefore, drugs larger than 2mm that are administered during a fasted state will be emptied out of the stomach fairly quickly, leading to a faster release of the drug into the patient's plasma. However, if the same large drug is administered in the digestive stage, it may remain in the stomach for a few hours until Phase II/III of the next MMC occurs.

Another factor that is known to have an important effect on gastric emptying and gastric retention is the caloric content of meals eaten around the time of drug administration. High caloric content meals generally show a delay in gastric emptying of both food and drug. In one particular study, a multiple-unit dose failed to empty for up to ten hours post-dosing in volunteers who consumed a high caloric meal (Varum et al. 2010). If, for example, a certain drug is modified to be released a few hours after administration with the intent that, at that time, the drug will be in the small intestine, a highly caloric meal might retain the drug in the stomach for too long and lead to a release of the drug in the stomach instead of the small intestine. Clearly, researchers can greatly benefit from knowledge of factors affecting gastric retention and emptying when formulating modified-release dosages.

Many studies were done to determine the effects of the fed/fasted state along with the caloric content of a meal on gastric emptying of a modified- release drug. One experiment in particular hypothesized that gastric emptying of different-sized enteric-coated pellets (enteric coating of pellets is a modified-release formulation characteristic that prevents dissolution in the stomach but allows rapid dissolution in the small intestine) would occur at different rates with the smaller pellets emptying in the fed state and the larger pellets emptying in the fasted state (Rhie et al. 1998). In this experiment, 12 healthy individuals were each given 0.7mm caffeine (CAFF) and 3.6mm acetaminophen (APAP) along with a viscous caloric meal at levels of 4000, 6000, and 8000 cP. The CAFF and APAP pellets were both enteric-coated spherical pellets formulated with sucrose nonpareils as the core which was coated with several suspension layers of the active ingredient, thereby achieving a target diameter, drug potency, and enteric coat level to aid in the release of the drug at a specific location. Gastric motility patterns were recorded using the monometric catheter, a technological device where the peaks on the machine represent the start and end of the different stages, such as Phases II and III of the MMC cycle. Blood samples were also obtained throughout the experiment in order to assess the plasma profiles of the drug, focusing specifically on the time when the drug was first detected in the plasma. Plasma results demonstrated that CAFF from the 0.7mm enteric-coated pellets were consistently (with all the different caloric level meals) measured in the plasma before the APAP from the 3.6mm enteric-coated pellets. Additionally, upon observing the timing of the release of the pellet dose, the results indicated that plasma profiles were strikingly superimposable upon the gastric motility patterns noted by the monometric catheter (especially with the 4000 cP meal); the time that CAFF from the smaller pellet was detected in the plasma correlated with the spikes on the monometric catheter which represented a fed state phase, backing up the assumption that small pellets are released from the stomach during the digestive phase. In contrast, APAP pellets were first observed in the plasma at the same time as the onset of the fasted contractile activity (Phases II and III). Overall, the meal viscosity levels in this experiment did not significantly affect the rate of drug absorption (Rhie et al. 1998). Knowledge of how

factors of gastric emptying affect the release of a drug assists in the development of modified release drugs that can take advantage of these factors.

It is important to note that, although most studies prove that a larger dosage form results in longer gastric retention, there have been studies that proved that different size dosages had no effect on the timing of gastric emptying. Clearly, more research should be done on this complex issue. Perhaps one of the many other physiological factors in the stomach, such as a pH level of 1-2 in the presence of food and 3-5 in the absence of food, can alter gastric emptying times if the experiment is not properly controlled.

The stomach empties its contents into the small intestine which provides a large surface area for drug absorption and where transit time of solids takes approximately 3-5 hours (Varum et al. 2010). Data obtained from various research projects is too varying to make conclusions on the effects fed and fasted states have on the transition of dosage forms along the small intestine. However, it was observed in numerous studies that the administration of modified-release multiple-unit enteric-coated dosage forms before eating resulted in a faster small intestinal transit time compared with the transit time of the drug in a fasted state (Varum et al. 2010). This information is extremely valuable. For example, if a drug is meant to be absorbed in the proximal small intestine, such a drug should be administered in pre-fed patients, resulting in modified-release of the drug in the upper GI tract. Administration of the drug in a fasted state might give the drug enough time to travel as far as to the colon where colonic conditions may make it impossible to be absorbed. Additionally, the presence of bacteria in the terminal part of the small intestine and its pH level of about 6 may also affect drug release in the small intestine.

The large intestine is the next and last step for a drug to be absorbed in the GI tract. A lack of fluids in the colon, besides for in the rectum, makes it difficult to absorb drugs passing through. The presence of bacteria in the colon can perhaps affect the absorption of modified-release drugs in the colon as well (Shargel et al. 2004).

The high variability in GI transit presents significant implications for the in-vivo performance of drugs in modified-release systems that are intended to delay or sustain release of drugs (Varum et al. 2010). The following studies represent how modified-release drug products can take advantage of the physiological conditions of the GI tract. Scientists do numerous studies on the gastrointestinal effects on a drug before creating a modified-release version of the drug. The majority of these experiments use the novel technique of pharmaco-scintography to assess regional drug absorption in humans. This technique works by co-administering a radiolabeled placebo pellet along with the coated modified-release drug of choice. The radiolabeled pellet's gastrointestinal transit is then monitored through a gamma camera. Blood samples are also generally collected periodically to assess plasma concentration of the drug in question and then compared to the scintigraphic results to help determine the exact time and gastrointestinal location of drug release (Basit et al. 2004).

