Strategic innovative products- Part 2

By Dr. Shruti Bhat, PhD, MBA, Enterprise Strategist and QbD Specialist.
Translates concepts to profits, consistently!

Website: www.DrShrutiBhat.com
Email: Shruti.Bhat@Innoworks.ca
Voice: 1.403.969.6219

(By Dr. Shruti Bhat, Article published in Chemical Industry News May 1998, p.513)

Controlled Release Drug Delivery System - definition, types, factors impelling transition to rate control delivery systems, classification and design of CRDDS, per oral CRDDS, dental, ocular, and intravaginal / intrauterine controlled release systems have already been dealt with in Part I of this review article.

The present article encompasses Implantable, Injectable CRDDS, Analytical control and Regulatory considerations of CRDDS and Novel CRDDS

1) IMPLANT CONTROLLED RELEASE DELIVERY SYSTEM :

Lafarge pioneered in 1861, the concept of implantable therapeutic systems for long-term, continuous drug administration with the development of a subcutaneously implantable drug pellet. The technique was then rediscovered in 1936 by Deanesly and Parkes, who administered crystalline hormones in the form of solid steroid pellets to mimic the steady, continuous secretion of hormones from an active gland for hormone substitution therapy.

Approaches to development of implantable therapeutic systems:

Historically, the subcutaneous implantation of drug pellet is known to be the first medical approach aiming to achieve prolonged and continuous administration of drugs. Over the years, a number of approaches have been developed to achieve controlled administration of biologically active agents via. Implantation of insertion in the tissues. These approaches are outlined as follows:

A. Controlled drug release by diffusion

1. Membrane permeation-controlled drug delivery using:
    a. Nonporous membranes
    b. Micro porous membranes
    c. Semi permeable membranes

2. Matrix diffusion-controlled drug delivery using:
    a. Lipophilic polymers
    b. Hydrophilic (swellable) polymers

c. Porous polymers

3. Micro reservoir dissolution-controlled drug delivery using:
   a. Hydrophilic reservoir / Lipophilic matrix
   b. Lipophilic reservoir / Hydrophilic matrix

B. Controlled drug release by activation

1. Osmotic pressure-activated drug delivery
2. Vapor pressure-activated drug delivery
3. Magnetism-activated drug delivery
4. Ultrasound-activated drug delivery
5. Hydrolysis-activated drug delivery

An ideal implantable therapeutic system should be with minimal tissue-implant interactions, nontoxic, non-carcinogenic, removable if required and should release the drug at a constant, programmed rate for a predetermined duration of medication. The polymers used in the therapeutic system must not cause irritation at the implantation site, or promote infection or sterile abscess. The most common polymers used are hydrogels, silicones and biodegradable materials.

A. Controlled Drug Release by Diffusion:

1. Membrane Permeation-Controlled Drug Delivery

In this mode of controlled drug delivery, the drug reservoir is encapsulated within a compartment totally enclosed by a rate-controlling polymeric membrane. The drug reservoir can be either solid drug particles or a dispersion (or a solution) of solid drug particles in a liquid - or a micro porous (or a semi permeable) membrane. The encapsulation of drug reservoir inside the polymeric membrane can be accomplished by molding, capsulation, micro encapsulation, or other techniques. Different shapes and sizes of drug delivery devices can be fabricated.

Representatives of this type of implantable therapeutic systems are Progestasert IUD and occusert system already discussed in Part I of the article.

