Strategic innovative products- Part 1

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Translates concepts to profits, consistently!

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The deployment of drugs within the body is becoming more precise with the advent of rate-controlled dosage forms. Building on an expanding knowledge of pharmacokinetic and the concentration effect relation of drugs, this development represents a logical extension of pharmaceutical technology.

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most drugs, conventional methods of formulation are quite effective. However, some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme dissolution problems, require localization to a particular site in the body, or require strict compliance or long-term use. In such cases, a method of administration of the drug is desirable to maintain fixed plasma drug levels and can be achieved by the use of specialized drug delivery system.

The continuing quest for precision is apparent from an examination of the evolution of pharmaceutical technology from imprecisely bioassay medicinals of modern pharmaceutical products of defined chemical composition and precisely specified content. Recently, there has been a sharpening focus on the kinetic properties of dosage forms, reflected on the concepts of bioavailability and bioequivalence. The move beyond content specified pharmaceuticals to those explicitly specified by the rate at which they liberate their active ingredients in vivo is now gathering momentum. The kinetic specification of rate is not an alternate to the static, specification of content, but a complement to it.

FACTORS IMPELLING TRANSITION TO RATE - SPECIFIED PRODUCTS:

Many kinds of factors; namely - technological, scientific, medical and commercial are cause for this change.

I) AVAILABILITY OF TECHNOLOGY:

The 1970's saw great technological advances in the rate-controlled administration of drugs. One of the first examples was the conversion of the large and cumbersome infusion pumps used in physiology laboratories into the compact, convenient and reliable infusion pumps now widely used for drug administration in acute intensive care. In another series of innovative methods of membrane controlled molecular movement were developed and entirely new rate-controlled pharmaceutical dosage forms such as long duration opthalmics, hormonal IUD's, transdermal drug delivery system, osmotically controlled tablets and bioerodible injections were created. The very existence of this technology is a force for transition. It has begun to

unleash the imagination of researchers in pharmacology and medicine, stimulating them to explore the action (s) of drugs. When drug concentrations in blood and tissues are controlled, the aim is either maintaining constant concentration or controlling release to follow pre-designed therapeutic drug level patterns.

2) RATE CONTROL IN INTENSIVE CARE :

Rate - controlled continuous drug delivery is now the rule rather than the exception in acute intensive care e.g. after major surgery, coronary occlusion and serious trauma. Rate control involves both safe and effective use of potent agents whose concentrations in the blood must be maintained within a narrow range. Molecules such as nitroprusside, dopamine, heparin, dobutamine, lidocaine, norepinehrine and nitroglycerin are examples of such agents. Rate control also makes it practical to utilize drugs that have very short half-lives and in general to design dosage forms that provide duration of function that are multiples of the pharmacokinetic half life of the drugs administered.

3) RATE - CONTROL AS PHYSIOLOGICAL PRINCIPLE:

The body's own control systems for regulating hormonal secretions are now recognized as operating on the basis of continuous rate control. Hormones manifest such selectivity of action only when their rate of secretion is controlled. Giving the same hormones by conventional dosing (e.g. insulin injections) is a poor imitation of nature. In acute diabetic ketoacidosis, rate-controlled IV infusion of insulin has replaced the practice of giving insulin by injections, because rate controlled infusion is a safer and more effective method of treatment. Improving the management of day-to-day insulin requirements has evoked great interest giving rise to various efforts to provide continuous insulin administration, which necessarily implies rate control. The actions of many drugs are related to their concentration in the blood. Controlling those concentrations can therefore be a method of improving the selectivity of a drug's beneficial actions, provided that the beneficial actions are elicited by lower concentrations than those needed to elicit unpleasant or adverse effects. Consequently, it is now generally recognized that a drug's full potential remains unknown until it has been studied with extended-duration, rate-controlled delivery. It is also generally recognized that the relationship between concentration and effect is much more easily discerned if drug concentration is maintained at a steady level rather than allowed to vary, as occurs with conventional dosing methods. Table1 mentions few examples of agents whose selectivity of therapeutic action or physiologic action is related to the rate of administration.

Table 1: Examples of Agents Whose Selectivity of Therapeutic or Physiological Action Is Related to the Rate of Administration

Acetazolamide	Hydrochlorothiazide
Adrenocorticotropic hormone (ACTH)	Insulin
Angiotensin II	Methoxyflurane
Bleomycin	Minocycline
Chlordiazepoxide	Morphine
Cytosine arabinoside	Nitrofurantoin
Diethylcarbamazine	Nitroglycerin

Diphenhydramine	Nitroprusside
Dopamine	Norepinephrine
Estradiol	Parathormone
Ether	Phenacetin
Furosemide	Pilocarpine
Glucagon	Scopolamine
Gonadotropin-releassing (GnRH)	Vasopressin
Heparin	

4) COMPETITION FROM GENERIC DRUGS:

Drug patents have defined life cycle and the products based upon them become subject to competition from generic-drug houses. Nevertheless, developing a new superior patent protected product based on an un-patented drug is sometimes possible by incorporating an unpatented drug into a patent protected, rate-controlled dosage form. The essential element in the strategy of innovation is proof that the resulting product is superior to the drug in conventional form.