One specific study was performed to evaluate the GI transit, release, and absorption of budesonide, a drug used for the treatment of inflammatory bowel disease (IBD), from its mutimatrix MMX® formulation. Budesonide's MMX formulation is designed to release the drug throughout the entire colon at a controlled rate (Brunner et al. 2006). Previously, budesonide had only been formulated to treat IBD in the right-sided colonic region in Chron's disease, and in left-sided ulcerative colitis. Therefore, in order to orally treat distally located IBD, gastric- resistant, extended-release budesonide tablets characterized by a multimatrix structure have been developed to allow a prolonged and steady release of budesonide along the entire colon at a controlled rate. This experiment tested the efficacy of the drug's prolonged-release characteristics on twelve healthy males. The volunteers were administered the budenoside multimatrix tablets, along with a ^{152}Sm-oxide tablet that was transformed into a γ-ray-emitting compound to be used for scintigraphy. Scintigraphic scans and blood samples were taken and compared periodically. MMX®-budesonide tablets were detected by scintigraphic imaging in the ascending colon between 4 and more than 24 hours after dosing, as is depicted in 2, and the drug left the descending colon at 12 to more than 24 hours post-dosing.

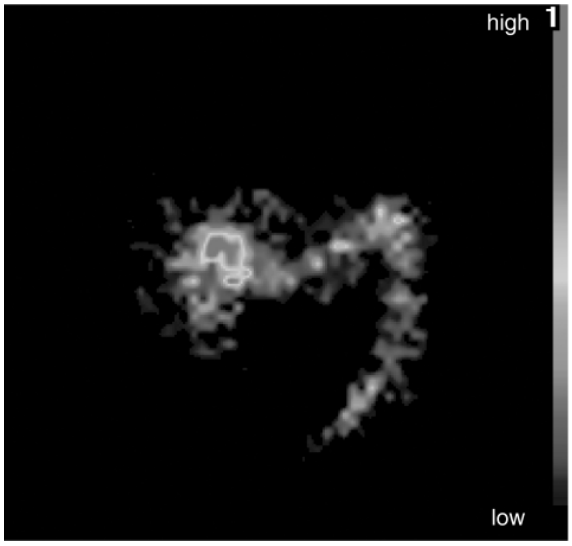

Figure 2: Scintigraphic imaging of the colon. Source: Brunner et al. 2006

An estimated 96% of the budesonide was absorbed in the target region (between the ascending and descending colon) as was calculated by the area under the curve (AUC), represented by the $AUC_{target/}AUC_{24}$ ratio where the AUC_{target} represented the plasma AUC where radioactivity was detectible in the target region, and the AUC_{24} was attained from the plasma AUC values of budesonide observed over the entire 24-hour period (Brunner et al. 2006). Clearly, this modified budenoside formulation was successful in delivering its active drug throughout the entire colon. Additionally, although budesonide plasma concentrations were first observed after 6.8 ± 3.2 h, maximum plasma concentrations were reached about seven hours later. The time difference between the initial detection of budesonide in the plasma and budesonide's time of max concentration (t_{max}) verifies the sustained-drug release characteristics of the budesonide MMX® tablets.

Phase two of this experiment tested the effect of food on budesonide pharmacokinetics. Plasma samples taken after the administration of a highly caloric and fatty meal reflected the fact that budesonide absorption decreased by 30% in relation to those who took the pill under fasted conditions (Brunner et al. 2006). This decrease of drug absorption may justify the administration of this drug with a meal to limit its potency and thereby improve the safety profile as a drug. Conclusively, the formulation of MMX®-budesonide tablets have clearly utilized knowledge of gastrointestinal transit as an aid in producing a sustained-release drug suitable for

targeted drug-delivery to the colon. However, further research should be done on this subject, since colonic infected individuals, for whom this drug is meant, may react differently to the drug than healthy individuals on whom the experiment was done.

Another study evaluated the absorption of the drug Ipsapirone along the human GI tract. In man, Ipsiparone, an anti-depressant, has an absorption half-life of less than 0.25 hours and an elimination half-life of about 1-3 h. This noticeably rapid absorption leads to a rapid peak in plasma concentration of the drug which often causes vertigo, dizziness, and dysphoria (Fuhr et al. 1994). Researchers have, therefore, studied the bioavailability (a term used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation) of Ipsapirone after its administration at different regions of the GI tract to help develop an effective and safe modified-release drug. Researchers hoped that a modified-release version of Ipsapirone would reduce unwanted side effects since the modified-release dosage form does not release its entire dose in one region, thereby avoiding a rapid plasma peak of the drug. Ipsapirone-HCl was administered to four healthy males orally, rectally, and locally in different locations along the GI tract by a remote control drug delivery device. Plasma results indicated that there was a 2-3-fold increase in the bioavailability of the drug administered directly into the colon than when the drug was administered into the upper GI tract. This 2-3-fold increase indicates an equivalence of a 5 mg dose of ipsapirone-HCl released in the colon with a 10-15 mg dose given orally. Oral doses of this size (10-15 mg) were tolerated, and administration of 5 mg ipsapirone into the colon was deemed safe. These results fulfill the criteria for the development of a prolonged-release preparation with 5 mg ipsapirone-HCl. Through modifications of the drug's coating, the drug could be modified to be released only in the colon; such a modification makes it unnecessary to administer a full 10-15 mg immediate-release dose which loses most of the drug by the time it reaches the colon. Considering the fact that this was a small sample of only four males, further research should be done to test if rectal administration of this drug to the colon really equals oral prolonged-release administration (Fuhr et al. 1994).