2. Matrix Diffusion-Controlled Drug Delivery

In this mode of controlled drug delivery, the drug reservoir is formed by homogeneous dispersion of solid drug particles throughout a lipophilic or hydrophilic polymer. The dispersion of solid drug particles in the polymer matrix can be accomplished by blending solid drugs with a viscous liquid polymer or a semisolid polymer at room temperature, followed by cross linking of polymer chains, or by mixing solid drugs with a melted polymer at an elevated temperature. These drug-polymer dispersions are then extruded to

form drug delivery devices of various shapes and sizes. It can also be fabricated by dissolving the solid drug and / or the polymer in a common organic solvent followed by mixing and solvent evaporation in a mould at elevated temperature and / or under vacuum which defines the flux of drug release at a steady state from a matrix diffusion-controlled drug delivery device. Representative of this type of implantable therapeutic system are:

a) Contraceptive Vaginal Ring

It is fabricated by dispersing a contraceptive steroid, e.g., medroxyprogesterone acetate, as micronized solid particles in a viscous mixture of silicone elastomer and catalyst and then extruding vaginal ring. It is designed to be inserted into the vagina and positioned around the cervix for 21 days to achieve a constant plasma progestin level and cyclic intravaginal contraception.

b) Syncro-Mate-B Implant

It is fabricated by dissolving norgestomet crystals in an alcoholic solution of ethylene glycomethacrylate (Hydron S) and then polymerizing the drug-polymer mixture by the addition of a cross linking agent, such as ethylene dimethacrylate, and an oxidizing catalyst to form a cylinder-shaped insoluble Hydron implant. This tiny subdermal implant is engineered to be inserted into the subcutaneous tissue, using a specially designed implanter to release norgestomet at a rate of 504 mcg/cm^2 /$day^{1/2}$ for up to 16 days for estrus control and synchronization in livestock.

c) Compusode Implant

It is fabricated by dispersing micronized estradiol crystals in a viscous mixture of silicone elastomer and catalyst and then coating the estradiol-polymer dispersion around a rigid silicone rod by extrusion technique to form a cylinder-shaped implant. This subdermal implant is designed for subcutaneous ear implantation. It steers for 200 to 400 days and to release a controlled quantity of estradiol for growth promotion.

3. Microreservoir Dissolution-Controlled Drug Delivery

In this mode of controlled drug delivery, the drug reservoir, which is a suspension of drug crystals in an aqueous solution of a water miscible polymer, forms a homogeneous dispersion of millions of discrete, unleachable, microscopic drug reservoir in a polymer matrix. The micro dispersion is accomplished by high-energy dispersion technique. Different shapes and sizes of drug delivery devices can then be fabricated from this micro reservoir-type drug delivery system by molding or extrusion technique. Depending upon the physicochemical properties of drugs and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release.

Representatives of this type of drug delivery devices are: -

a) Syncro-Mat-C Implant

It is a cylindrical implant with improvement in both release rate profile and cost saving over the Syncro-Mate-B implant discussed earlier. It is fabricated by dispersing the drug reservoir, which is a suspension of norgestomet in an aqueous solution of PEG 400, to form millions of microscopic drug reservoirs in a viscous mixture of silicone elastomers by high-energy dispersion technique. After the addition of catalyst, the resultant composition is delivered into a silicone medical-grade tubing, which serves as the mould as well as the coating membrane, by extrusion technique and is polymerized in situ. The polymerized solid drug-polymer composition is then cut into cylinder-shaped drug delivery device with open ends. This tiny subdermal implant is designed to be inserted, by a specially designed implanter, and to deliver norgestomet in the subcutaneous tissue in livestock's earflap for up to 20 days for the control and synchronization of estrus and ovulation.

b) Dua-Release Vaginal Contraceptive Ring

It is fabricated by dispersing the drug reservoir, which is a suspension of a progestin and an estrogen in an aqueous solution of PEG 400, to form many microscopic drug reservoirs in a viscous mixture of silicone elastomers by high-energy mixing technique. After addition of catalyst, the resultant composition is extruded into a mould, by extrusion technique, and is polymerized by heat to form a donut-shaped vaginal ring. It is designed to permit the user to insert the ring themselves and to release both progestin and estrogen, at a specific rate ratio, in the vagina for 21 days to achieve a cyclic intravaginal contraception.