5) DISCOVERY OF NEW THERAPEUTIC ACTIONS:

Sometimes an older pharmaceutical product is discovered to have an entirely new use. Examples are minocycline (prevention of traveler's diarrhea & treatment of chlamydial infections), metronidazole (prevention and treatment of anaerobic infections) and sulfinpyrazone (prevention of myocardial reinfarction) etc. By establishing that a dosage form can be produced that is bioequivalent to that of the innovating firm, manufacturer can make all therapeutic claims associated with the innovator's product. Dosing so, however, becomes far more difficult if clinical trials to establish new therapeutic claims are preceded by dosage form innovation that results in a patent-protected, rate-controlled product superior to the drug in conventional form.

6) ECONOMIC CONSIDERATION:

The research and development costs of bringing a new drug to market can run as high as US $ 15-70 million. Any approach that could reduce these costs or the risks associated with drug development would be welcome. The screening of potential new drugs focus most often on maximum oral activity. Toxic side effects that are usually dose related are then titrated against therapeutic efficacy until an analog is found that has a sufficient therapeutic index. During this screening procedure many potent drugs with low side effects are eliminated because they are not orally active or lack sufficiently long half-life to be parenterally useful. It is here that rate control delivery presents its advantage.

Bioactive proteins such as interferons, growth hormones, monoclonal antibodies and human insulin represent a new driving force behind accelerated research into controlled release technology. These drugs often have low bioavailabilities, low stability, pose substantial formulation problems and often must be delivered continuously within narrow therapeutic range. For e.g. human growth hormone, an unstable polypeptide should ideally be parenterally delivered to hormone deficient children continuously at a rate of 0.5 - 2mg./ day.

Also, the realization that these new drug delivery systems can add therapeutic value to proprietary drugs and economic value to off patent drugs, the pharmaceutical companies are now engaged in improving their product pipeline through development of improved drug delivery system. Table 2 enlists potential market for controlled release systems.

Table 2: Potential global market for controlled released drug delivery systems administered via different routes.

Sr.No.	Controlled Release Drug Delivery	**Potential Market US $ million**
1	Oral	18000
2	Pulmonary Site Specific	10800
3	Transdermal	7600
4	Parenteral	5000
5	Nasal Site Specific	1600
6	Transmeusal Peptides Molecules	1400
7	Others	2000

TERMINOLOGY:

In the past, many terms viz. time-release, pulse-release, prolonged-release, sustained release, controlled release etc. have been used to refer to therapeutic systems. However, "sustained" and "controlled" release represent separate delivery processes. "Sustained release" systems describe a drug delivery system with delayed and / or prolonged release of drug. It also implies delayed therapeutic action and sustained duration of therapeutic effect.

"Controlled release" implies a predictability and reproducibility in the drug release kinetics. In other words, sustained release dosage forms provide medication over an extended time period whereas controlled release systems attempt to control drug concentrations on the target tissue. Site-specific systems and targeted delivery systems are the descriptive terms used to denote this type of delivery control.

CLASSIFICATION OF CONTROLLED RELEASE SYSTEMS:

Broadly, controlled release systems can be classified into two categories:

1) Based on Route of Administration:

- Peroral dosage forms
- Dental Systems
- Ocular systems
- Vaginal and Uterine systems
- Injections and implants

2) Based on Formulation Aspect:

- Polymer based CR technology (dissolution/diffusion controlled)
- Osmotic pumps
- Mechanical pumps
- Biodegradable carrier based CR system

- Ion-exchange system
- Prodrug approach
- Micro emulsion / Multiple emulsions

Table 3 enlists some drug molecules available in controlled release form

Table 3: Drug molecules available in co

Vitamins, Minerals, and Hormones
Ascorbic acid
Iron preparations
Methyltestosterone
Nicotinic acid
Potassium
Pyridoxine
Vitamin combinations

Diuretics and Cardiovascular Drugs

Chlorthalidone
Disopyramide
Furosemide
Heptaminol
Isosorbide dinitrate
Metipranolol
Motoprolol
Mexiletine
Nitroglycerin
Oxprenolol
Papaverine
Prenalterol
Propranolol
Trimazosin
Vinacamine
Acetazolamide
Ethaverine HCl
Nicotinyl alcohol
Pentaerythritol tertranitrate
Procainamide
Quinidine gluconate and sulfate
Reserpine