An example of a new oral modified-release drug that was formulated based on knowledge and applications of the varying characteristics of the GI tract is Rifamycin SV MMX (Di Stefano et al. 2011). Rifamycin SV is an oral, non-absorbable antibiotic which can be used in the treatment of colonic bacterial infections. These tablets are formulated using a multimatrix structure which, like budesonide, delivers the active drug ingredient (200mg of sodium rifamicyn SV) directly to the colon. In immediate-release drugs, the active ingredient would be released immediately upon administration, and maximum bioavailability in the colon would not be achieved (Di Stefano et al. 2011). With the modified-release tablets, however, the maximum bioavailability of the active ingredient is achieved, and the biological effect is optimized at the target region, the colon.

The Rifamicyn SV MMX tablet contains a double-matrix system. Microparticles of the active ingredient are dispersed in a lipophilic matrix which is in turn dispersed in a hydrophilic matrix. The hydrophilic coating inhibits the penetrations of fluids into the tablet, thereby lowering the rate of drug dissolution in the upper GI tract. The tablet is coated with a pH dependent, gastro-resistant polymer film which also inhibits dissolution of the tablet in the upper GI tract. This MMX tablet begins to disintegrate when the pH is ≥ 7. With the pH-sensitive and hydrophilic

coating, the tablet reaches the cecum intact and it is there that the release of the drug begins. The pH-sensitive coating disintegrates, and the intestinal fluids interact with the hydrophilic coating which forms an outer gel mass that slows diffusion of the antibiotic into the colonic lumen (Di Stefano et al. 2011). As the tablet progresses towards the rectum, debris of the gel mass disaggregates and releases the antibiotic directly near the mucosa of the rectum. Studies done through pharmaco-scintigraphic investigations clearly demonstrate an effective colonic delivery of this drug, supporting the production of rifamycin in a modified-release formulation.

These studies all give us valuable insight into the natural absorption of different drugs. Using this knowledge allows for the creation of drugs specially suited for different releases.

PHARMACOKINETICS

Pharmacokinetics is the study of the time-course of drug concentrations in the body, based on various characteristics of drug absorption, distribution, metabolism, and excretion (Mager 2006). As stated above, conventional drug delivery systems very often rely on frequent dosing in order to attain a therapeutic level, which leads to large fluctuations in drug blood levels. The frequency at which a conventional dosage must be given is dependent on two pharmacokinetic properties: elimination half-life ($t_{1/2}$) and therapeutic index (TI) (Sood and Panchagnula 2003). Half-life is the time interval in which half of the active drug in a system is lost, and therapeutic index is the concentration range in which a drug works (Sahin and Benet 2008). Knowing the half-life of a drug assists pharmaceutical companies in setting dosage frequency intervals so that the right amount of active drug will be in circulation at all times, since the dosing interval directly influences the ratio of maximum (C_{max}) to minimum (C_{min}) blood drug concentrations. Although this seems quite simple, it should be noted that there are many other factors involved in half-life and other pharmacokinetic properties and equations which are beyond the scope of this paper. Obviously, drugs with shorter half-lives require a more frequent administration in order to keep blood-drug concentration levels within the therapeutic index. The goal of controlled-release drugs is to release the active drug ingredient at a sufficient rate, frequency, and dose so that the ratio C_{max}/C_{min} is maintained at an effective steady state throughout the therapy without having to be so dependent on half-life and therapeutic indexes which often leads to the necessity of frequent dosing (Sood and Panchagnula 2003). Drugs with zero-order kinetics are generally the easiest to deal with when producing controlled-release dosage forms because they are predictable. They release the active ingredient at a constant rate that is independent of the concentration of the reactants; it is much easier to create a modified-release formulation when the drug's exact rate of release is already known.

RELEASE CONTROL MECHANISM

The knowledge of the gastrointestinal and pharmacokinetic implications on a drug's efficacy aided researchers in manufacturing extended-release drugs which can help in lowering the fluctuations in blood-drug levels. Most extended-release drugs are manufactured through the use of a matrix structure. The drug is suspended or dissolved within the matrix and/or within a rate-controlling membrane through which the drug diffuses (Shargel et al. 2004). In this context, the matrix refers to an inert solid in which the drug is suspended throughout and diffuses out of quite slowly.