B. Controlled Drug Release by Activation:

i) *Osmotic Pressure-Activated Drug delivery*

A brief of osmotically active systems have already been discussed in Part I of this article. Osmotically acting implantable device can be represented by Alzet Osmotic Pump. (Fig. 1)

Alzet Osmotic Pump

In such a device, the drug reservoir is contained inside a collapsible, impermeable polyester bag, whose external surface is coated with a layer of osmotically active salt. This reservoir compartment is then sealed inside a rigid housing walled with semi permeable polymer membrane. At the implantation site, the water content in the tissue fluid will penetrate through the semi permeable membrane to dissolve the osmotically-active salt, creating an osmotic pressure in the narrow spacing between the flexible reservoir wall and the rigid semi permeable housing. Under the osmotic pressure created, the reservoir compartment is reduced in volume and the drug solution is forced to release

at a controlled rate through the flow moderator. By varying the drug concentration in the solution, different amounts of drug can be released at constant rate, for a duration of 1-4 weeks. Table 1 enlists few drugs delivered by miniature osmotic pumps.

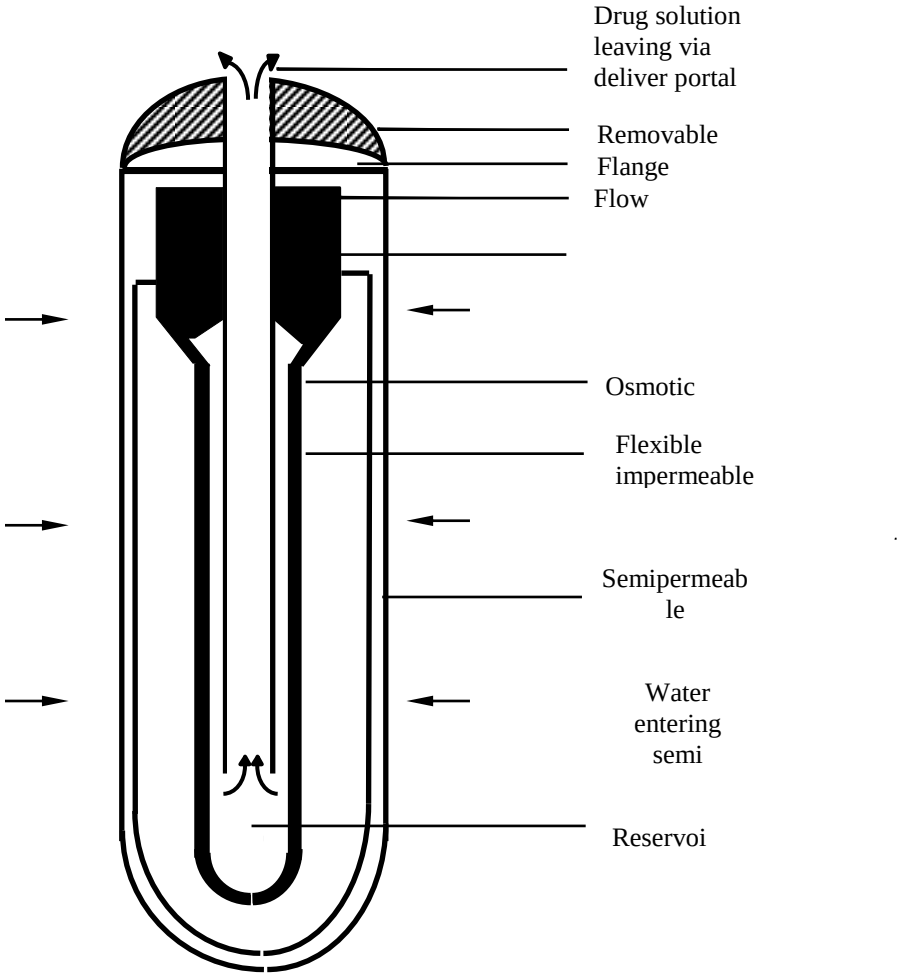

Fig 1 Cross-sectional view of various structural components of a solution-type osmotic pressure-activated drug delivery system, e.g., Alzet Osmotic Pump

Table 1 : **Agents delivered through osmotic pumps**.