CNS Drugs

Aminosalicylic acid
Amitriptyline
Butriptyline
Naltrexone
Phenytoin
Salicylic acid
Trihexyphenidyl
Valproic acid
Amphetamine sulfate
Aspirin
Caffeine
Chlorpromazine
Dextroamphetamine sulfate
Diazepam
Diethylpropion HCl
Fluphenazine
Meprobamate
Methamphetamine HCl
Orphenadrine citrate
Pentobarbital
Pentylenetetrazole
Perphenazine
Phenmetrazine HCl
Phenobarbital
Phentermine HCl
Fluphenazine

Respiratory Agents

Aminophylline
Betamethasome
Brompheniramine
Chlorpheniramine
Dyphylline
Hydroxyethyltheophylline
Phenylpropanolamine
Pseudoephedrine
Proxyphylline
Terbutaline
Theophylline
Triprolidine
Chlorpheniramine maleate
Combination, antitussive
Combination, expectorant
Combination, upper respiratory
Dyphenylpraline HCl
Dyphylline
Trimeprazine
Tripelennamine HCl
Xanthine combination
Carbinoxamine maleate
Dimethindene maleate
Dexchlorpheniramine maleate

Antimicrobial Agents

Diethylcarbamazine
Nitrofurantoin
Sulphamethizole
Tetracycline

Gastrointestinal Drugs

Belladonna alkaloids
Hexocyclium methylsulfate
Hyoscyamine sulfate
Isopropamide iodide
Prochlorperazine maleate
Tridihexethyl chloride

Other Drugs

Bezafibrate
Coumarin
7-Hydroxycoumarin
Glibenclamide
Metformin

Dihydrocodeine
Diazepam
Indomethacin
Ketoprofen
Lithium Carbonate, Morphine

DESIGN OF CONTROLLED - RELEASE DRUG DELIVERY SYSTEM:

The design of controlled - released drug delivery system (CRDDS) accounts three important criteria viz. drug, delivery and destination. CRDDS can be designed using open or closed loop systems.

OPEN LOOP SYSTEM:

These systems comprise a drug platform; a reservoir, where the drug is stored; an energy source and in more sophisticated systems, a therapeutic program which meters the amount of agent passing through the rate-controlling mechanism. Once the agent gets into the biological environment, a pharmacokinetic process occurs before distinguishable therapeutic and side actions manifest themselves.

*CLOSED LOOP SYSTEM***:**

In more complex closed loop systems, the pharmacokinetic process-taking place systemically is feed back to the drug delivery system. This mechanism instructs the delivery system to alter its therapeutic program appropriately. These systems are more complicated than open-loop systems because they require a very sensitive sensor in the biological environment that is capable of sending a negative feed back signal to the delivery system.

To date, most research in controlled release has involved an open-loop system. The design of the loop in turn is based on the pathway of drug distribution / disposition in the body. Table 4 enlists characteristic that may make a drug unsuitable for controlled release dosing, while the factors influencing the design of CRDDS are mentioned in Table 5.

Table 4: Characteristics That May Make a Drug Unsuitable for Controlled Release Dosing

1. Short elimination half-life
2. Long elimination half-life
3. Narrow therapeutic index
4. Large doses
5. Poor absorption
6. Active absorption
7. Low or slow solubility
8. Time course of circulating drug levels different to that of pharmacological effect

9. Extensive first-pass clearance

Table 5: Factors affecting design of CRDDS

A) Patient Disease Property:

- Age & physiological state of patient
- Acute or chronic therapy required
- Pathology of disease
- Circardian changes in disease
- Ambulatory or bed ridden
- Location of target area
- Route of drug administration
- Duration of intended drug action

B) Drug Properties:

(i) Physiochemical properties of drug

- Aqueous solubility
- Partition coefficient
- Charge, Pka value
- Molecular size
- Stability

(ii) Biological properties of drugs:

- Dose
- Therapeutic index
- Absorption rate constant
- Distribution
- Protein binding
- Metabolism
- Biologic half life

C) Delivery System Design:

(i) Physio - chemical

- Dissolution
- Diffusion

(ii) Chemical modification

- Analogs
- Prodrugs

D) Targeted Delivery

- Synthetic / mechanical carriers
- Biological carrier systems

E) Choice of Excipients / Polymer

- Polymer type, content, viscosity
- Drug to polymer ratio, drug / polymer interaction, polymer / excipient interaction
- Type of application of polymer
- Aqueous solubility of polymer
- Swelling / diffusion index of polymer
- Agents enhancing polymer

- Osmotic pump
- Mechanical pump
- Ion-exchange
- Combination of above

I) PER ORAL CONTROLLED RELEASE SYSTEMS:

Historically, the oral route to administration has been used the most for both conventional and controlled release delivery systems. The earliest work in area of oral sustained release drug delivery system (dds) can be traced to the 1938 patent of Israel Lipowski. This work involved coated pellets for prolonged release of drugs and was presumably the forerunner to the development of the coated particle approach to sustained dds that was introduced later by Blythe in the early 1950's- 'Spansule' by Smith Kline French.