There are basically three different types of modified release matrix mechanisms. In the first type, the drug is dissolved in a matrix material that is coated with a soluble coating. In such a case, the rate of drug release depends entirely on the matrix material; a porous matrix will lead to a fast absorption of water, resulting in rapid drug release from the matrix material, whereas a less porous matrix will not absorb much water right away and will, therefore, cause a slower and lengthier drug release. The second system is that of a matrix with an insoluble membrane. When a drug is prepared in such a manner, its release is not only dependent on the permeability of the matrix; it is dependent on the membrane's permeability as well. The third system is a matrix tablet with a combined membrane where the membrane becomes porous after dissolving the soluble part of the membrane in water. Aside from matrix and membrane factors in creating extended-release products, most extended-release drugs release their drug product as a result of a combination of processes including dissolution, permeation, and diffusion. Water permeation is probably the most important factor that drug manufacturers consider since, as the influx of water into the product is controlled, the rate at which the drug dissolves is essentially controlled. Once the drug dissolves, drug diffusion out of the tablet/capsule is further controlled by the permeability of the membrane (Shargel et al. 2004). All of these factors are considered and used to aid in the development of modified-release drugs.

Oral Extended-Release

Of all the different kinds of extended-release products, oral extended-release products prove to be the simplest and easiest to manufacture, lowest cost, high level of reproducibility, and stability (Siddique et al. 2010). The following examples touch the surface of the numerous kinds of applications that can modify the release of oral drugs to maintain homeostatic conditions in the human body.

Gum-Type Matrix Tablets

Gum-type matrix tablets are manufactured with a matrix that swells in the presence of water to form a gel-like consistency. This gel is generally very thick and, therefore, provides a barrier for drug diffusion out of the tablet. Such a matrix is commonly formed with excipients (carrier of active drugs) such as methylcellulose, gum tragacanth, Veegum, and alginic acid. The thickness of the gel caused by these excipients provides controlled-release results in that they prevent drug dissolution until the gel-like matrix breaks up and the drug completely dissolves and gradually diffuses into the intestinal fluid (Shargel et al. 2004).

Diazepam, a benzodiazepine drug used for acute management of severe seizures, is an example of a drug that has been manufactured in a gum-type matrix tablet, thereby providing sustained-release of this drug for hours (Shargel et al. 2004). A study was done on Diazepam which investigated the feasibility of incorporating Diazepam, a poorly water-soluble drug, into solid-lipid nanoparticles (such as a gum-type matrix) that can offer rapid onset (for early termination of seizures) and prolonged-release of the drug for long-acting protection against further seizures. The particular characteristics of the solid-lipid nanoparticles (SLNs) used (such as the SLN's biocompatible lipid core but ampiphillic outer shell in this case) allowed for immediate and prolonged release which, in essence, is the main characteristic of a sustained release drug system. Different SLN formulations were then tested to see which combination of lipid matrices and surfactant would result in the best prolonged-

release results. (SLN formulations composed of Tween 80 as a surfactant and lipid matrix of 5% Compritol ATO 888 and 5% Imwitor 900k provided the best in vitro prolonged-release effects for diazepam (Abdelbary and Fahmy 2009).)

Clearly, a gum-type/lipid matrix is one effective manner of prolonging the release of a drug, thereby preventing the need of frequent dosing and dangerous fluctuations of blood drug levels. However, it should be noted that since this experiment tested results in vitro, more research should be done to obtain in vivo results which would be more beneficial in determining the actual effects of such drugs in the human body.

Polymeric Matrix Tablets

Of recent, drug manufacturers have been very interested in using polymeric material in the matrix to prolong the rate of drug release. The significance of polymeric matrix tablets over other kind of matrix tablets is that polymeric matrix tablets can prolong the release of a drug to last for days or even weeks (Shargel et al. 2004). The polymers that are available for drug formulation include hydrophilic polymers, such as polylactic acid and polyglycolic acid, and hydrophobic polymers, such as ethylene-vinyl acetate copolymer (EVA). The hydrophilic polymers release the drug gradually while the hydrophobic polymers release the drug over a much longer period of time because of its hydrophobic characteristic which blocks water from entering and causing drug dissolution. Additionally, the rate of drug release can be further controlled by combining different polymers, such as adding a hydrophobic polymer to a hydrophilic one to decrease the rate of the drug's release. Light, heat, and other factors may also be administered to change the properties of the polymers being used (Shargel et al. 2004).

One particular study investigated the influence of polymer level and type of some hydrophobic polymers including hydrogenated castor oil; Eudragit RS100; Eudragit L100; and some fillers, mainly mannitol; dibasic calcium phosphate dihydrate; and anhydrous dibasic calcium phosphate on the release rate and mechanism of the drug baclofen. Results showed that a high polymeric content (40%) in the matrix lowered the release rate of baclofen, whereas a low polymeric content (20%) elevated the rate of drug release from the matrix. Additionally, hydrogenated castor oil was proven to be the polymer that caused the strongest retardation of drug release (Abdelkader et al. 2008). Thus, in addition to knowing the kinetics and half-life of a particular drug, the correct combination of polymers can be formulated to bring about the perfect amount and rate of drug release.