Acetazolamide	Dopamine	hormone analogs, antagonists, agonists
Acrosin inhibitors	Dopamine agonists, antagonists	
Aldosterone	Endorphin	LSD tartrate
Angiotensin II	Enkaphelin analog	Methotrexate
Antigen	Enkephalin	Morphine
Ara-A analog	Epinephrine	Muramyl dipeptide
Ascitic fluid antibody	Erythropoietin	Nickel chloride

ACTH	Estradiol	Norepinephrine
Barbital	Estrogen	Parathyroid hormone
Bleomycin	Ethylene glycol tetracetic acid	Penicillamine
Bupacaine	Etorphine HCl	Phenobarbital
Cadavetine	Fluoroserin sodium	Progesterone
Cadmium	Folinic acid-SF	Propranolol
Calcitonin	Fructose	Propylene glycol
Calcium	Gentamicin sulfate	Prostaglandin E_1
Captopril	Glucagon	P3 antibody
Carbachol	Glucose	Saralasin
Chloroamphetamine	Glycerol	Serotonin
Cholechystokinin	Gonadotropin-releasing hormone	Superoxide dismutase
Citrovorum factor	Haloperidol	Thyrotropin-releasing hormone
Clonidine	Hybridoma antibody	Thyroxine
Cobaltous chloride	Hydroxybutyrate	Triethylenemelamine
Cyclic GMP	Hydroxydopamine	Triethylenetetramine
Cysteamine	Insulin	Trioiodothyronine
Deferoxamine	Lidocaine HCl	Vasopressin
Deoxycorticosterone	Luteinizing hormone-releasing	Vitamin D_1
Diethyldithrocarbamate	hormone	
Dihydroxycholecalcifetol	Luteinizing hormone releasing	

ii) Vapor Pressure-Activated Drug Delivery

In this mode of controlled drug delivery, the drug reservoir, in a solution formulation, is controlled inside an infusate chamber, which is physically separated from the vapor chamber by a freely movable bellow. The vapor chamber contains a vaporizable fluid, e.g. fluorocarbon, which vaporizes at body temperature and creates a vapor pressure. Under the vapor pressure created, the bellows moves upward and forces the drug solution in the infusate chamber to release, through a series of flow regulator and delivery canal, into the blood circulation at a constant flow rate. A typical example is the development of Infused, an implantable infusion pump, for the constant infusion of heparin for anticoagulation treatment, of insulin for antidiabetic medication and of morphine for patients suffering from the intensive pain of terminal cancer.

iii) Magnetism-Activated Drug Delivery

Macromolecular drugs, such as peptides, have been known to release only at a relatively low rate from a polymeric drug delivery device. This low release rate has been improved by incorporating a magnetism triggering mechanism into the polymeric drug delivery device and a zero-order drug release profile has also been achieved by a hemisphere shaped geometry design. By combining these two approaches, a subdermally implantable, magnetic-modulated hemispheric drug delivery device (Fig. 2) has been developed. It is fabricated by positioning a donut-shaped magnet at the center of a biocompatible polymer matrix, which contains a homogeneous dispersion of macromolecular drugs at a rather high drug to polymer ratio to form a hemispheric magnetic pellet. The hemispherical pellet is then coated with a pure polymer e.g. ethylene-vinyl acetate copolymer or silicone elastomers on all sides, except the cavity at

the center of the flat surface, to permit the release of macromolecular drug only through the cavity.

iv) Ultrasound-Activated Drug Delivery

It was recently discovered that ultrasonic wave can also be utilized as an energy source to facilitate the release of drug at a higher rate from polymeric drug delivery device containing a bioerodible polymer matrix. The potential application of ultrasonic wave for the modulation of drug release is still undergoing evaluation.

v) Hydrolysis-Activated Drug Delivery

This type of implantable therapeutic system is fabricated by dispersing a loading dose of solid drug, in micronized form, homogeneously through a polymer matrix made from bioerodible or biodegradable polymer, which is then molded into a pellet - or bead-shaped implant. The controlled release of the embedded drug particles is made possible by the combination of polymer erosion through hydrolysis and diffusion through polymer matrix. The rate of drug release is determined by the rate of biodegradation, polymer composition and molecular weight, drug loading, and drug / polymer interactions.

2) PARENTERAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM :

The intravenous, subcutaneous, intramuscularly, intraperitoneal and intrathecal routes are examples of parenteral routes of drug administration. Up to the present, efforts in developing controlled release parenteral dosage forms seem to have concentrated on the subcutaneous and intramuscularly routes, resulting in products such as aqueous and oily suspensions and oily solutions.

There are a number of injectables depot formulations on the market e.g. Penicillin & Procaine suspensions (Duracillin Squibb); medroxyprogesterone acetate suspension (Depo-Provera, Upjohn) ; Fluphenazine enanthate and decanoate in oil solutions (Prolixin enanthate and Prolixin decanoate; Squibb) ; ACTH - Zn tannate / gelatin preparation (H.P. Acthar, Armour); Microcrystalline deoxycorticosone pivalate in oleaginous suspension (Percortan pivalate; Ciba); Testosterone enanthate (Delasteryl; Squibb); Testosterone enanthate / estradiol valerate in ethyl oleate BP repository vehicle (Ditate - DS, Savage); Nandrolone decanoate injection (Decadurabolin, Organon) and Insulin Zinc suspensions (Utralente, Lente and semi-lente, Novo)
The rate of drug absorption and hence duration of therapeutic activities will be determined by the nature of the vehicle, the physico-chemical characteristics of the drug or its derivatives and the interactions of drug with vehicle and tissue / fluids.

Biopharmaceutics of CR Parenteral Products :

When a CR drug formulation is administered parenterally into a tissue space, muscle or adipose tissue, a depot is formed. Before the drug can exert its therapeutic action, it must first be released from the formulation into the general circulation and then to the site of drug action. A possible sequence of events is depicted in Fig. 3.

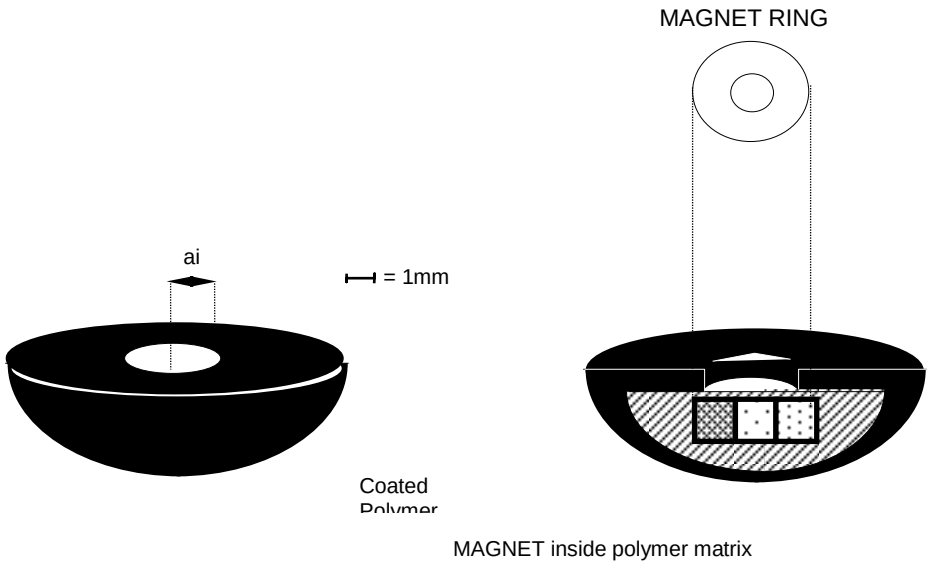

Fig 2 Diagrammatic illustration of a magnetism-activated drug delivery device e.g. hemispheric magnetic pellets