The Oral CRDDS may be formulated by employing the following mentioned kinetic phenomena:
i) Dissolution control (Reservoir / matrix)
ii) Diffusion control (Reservoir / matrix)
iii) Bioerodible and combination diffusion and dissolution systems
iv) Osmotically controlled systems
v) Ion-exchange systems
vi) Pro-drug approach

I) DISSOLUTION CONTROL SYSTEM:

Dissolution - controlled systems can be made to be sustaining in several different ways. By alternating layers of drug with rate-controlling coats; a pulsed delivery can be achieved. An alternative method is to administer the drug as a group of beads that have coatings of different thickness. This is the principle of the 'spansule' capsule marketed by Smith Kline Beecham. Some of the commercially available encapsulated dissolution products and matrix dissolution products are mentioned in Table 6 and Table 7 respectively.

Table 6 Encapsulated Dissolution Products

Product	Active ingredients (s)	Manufacturer
Ornade Spansules	Phenylpropanolamine hydrochloride, Chlorpheniramine maleate	Smith Kline Beecham
Thorazine Spansules	Chlorpromazine hydrochloride	Smith Kline Beecham
Contac 12-Hour capsules	Phenylpropanolamine hydrochloride,	Smith Kline Consumer Products

	Chlorpheniramine maleate, Atropine sulfate, Scopolamine hydrobromide, Hyoscyamine sulfate	
Artane Sequels	Trihexyphenidyl hydrochloride	Lederle
Diamox Sequels	Acetazolamide	Lederle
Nicobid Temples	Nicotinic acid	Rorer
Pentritol Temples	Pentaerythritol tetranitrate	Rorer
Chlor-Trimeton Repetabs	Chlorpheniramine maleate	Schering
Demazin Repetabs	Chlorpheniramine maleate, phenylephrine hydrochloride	Schering
Polaramine Repetabs	Dexchlorpheniramine maleate	Schering

Table 7 Matrix Dissolution Products

Product (tablets)	Active ingredients (s)	Manufacturer
Dimetane Extentabs	Brompheniramine maleate	Robins
Dimetapp Extentabs	Brompheniramine maleate, Phenylephrine hydrochloride, Phenylpropanolamine hydrochloride	Robins
Donnatal Extentabs	Pentobarbital, Hyoscyamine sulfate, Atropine sulfate, Scopolamine hydrobromide	Robins
Quinidex Extentabs	Quinidine sulfate	Robins
Mestinon Temespans	Pyridostigmine bromide	ICN
Tenuate Dospan	Diethylpropion HCl	Merrel
Disophrol Chromotabs	Dexbromphenixaxine maleate, Pseudoepherine sulfate	Shering

II) DIFFUSION CONTROL SYSTEM:

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types of subclasses of diffusional systems are recognized; reservoir devices and matrix devices.

Reservoir Devices as the name implies are characterized by a core of drug, the reservoir, surrounded by a polymer membrane. The nature of the membrane determines the rate of

release of drug from the system. Characteristics of reservoir diffusion system are mentioned in Table 8.

Table 8 Characteristics of Reservoir Diffusional Systems

Description	Drug core surrounded by polymer membrane that controls release rate
Advantages	Zero-order delivery is possible Release rate variable with polymer type
Disadvantages	System must be physically removed from implant sites Difficult to deliver high-molecular-weight compounds Generally increased cost per dosage unit Potential toxicity if system fails

Reservoir diffusional systems have several advantages over conventional dosage forms. They can offer zero-order release of drug, the kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions. The inherent disadvantage is that, unless the polymer is soluble, the system must somehow be removed from the body after the drug has been released. Table 9 gives a representative listing of available products employing reservoir diffusion systems.

Table 9 Reservoir Diffusional Products

Product	Active ingredients (s)	Manufacturer
Duotrate	Pentaerythritol tetranitrate	Jones
Nico-400	Nicotinic acid	Jones
Nitro-Bid	Nitroglycerin	Marion
Cerespan	Papaverine hydrochloride	Rhone-Poulene Rorer
Mitrospan	Nitroglycerin	Rorer
Measurin	Acetylsalicylic acid	Sterling Winthrop

Matrix Device as the name implies, consists of drug dispersed homogeneously through out a polymer matrix. Diffusion of the drug is based on: -

a) Initial concentration of drug in the matrix.
b) Porosity of matrix
c) Tortuosity of matrix
d) Polymer system forming the matrix and
e) Solubility of the drug.

Matrix system offers several advantages. They are in general, easy to make and can be made to release high-molecular weight compounds. The primary disadvantage of this system is that the remaining matrix "ghost" must be removed after the drug has been released. The characteristics of the system are summarized in Table 10 and a representative listing of available products is given in Table 11.