Multiple Unit Pellets

Modified-release dosage forms which have been proven to control the release of the active drug, thereby reducing the side effects associated with peak and trough drug plasma levels, have been improved upon in the development of modified-release multiple unit pellets. Whereas single-unit formulations contain the active ingredient within one single tablet or capsule, multiple-unit dosages are manufactured so that a number of discrete particles are combined into one dosage form. These particles could come in the form of pellets, granules, sugar seed (non-pareils), mini-tablets, or powders which contain within them the active ingredient. One advantage of multiple unit pellets over single unit pellets is that when taken orally, multiple unit pellets spread over a large surface in the GI tract, and the particles behave like liquids that

can leave the stomach shortly after entering without waiting for the series of waves to push them along the GI tract (Abdul et al. 2010). In addition, the fact that the pellets disperse throughout the GI tract improves the drug's bioavailability and can reduce drug concentration in a specific location which might otherwise have lead to toxicity. Additionally, sometimes if a drug is released too early along the GI tract, it can irritate the gastric mucosa. Multiple unit pellets definitely reduce the risks associated with premature drug release because of the rapid transition of smaller enteric-coated pellets along the GI tract. Failure of some of these units from reaching their target will also not be as consequential as the failure of a single-unit dose. Theophylline (Gyrocap) is an early example of a beaded form extended-release pellet (Shargel et al. 2004). The frequency of adverse reactions such as nausea, headache, and vertigo, were greatly reduced after the administration of Theophylline in pellet form as opposed to a liquid form. The reduction of side effects in multiple pellet dosage forms comes from the fact that, unlike liquid, the multiple pellet dosage allows drugs to be absorbed gradually instead of rapidly (Shargel et al. 2004).

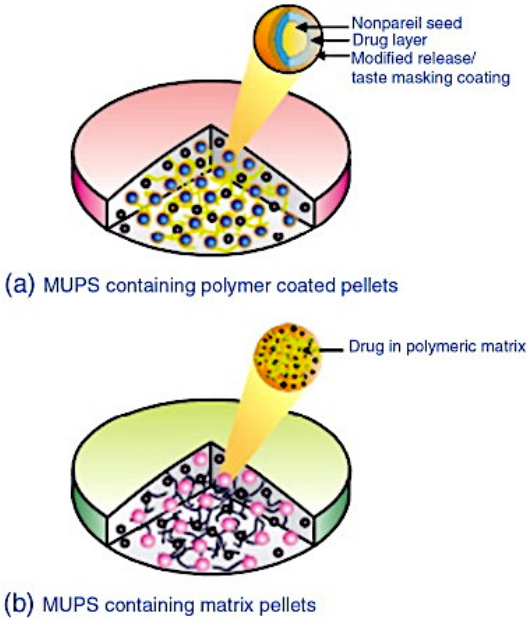

Figure 3: MUPS. Source: Abdul et al. 2010

Because it is difficult to compact the multiple pellets into one system, there are currently only a few multiple-unit tablet products available. They include Beloc® ZOK, Antra® MUPS, and Prevacid® SoluTb™. The difficulties in compaction arise when trying to fuse the pellets together without fusing them mistakenly into non-disintegrating matrixes. If the pellets are fused into a non-disintegrating matrix, they can no longer provide the benefits of a multiple-unit pellet system that disintegrates into individual pellets in the GI fluids leading to a more uniform concentration of active drug in the body (Abdul et al. 2010). Scientists should, therefore, develop safe ways to compact pellets so that the maximum benefits of multiple-unit pellets can be available to the world of modified-release drugs.

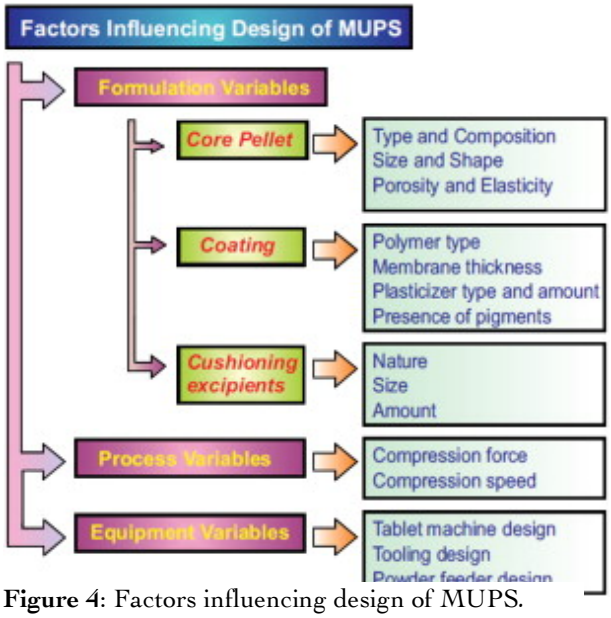

Figure 4: Factors influencing design of MUPS. Source: Abdul et al. 2010

TRANSDERMAL DRUGS

Transdermal drug delivery systems have recently turned into a promising field of study for scientists involved in the production of extended-release drug products. The transdermal drug delivery system, generally in the form of a patch, is designed to deliver the active medication across the skin in a controlled rate over an extended period of time (Shargel et al. 2004). Transdermal drug delivery systems obviously provide benefits over immediate-release oral dosages since the controlled rate of drug delivery eliminates frequent dosing which leads to dangerous plasma level peaks and valleys. Transdermal drugs also seem to have added benefits over the oral modified-release drugs. One major benefit is that drugs administered transdermally avoid hepatic first-pass metabolism. Such a feature can greatly benefit individuals who are hepato-compromised, since the drug avoids the liver altogether. Transdermal delivery routes also completely avoid passage through the GI tract. In this case, poorly bioavailable drugs can clearly take advantage of avoiding the GI tract through a transdermal route (Paudel et al. 2010).