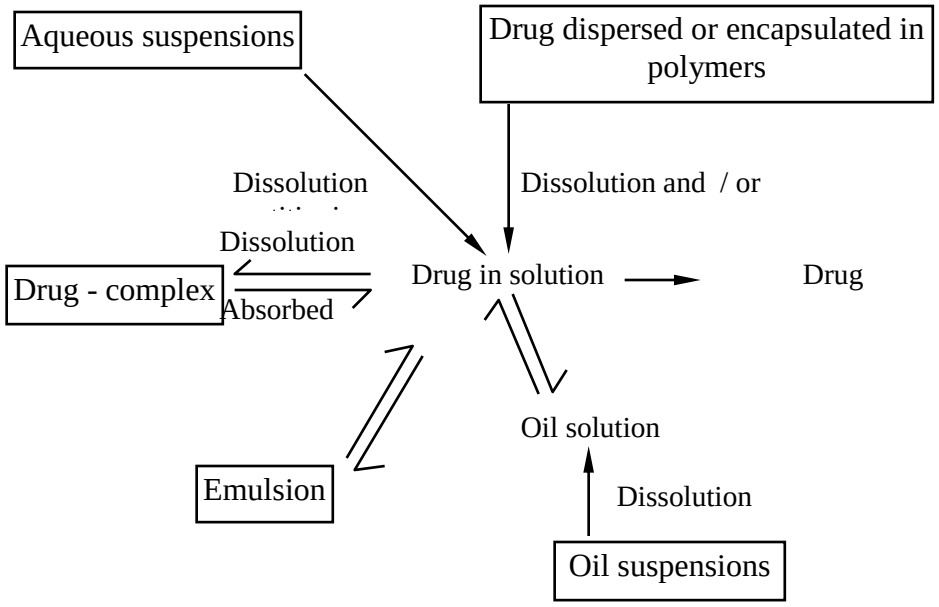

Fig. 3 Approaches to CR Parenteral delivery of drugs.

Generally, the release rate of a drug is affected by the dissolution, partitioning or absorption step. However, in many cases, the rate-limiting step is dissolution of drug particles in the formulation and / or partitioning of drug molecules from the vehicle to the surrounding tissue fluid. Thus, factors that affect the dissolution step and / or the partitioning step will affect parenteral drug absorption.

QUALITY CONTROL AND REGULATORY REQUIREMENTS OF CRDDS :

Quality parameters such as assay, content uniformity, and dissolution rate test along with the already established destructive & non-destructive tests for physical parameters need to be carried out for the controlled release systems as well.

In order to gain FDA approval of New Drug Application for a new chemical entity initially marketed in Controlled Release Dosage forms (as with all other similar products), clinical studies in patients establishing the safety and efficacy of each particular dosage form are required. For drugs that have been previously approved as safe and effective in controlled release dosage forms, data are required to establish bioavailability / bioequivalence to an approved controlled release drug product. Single dose bioavailability studies are acceptable for determining the fraction of the amount absorbed, lack of dose dumping, lack of food effects etc. Pharmacokinetic studies, performed under steady-state conditions are acceptable to demonstrate comparability to an approved immediate release drug product, occupancy time within a therapeutic window, percent fluctuation etc. The specific types of in-vivo studies include:

1) Fasted single dose studies
2) Post prandial study
3) Multiple dose steady-state studies.

Regulatory Considerations for Specialized CRDDS:

Novel CRDDS evolved in recent years viz. Ocusert, Oros, Copper and Progesterone releasing IUD's and transdermal systems are considered new drugs requiring full new drug applications (NDA) as a basis of drug approval. In addition to safety and efficacy considerations which includes an understanding of the drug input function, plasma blood level oscillation and the drug's pharmacodynamics, there are biopharmaceutic and pharmacodynamic issues that need to be addressed by the manufacturer such as :

1) Reproductivity of the new drug delivery system by in-vivo or in vitro studies.

2) A defined bioavailability profile which rules out dose dumping.

3) Demonstration of reasonably good absorption relative to an appropriate standard and which considers important elements e.g. obviating of first pass gut or liver metabolism.