Table 10 Characteristics of Matrix Diffusion Systems

Description	Homogeneous dispersion of solid drug in a polymer mix
Advantages	Easier to produce than reservoir devices
	Can deliver high-molecular-weight compounds
Disadvantages	Cannot obtain zero-order release Removal of remaining matrix is necessary for implanted systems

Table 11 Matrix Diffusional Products

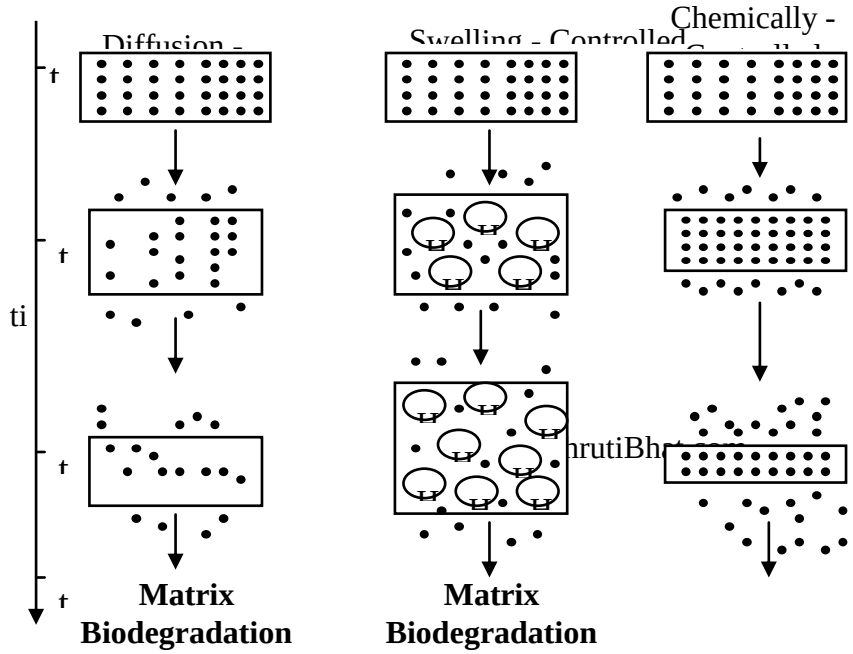
Product (tablets)	Active ingredients (s)	Manufacturer
Desoxyn-Gradumet	Methamphetamine hydrochloride	Abbott
Fero-Gradumet	Ferrous sulfate	Abbott
Tral Filmtab	Hexocyclium methylsulfate	Abbott
PBZ-SR	Tripelennamine	Geigy
Procan SR	Procainamine hydrochloride	Parke-Davis
Choledyl SA	Oxtriphylline	Parke-Davis

III) BIOERODIBLE AND COMBINATION DIFFUSION AND DISSOLUTION SYSTEMS:

Therapeutic system strictly will never be dependent on 'dissolution' only or 'diffusion' only Fig. 1 shows a schematic drawing illustrating three mechanisms for controlled release from a biodegradable / erodible matrix. The complexity of the system arise from the fact that, as the polymer dissolves, the diffusional path length for the drug may change. This usually results in moving-boundary diffusion system. Zero order release can occur only if surface erosion occurs and surface area does not change with time. The inherent advantage of such a system is that the bioerodible property of the matrix does not result in a 'ghost matrix'.

Albumin, Celluloses, Gelatin, Chitosan, Methacrylic polymers, Carbopols etc. are few of the polymers employed in dissolution / diffusion CRDDS.

Fig 1 : Three mechanisms for controlled drug release from a polymer matrix



IV) OSMOTICALLY CONTROLLED SYSTEM:

In these systems, osmotic pressure provides the driving force to generate controlled release of drug. These systems generally appear in 2 different forms; Fig.2. The first contains the drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference. The second system contains the drug in solution in an impermeable membrane within the device. The electrolyte surrounds the bag. Both systems have single or multiple holes bored through the membrane to allow drug release.