Although transdermal patches may vary, most designs store the active drug in a reservoir that is enclosed on one side with an impermeable backing and with an adhesive on the other side that contacts the skin (Prausnitz and Langer 2008). There are generally four layers in a patch: an impermeable backing membrane, a drug reservoir, a semi-permeable membrane that may serve as a rate-limiting barrier, and an adhesive layer. Nitroglycerin is a drug that is commonly administered transdermally and formulated in the described manner (with the four layers). Nitroglycerin delivered transdermally may provide protection against angina (chest pains that results from a lack of oxygen-rich blood reaching heart muscles) for hours whereas as sublingual (oral) tablets only provide relief for a few minutes (Shargel et al. 2004).

Although transdermal drugs do seem to be a fantastic way to administer drugs at a controlled rate while avoiding possible complications that arise along the GI tract, they have not yet taken over the controlled-release drug market because of several limitations. One such limitation is that the skin, the most important natural barrier against the efficacy of transdermal drugs, only allows moderately lipophilic and low molecular weight drugs to cross over transdermally (Paudel et al. 2010). The solubility of the drug across the skin rather than the concentration of the drug in the patch is the most important of the rate-controlling factors of a transdermal drug (Shargel et al. 2004). Therefore, overcoming low skin permeability through different chemical and physical means has become an active field of research in order to allow many more pharmaceutical products entrance into the world of transdermal drugs (Paudel et al. 2010). Other factors such as humidity and temperature can also affect the rate of absorption across the skin (Shargel et al. 2004).

Interestingly enough, transdermal drug delivery has been proven to provide an even more stable blood level of drug than provided by oral dosages (Shargel et al. 2004). Thus, if the drug is found to be successful against transdermal barriers, scientists will probably be interested in manufacturing the drug almost exclusively as a patch because of the stable blood levels, avoidance of GI tract, and other benefits of transdermal drugs over oral modified-release dosages. Many experiments have, therefore, been done to compare the effects of transdermal versus oral dosage forms. For example, a series of experiments were done to determine the dose-response effects

of oral versus transdermal selegiline on anti-depressant-like activity in rats. Rats received selegiline orally by gavage (0-100 mg/kg) or via transdermal patches (0-4.8 cm^2; 0-8.7 mg/kg) daily for seven days. Antidepressant-like activity was then determined in two ways. The first was through the forced-swim test in which immobility and latency times during a five-minute forced swim test were measured. The latency time, which is the measurement of the swimming time from the beginning of the trial until the onset of immobility, increases under therapeutically effective anti-depressants. The second way through which anti-depressant activity was assessed was through assaying the cerebral cortices of the rats after day seven for MAO-A and MAO-B activities, since inhibition of MAO-A is an indication and requirement for clinical improvements in depressed patients. Results demonstrated that selegiline is an effective anti-depressant, as represented in the forced-swim test after both oral and transdermal delivery, that the anti-depressant-like effect of selegiline requires greater than 70% inhibition of MAO-A activity, and that the transdermal delivery of slelgiline is 10-20 times more potent than the oral selegiline in producing both its anti-depressant-like effects and in inhibiting cortical MAO-A (Gordon et al. 1999). Clearly, transdermal administration of selegiline, which bypasses first-pass metabolism, allows for the usage of lower doses than in oral administration.

Scientists have also put massive focus on the development of a transdermal treatment for menopausal syndromes. One particular experiment was done to determine the efficacy of Busipirone hydrochloride (BH) administration in animal models in the treatment of the main menopausal syndromes of hot flushes and anxiety (Shumilov and Touitou 2010). With oral administration, BH is rapidly absorbed in the GI tract and undergoes extensive first-pass metabolism, so it has a very short elimination half-life. Because of the short half-life elimination, efficient oral treatment requires frequent dosing. Scientists hypothesized that administering this drug transdermally would avoid the drawbacks of oral treatment. This study was therefore done to test the efficacy of the BH transdermal system using ethosomes (vesicular carriers that enhance permeation through the skin). Figure 5 represents the plasma drug concentration profiles following transdermal administration of 15 mg/kg BH from a formulation containing 30 mg/g drug and a single dose of 3 mg/kg oral administration of aqueous drug solution.

Clearly, when administered transdermally, the drug was present in rat plasma for a much longer period compared to the oral administration, 12 hours versus 4 hours, respectively. The continuous delivery of BH into the bloodstream under transdermal administration can offer sustained efficacy with reduced side effects, a huge benefit in the world of modified-release drugs. Additionally, the application of BH ethosomal system on the skin of rats caused a decrease in the temperature at three hours after administration and continued for a total period of 6 hours, proving that transdermal BH could be effective against hot flushes. This should, therefore, be further researched in humans (Shumilov and Touitou 2010).