4) A well-defined pharmacokinetic profile to support drug labeling.

5) In vitro characterization (when possible)

NOVEL ORAL CRDDS:

Technology in the field of controlled delivery has gone forward at a rapidly accelerating pace and promises many new and exciting developments.

Research on novel oral controlled release delivery systems focuses on increasing gastric retention or gastro-intestinal absorption. Currently, retention time is quite variable and depends on the individual. Gastric platforms have been developed that adhere to the stomach wall, thereby increasing gastric residence time and allowing for prolonged duration of therapy.

Latest Advances in Oral Transmucosal Delivery:

The controlled delivery of macromolecular drugs represents one of the greatest challenges in drug delivery. Transmucosal delivery across the tissues of the oral cavity is an attractive means for non-invasively administering such drugs. Oral transmucosal (OTM) administration offers several advantages for controlled drug delivery. Viz. bypass hepatic first pass effect. The oral mucosa can be generally divided into two categories: Keratinized tissues (gingiva and palate) and non-keratinized epithelial tissues (sublingual & buccal). The non-keratinized oral mucosa is highly permeable and blood flow to the oral mucosa is exceptionally high. In addition, an oral mucosal tissue is readily accessible and localization of dosage form with a defined surface area over extended periods should maximize absorption and provide higher degree of control and reproducibility relative to other mucosal delivery routes. These factors combined with the relatively rugged nature of the oral mucosa to physical and chemical injury make OTM an attractive mode for macromolecular drug administration.

One example of OTM based DDS is a bilayered tablet, which consists of a biocompatible adhesive layer that adheres to the gingiva and an active layer containing drug and optionally a tissue permeation enhancer. The active layer contacts the inner surface of the upper lip opposite the gingival application site and delivers the drug as the entire tablet dissolves. The choice of formulation components of the adhesive and active layers of the OTM system is dependent on the desired release characteristics of the active compound, dissolution time can be varied based on the physicochemical properties of the drug and the profile desired by the glucagon-like peptide (GLP-1) containing tablet for NIDDM therapy. Potentially therapeutic plasma levels of GLP-1 were achieved after administration of a single OTM tablet in type 2 diabetic patients. The peptide had marked glucose lowering effect during the first two hours. The bioavailability of GLP-1

after oral transmucosal administration was estimated as 47% relative to subcutaneous administration.

Novel CRDDS with Prolonged gastric residence time:

Dosage forms with a prolonged gastric residence time (GRT) i.e. gastro-remaining or gastro retentive dosage forms (GRDF) have brought new and important therapeutic options. For instance, they significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage forms. Also, GRDF's greatly improve the pharmacotherapy of the stomach itself through local drug release, leading to high drug concentration at the gastric mucosa, which are sustained over long period of time. For example, the eradication of helicobacter pylori which today requires the administration of various medication several times a day according to a complicated regimen and which frequently fails as a result of insufficient patient compliance, could perhaps be achieved more reliably using GRDF to administer smaller drug doses fewer times. Finally GRDF will be used as carriers for drugs with so called "absorption windows", these substances are taken up only from very specific sites of the gastro-intestinal mucosa, often in a proximal region of the small intestine. Conventional controlled release dosage forms pass the absorption window while they still contain a large and rather undefined portions of the dose which is consequently lost for absorption. In contrast an appropriate GRDF would slowly release the complete dose over its defined GRT and thus make it continuously available to the appropriate tissue regions for absorption.

The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion or by the simultaneous administration of pharmacological agents which delay gastric emptying.

1) Mucoadhesive Systems :

Muco adhesion tends to be not strong enough to impart dosage forms, the ability to resist the strong propulsive forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous which is lost through the peristaltic contraction and the dilution of the stomach content also seem to limit the potential of muco adhesion as a gastro-retentive force. Flotation as a retention mechanism requires the presence of liquid on which the dosage form can float and it also presumes that the patient remains in an upright posture during the GRT; in a supine position the pylorus is located above the stomach body and allows the accelerated emptying of floating material.