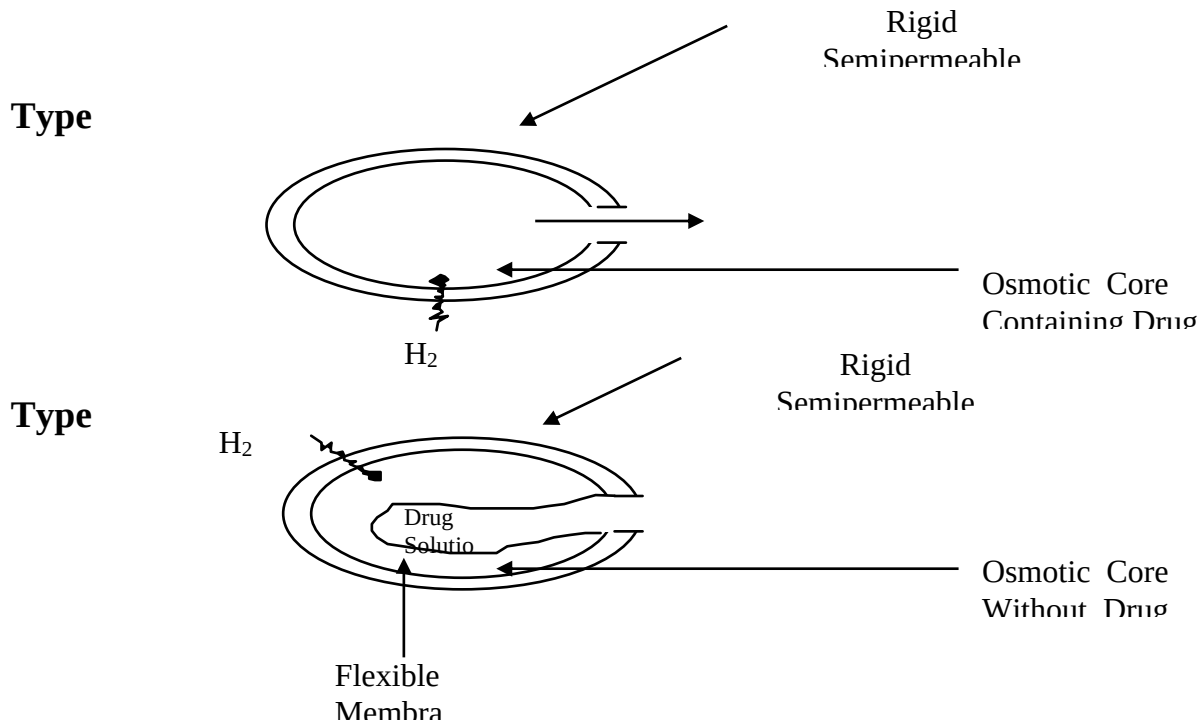


Fig. 2 : Diagrammatic representation of two types of osmotic ally controlled systems. Type A contains an osmotic core with drug. Type B contains the drug

In systems with solid drug dispersed with electrolyte, the size or membrane of bored hole (s) are the rate limiting factors for release of drug; since any variations in boring of the hole, accomplished with a laser device, can have a substantial effect on release characteristics. Most of the orally administered osmotic systems, are of this variety e.g. OROS (Acutrim) by Alza Corp. Inc. A variation on this theme is an osmotic system of similar design without a hole. The building osmotic pressure causes the tablet to burst, causing the entire drug to be rapidly released. This design is useful for drugs that are difficult to formulate in tablet or capsule form.

The osmotic systems are advantageous in that they can deliver large volumes. Most important, the release of drug is in theory independent of the drug's properties. This allows one dosage form design to be extended to almost any drug. Disadvantages are that the systems are relatively expensive and are inappropriate for drugs unstable in solution.

V) ION-EXCHANGE SYSTEMS:

Ion-exchange systems generally use resins composed of water-insoluble cross-linked polymers. These polymers contain self-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$Resin^{+} - drug^{-} + X^{-} \text{ ----------> } resin^{+} - X^{-} + drug^{-}$

Conversely,

$Resin^{-} - drug^{+} + Y^{+} \text{ ----------> } resin^{-} - Y^{+} + drug^{+}$

Where X^{-} and Y^{+} are ions in the GI tract. The free drug then diffuses out of the resin. The drug resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column or by prolonged contact in solution.

The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusional path length and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin. This system is advantageous for drugs that are highly susceptible to degradation by enzymatic processes, since it offers a protective mechanism by temporarily altering the substrate. This approach to sustained release, however, has the limitations that the release rate is proportionate to the concentration of the ions present in the area of administration. Although the ionic concentration of the GI tract remains more or less constant, the release rate of drug can be affected by variability in diet, water intake and individual intestinal content. A representative listing of ion-exchange products is given in Table 12.

Table 12 Ion-Exchange Products

Product	Active ingredients (s)	Manufacturer
Biphetamine capsules	Amphetamine,	Fisons

	Dextroamphetamine	
Tussionex suspension	Hydrocodone, Chlorpheniramine	Fisons
Ionamin capsules	Phenteramine	Pennwalt
Delsym solution	Dextromethorphan hydrobromide	

An improvement in this system is to coat the ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethyl cellulose or wax. These systems rely on polymer coat to govern the rate of drug availability.

VI) PRODRUG APPROACH:

The applications of the classical pro-drug approach in the design of oral sustained drug delivery forms has been limited due to various toxicological considerations. However, theophylline, a fairly water soluble compound with good bioavailability having short biological half life and narrow therapeutic range (10 - 20 um /ml in plasma) when given orally but makes plasma concentration monitoring essential. In an effort to overcome these shortcomings, several sustained release products of theophylline have been designed.