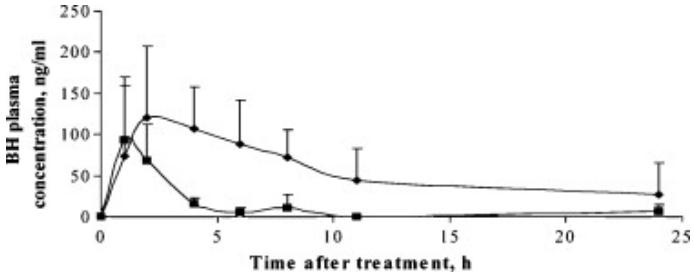

Figure 5: Plasma drug concentration profile following transdermal versus oral administration of BH.
Source: Shumilov and Touitou 2010

Another study was done to compare the efficacy of the Lidocaine Patch 5%, a transdermal, noninvasive treatment, versus Naproxen 500 mg two times daily for the treatment of Carpal Tunnel Syndrome. Results of this experiment proved that Lidocaine Patch 5% provided a comparable level of pain relief to the oral alternative while avoiding risk factors associated with systemic and invasive treatments (Nalamachu et al. 2006).

Transdermal delivery definitely presents an attractive alternative to the oral delivery of drugs. Transdermal delivery has provides an advantage for poorly bioavailable drugs in that it avoids hepatic first-pass metabolism (which can prematurely metabolize drugs) and the GI tract (Prausnitz and Langer 2008 and Gordon et al. 1999). Transdermal delivery of drugs also eliminates frequent dosing and allows for steady, controlled delivery which lowers plasma level peaks and valleys (Paudel et al. 2010). Transdermal drugs are also non-invasive and can generally be self-administered—a big advantage for patients requiring long-term treatment (Paudel et al. 2010). The advantages of the transdermal route over the conventional oral route have led to much interest in producing modified-release drugs through a transdermal route. Eventually, when transdermal challenges, such as permeation of the hydrophobic skin barrier and possible skin irritation from patches, are eliminated, transdermal drugs may become a popular choice on the modified-release drug market.

Implantable Drug Delivery Systems

In the late 1930s, Deasby and Parkes began researching sustained release implantable drug delivery systems as a possible solution to the problem of high plasma concentrations of drugs that may lead to toxicity or low drug levels that may cause sub-therapeutic levels found with immediate-release products (Dash and Cudworth 1998). This relatively novel idea involves implanting a drug delivery system that has been previously modified to release the active drug in a controlled manner into the human body at a specific location. Implantable systems are geared specifically to deliver drugs to a specific site, thereby reducing the amount of drug necessary and limiting its side effects, since the drug does not have to travel throughout the body before reaching its target. Pharmaceutical literature has shown that when the drug used is selective to its site of action, fewer drugs need to be administered. In this manner, drugs which were previously too unstable to administer in-vivo because of bodily temperature and pH conditions that may diminish the drug's efficacy can now be administered directly to the site requiring treatment. Another advantage of implantable drug delivery systems over conventional oral dosages is that while an oral dose may need to be administered one, two, or even multiple times daily, some of the implantable systems have been developed to last as long as five years with minimal monitoring as opposed to administering the oral dose one, two, or even multiple times daily (Dash and Cudworth 1998). These advantages notwithstanding, since the system is to be implanted, care must be taken that it be biocompatible with the human environment. All materials used must be chemically inert, non-carcinogenic, hypoallergenic, and mechanically stable so that the human body does not reject the implantable system.

There are two main classes of implantable drug delivery: drug implants and implantable pumps containing the drug (Dash and Cudworth 1998). The class of drug implants can be further divided into non-degradable and biodegradable implant

systems. One common form of the non-degradable implant system is the matrix system. In this system, the drug is dispersed inside the matrix material, and slow diffusion of the drug out of the matrix provides sustained release of the drug. However, the kinetic release of the drug is not at a constant (zero-order) rate since it depends on the volume fraction of the drug ingredient in the matrix. A non-zero order release rate can be hard to handle in sustained-release drugs since it is difficult to predict its rate of release. A second common form is the reservoir-type system which contains a compact drug core within a permeable non-degradable membrane. The permeability and thickness of this membrane controls the rate of diffusion of the drug into the body. This type of system generally releases its drug at a constant zero-order kinetic release rate because the drug is released based on the properties of diffusion; as soon as some drug is swept away by the surrounding material in the body, more drug diffuses out of the reservoir, leading to the constant rate of diffusion (Dash and Cudworth 1998). Levonorgesterol (LNG), a sustained-release birth control, is the most commonly used reservoir system. In this system, the hormone LNG is encapsulated in a silicone membrane and is implanted on the underside of the upper arm. This LNG system has been proven to effectively provide sustained-release of LNG for up to five years.