Sedimentation on the other hand has been successfully employed by few research workers as a retention mechanism for pellets which are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately $3g/cm^3$) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall.

Expansion has been shown to be a potentially reliable retention mechanism. Several devices features which extend, unfold or which are inflated by carbon dioxide generated in the device after administration. These dosage forms are excluded from the passage of the pyloric sphincter if they exceed a diameter of approximately 12-18 mm in their expanded state. Various mechanisms ensure the full reversibility of the expansion. Prototypes have already achieved the desired expansion and release profiles with model drugs in pilot clinical trials in which ultrasound and magnetic resonance imaging were employed as methods to visualize the gastric residence of the dosage form. There are few pharmacological approaches to achieve a moderately increased GRT of oral dosage forms. However, the concept of simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug will most likely not receive the favor of clinicians and regulatory agencies because of the questionable benefit to risk ratio associated with these devices.

NOVEL IMPLANT CRDDS:

Pulsating polymer Gel for Episodic Drug Delivery:

In the field of controlled release, constant rate of zero order delivery of drugs is often considered to be the gold standard. This philosophy reflects the notion that drug effect is directly related to the instantaneous concentration of drug in an appropriate biosphere. However, in recent decades evidence has accumulated that certain clones of drugs particularly hormones are best administered with a periodic pulsatile program. Such a program will mimic the normal endogenous pattern of hormone release from endocrine glands. In fact, hormone replacement therapy using zero order delivery has been shown to fail in some cases with the target endocrine fraction restored only when the normal pulsatile pattern of release is imitated by the delivery system.

Research workers then geared towards developing an implantable, autonomously pulsing drug delivery system which can be used for such hormones and whose pulse pattern is controlled by device design. No external energy source, such as electricity, magnetism or heat is required to activate the system. The system is based on a cross-linked poly (N-isopropyl acrylamide - co - methacrylic acid) hydrogel (HG) and the enzyme glucose oxidase (GO). GO is situated in a chamber and communicates with body fluids through the HG membrane. Glucose, at constant activity in the body permeates through the HG and causes the latter to collapse by neutralizing pendant carboxylic acid groups. By this means, glucose permeation is sharply reduced, and is subsequent proton production. Eventually the protons are released from the HG membrane and the latter re-swells, restoring glucose permeability. This process can be repeated indefinitely, provided the system maintains its integrity and the external glucose concentration remains constant. Drug release from the chamber will follow the pulsatile swelling of membrane.

The Novel Parenteral Controlled Drug Delivery Systems – Targeted approach to disease management would be dealt with in Part III of this series.

About the author:

SHRUTI U. BHAT, PH.D, MBA

MANAGEMENT CONSULTANT

Shruti Accelerates ROI …

For the past 18 years, Shruti has been consistently endorsed as - “Thought Leader par excellence”, and “Strategy Expert” spearheading profitable business process improvement initiatives for her clients.

Her mantra is to "Create a Positive Change" in an organization by providing "Strategic, Substantial and Pragmatic advise" to meet organization’s "Fast to Market", "Lean Processes" and “Super-Profit” objectives.

Shruti has her handle on Enterprise wide strategy including- Business strategy, Business process re-engineering & continuous improvement, Intellectual property management & capitalization, Organizational leadership & team development, Market expansions, mergers & acquisitions, Startup & early stage business development & growth, Quality risk management, Quality by design, Strategic alliances & Business process outsourcing. Through her customized “ROI strategy design”, Shruti provides cutting- edge concepts of innovation to create affordable quality products that are "Tough to copy".

She is a gold-medalist, with PhD, MBA from ITM- Southern New Hampshire University School of Business, USA with numerous patents and publications to her credit.

She is an invited keynote speaker at several international conferences and workshops. She blogs ardently and contributes her thoughts to journals, magazines & newspapers.

Reach Shruti at-
Website: www.DrShrutiBhat.com
Email: Shruti.Bhat@Innoworks.ca
Voice: 1.403.969.6219