II) DENTAL SYSTEMS:

Controlled and sustained drug delivery has recently begun to make an impression in the area of treatment of dental diseases. Many researchers demonstrated that CRDDS of antimicrobial agents such as chlorhexidine, ofloxacin and metronidazole could effectively treat and prevent peridontitis. The incidence of dental carries and formation of plaque can also be reduced by CRDDS of fluoride. Delivery systems used are film forming solutions, polymer inserts, implants and patches. Since dental diseases are usually chronic, sustained release of therapeutic agents in the oral cavity would obviously be desirable.

III) OCULAR SYSTEMS :

The eye is unique in its therapeutic challenges. An efficient mechanism, that of tears and tear drainage, which quickly eliminates drug solution, makes topical delivery to the eye somewhat different from most other areas of the body. Usually less than 10% of a topically applied dose is absorbed into the eye, leaving the rest of the dose to potentially absorb into the blood stream resulting in unwanted side effects. The goal of most controlled delivery systems is to maintain the drug in the precorneal area and allow its diffusion across the cornea. Suspensions and ointments, although able to provide some sustaining effect, do not offer the amount of control desired. Polymeric matrices can often significantly reduce drainage but other newer methods of controlled drug delivery can also be used.

The application of ocular therapy generally includes drugs for glaucoma, artificial tears, and anticancer drugs for intraocular malignancies. The sustained release of artificial tears has been achieved by hydroxypropylcellulose polymer insert. However, the best-known application of diffusional therapy in the eye, Ocusert-Pilo, the device shown in Fig. 3 is a

relatively simple structure with two rate-controlling membranes surrounding the drug reservoir containing pilocarpine. Thus, a thin, flexible lamellar ellipse is created and serves as a model reservoir device. The unit is placed in the eye and resides in the lower cul-de-sac, just below the cornea. Since, the device itself remains in the eye, the drug is released into the tear film.

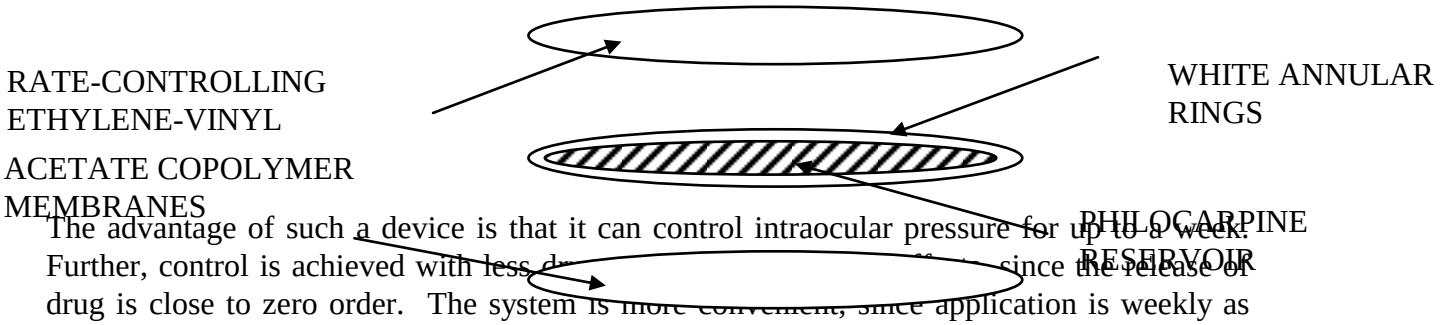


Fig. 3: Schematic diagram of the Ocusert Intraocular device for release of pilocarpine

The advantage of such a device is that it can control intraocular pressure for up to a week. Further, control is achieved with less drug [illegible] since the release of drug is close to zero order. The system is more convenient, since application is weekly as opposed to the four times a day dosing for pilocarpine solutions. This greatly improves patient compliance and assures round-the-clock medication, which is of great importance for glaucoma treatment. The main disadvantage of the system is that it is often difficult to retain in the eye, and can cause some discomfort.

Another method of delivery of drug to the anterior segment of the eye, which has proved successful, is that of prodrug administration. Since the corneal surface presents an effective lipoidal barrier, especially to hydrophilic compounds, it seems reasonable that a prodrug that is more lipophilic than the parent drug will be more successful in penetrating this barrier. Many drugs have been derivatized for prodrug ocular delivery e.g. timolol, nadolol, pilocarpine, prostaglandin F 2 α , terbulatine, aciclovir, vidarabine and idoxuridine.

New sustained release technologies are gaining importance in ocular delivery as in other routes. Liposomes as drug carriers have achieved enhanced ocular delivery of certain drugs; antibiotics and peptides. Biodegradable matrix drug delivery of pilocarpine can be achieved with a polymeric dispersion. Implantation of polymers containing endotoxin for neovascularization, gancyclovir, 5-flurouracil and injections of doxorubicin have also resulted in sustained delivery. However, topical ocular delivery is preferred considerably over implants and injection.