However, there are still some problems with non-degradable implants that prevent such a system from being an extremely popular sustained-release route. One issue is that minor surgery is required to insert and remove the implant system, especially with non-degradable systems because they do not disintegrate in the body. Additionally, there is also the fear that the membrane will rupture and lead to "drug dumping," causing drug-plasma concentration to exceed maximum safety levels and have toxic side effects. This fear is especially relevant with reservoir systems because the membrane is the only barrier blocking the drug from diffusing throughout the body, unlike the matrix systems in which the drug must first dissolve out of the matrix and then out of the membrane. Therefore, although implantable systems do seem like a fantastic approach to modified-release drugs, there are clearly some factors that make scientists wary of its use. Biodegradable drug implant systems improve a bit upon non-degradable drugs since the polymers used in biodegradable systems are eventually absorbed or excreted by the body. Surgery to remove the system is avoided, so patients are more accepting to the idea of an implantable drug. However, since the polymers in such a system are biodegradable, many added factors have to be considered. For example, in order to maintain the sustained-release characteristics of the drug in-vivo, the degradation rate of the polymer must be maintained at a constant rate as well as the drug, since the release kinetics, solubility, and diffusion of the drug depend upon the degradation of the polymer (Dash and Cudworth 1998). Factors such as pH, temperature, and increased surface area can lead to early erosion of the degradable system. All of these factors, therefore, become a major challenge when developing a biodegradable system with extended-release goals. The reservoir and matrix systems of biodegradable implants are similar to the non-degradable systems except for the fact that the material used in biodegradable implants is degraded in-vivo at a controlled rate as the drug is released.

The second major class of implantable drug delivery systems is the implantable pump containing the drug. Implantable pumps provide precise control of delivery rate that biodegradable and non-degradable systems cannot provide. Pump systems have

been made possible through advances in micro technology which developed small enough pumps that release drugs at a controlled rate as result of an electronically generated pressure difference gradient (Dash and Cudworth 1998). Implantable drug delivery systems have definitely created a breakthrough in sustained-release drug therapy. However, the limitations mentioned above, such as possible dose dumping and the need for surgery, along with the costliness of these products limits the use of implantable systems. Hopefully, the future will bring possible methods to lower the cost of these products so that implantable drug delivery systems can be used as standard therapeutic practice.

CONCLUSION

Oral, transdermal, and implantable extended-release drug products definitely offer many important advantages over immediate-release dosage forms. The most important advantage is that extended-release characteristics allow for a sustained therapeutic drug-blood level, providing a clinical response in patients that lasts much longer and steadier than with immediate-release products. This sustained therapeutic level also reduces fluctuations between a drug-plasma minimum and maximum that comes from a multiple dose regimen of an immediate-release product. In this manner, the side effects that come as result of the highly fluctuating drug-blood concentrations, such as toxicity and sub-therapeutic levels, are basically eliminated. Another advantage of extended-release products is that such products generally lead to better patient compliance, because taking an extended-release oral dosage once a day, applying a patch once a week, or inserting a pump that lasts five years, is much more convenient than having to remember to take the dosage multiple times a day to maintain a therapeutic level. Clearly, drugs with a short half-life, which under immediate-release characteristics would need to be given frequently, will greatly benefit from an extended-release formulation that can lower dosage frequency and maintain efficacy over a longer duration of time.

One major concern that came with the introduction of extended-release drugs was that although extended-release products would lower fluctuations, they would not provide the same effective therapeutic levels as the immediate-release counterpart. However, all of the studies mentioned in this paper show that the extended-release products do provide the same effective therapeutic effects along with the benefit of lowering fluctuations of the blood-drug levels.

However, some concerns have yet to be resolved. One such concern is the possibility of dose dumping and the difficulty of removing the spilled drug from the body. Immediate-release products definitely have the benefit over extended-release products in this case since it is a much smaller dosage that is causing the adverse reaction and is, therefore, not as toxic, and it is also easier to remove. Another concern is the lack of in-vivo testing conducted on human models. In-vivo testing on human models is crucial since different gastro-intestinal factors and in-vivo characteristics can perhaps interact with the different formulations in possibly destructive ways. Ideally, the study should be done on patients with the disease the drug is meant to treat in order to see if and how the disease affects the release rate and/or efficacy of the drug. Sometimes, slight differences between different individuals, such as caloric content of a meal, body temperature, and weight, can also affect drug release and must, therefore, be taken into account. It may not either be worthwhile to formulate an oral extended-

release drug for products that are administered at high dosages for the practical reason that the size of the pill will be too large to swallow. Therefore, all these factors must been studied extensively to determine the cost/benefit ratio of the extended-release drug.

Clearly, there are a couple of considerations that must be acknowledged when dealing with extended-release products. More research should be done in-vivo to determine if the disadvantages of the extended-release products can be reduced, thereby providing the benefits of lowering fluctuations in blood-drug plasma and maintaining a homeostatic profile without the added disadvantages. For example, further research should determine whether products demonstrate sustained-release characteristics without dose dumping and if products are consistent with minimum patient-patient variations. Further research should also definitely be done on transdermal and implantable drugs since they have the benefit of completely avoiding the intricacies of the gastro-intestinal tract. Perhaps the transdermal and implantable methods can be applied to many more drug products, thereby benefitting patients in the long run.

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