IV) TRANSDERMAL SYSTEMS:

The transdermal route of drug administration offers several advantages over other methods of delivery. For some cases, oral delivery may be contraindicated, or the drug may be poorly absorbed. This would also include situations for which the drug undergoes a substantial first pass effect and systematic therapy is desired.

The skin, although presenting a barrier to most drug absorption, provides a very large surface area for diffusion. Below the barrier of the stratum corneum is an extensive network of capillaries. Since the venous return from these capillary beds does not flow directly to the liver, compounds are not exposed to these enzymes during absorption. A most notable

example of such a drug is nitroglycerin, which has been administered both sublingually and trandermally to avoid first-pass metabolism. Other drugs that have seen success in controlled trandermal delivery are testosterone, fentanyl, bupranolol and clonidine.

Transdermal controlled-release systems can be used to deliver drugs with short biological half-lives and can maintain plasma levels of very potent drugs within a narrow therapeutic range for prolonged periods. Should problems occur with the system, or a change in the status of the patient require modification of therapy, the system is readily accessible and easily removed.

One of the primary disadvantages of this method of delivery is that drugs requiring high blood levels to achieve an effect are difficult to load into a trandermal system owing to the large amount of material required. These systems would naturally be contraindicated if the drug or vehicle caused irritation to the skin. Also, various factors affecting the skin, such as age, physical condition, and device location, can change the reliability of the system's ability to deliver medication in a controlled manner. In other words, both the drug and the nature of the skin can affect the system design.

SKIN DEPOT EFFECT - Difference between transdermal dds Vs. other delivery routes :-

When a transdermal patch is applied to the skin, the steady-state systemic dosage may not be reached for some time because of absorption of the drug in the skin. If skin absorption is large, the time required to saturate the skin with drug may be long compared to the time the device is on the skin. It is not possible then to simply equate the rate of drug delivery with the rate of appearance of drug in the systemic circulation even for device rate controlling systems. This effect is illustrated in Fig. 4.

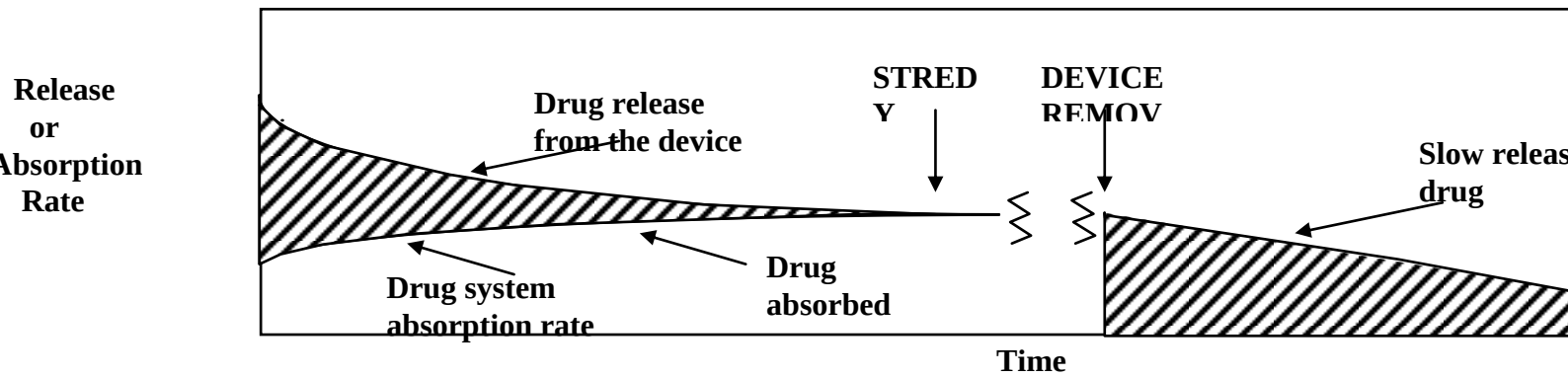


Fig. 4 : Schematic showing the difference between the drug release rate from a transdermal device and the rate at which the drug appears in the body.

For the majority of drugs, a plot of drug release from the device and drug absorption rate at the site of action has the general shape shown in this figure. Initially, there is a difference

between the drug release from the device curve and drug systemic absorption curve, because some drug is immobilized in the skin. Ultimately, the skin absorption sites are saturated and the steady state is reached, when the rate of drug released equals the rate of appearance in the blood. When the rate device is removed, drug release from the device abruptly halts. Release of drug absorbed in the skin, however, will continue for some time. In many cases, this depot effect may be sufficiently marked that the skin-loading time is comparable with the time the device is on the skin, so that the drug delivery does not reach steady state before the device is exhausted or removed. However, if therapy involves repeated applications of trandermal patches, this may not matter since the depot effect due to one device will be compensated for by the release of drug from an earlier device. Nevertheless, the depot effect is a major factor to be taken into account in device design.

DESIGN OF TRANSDERMAL THERAPEUTIC SYSTEMS:

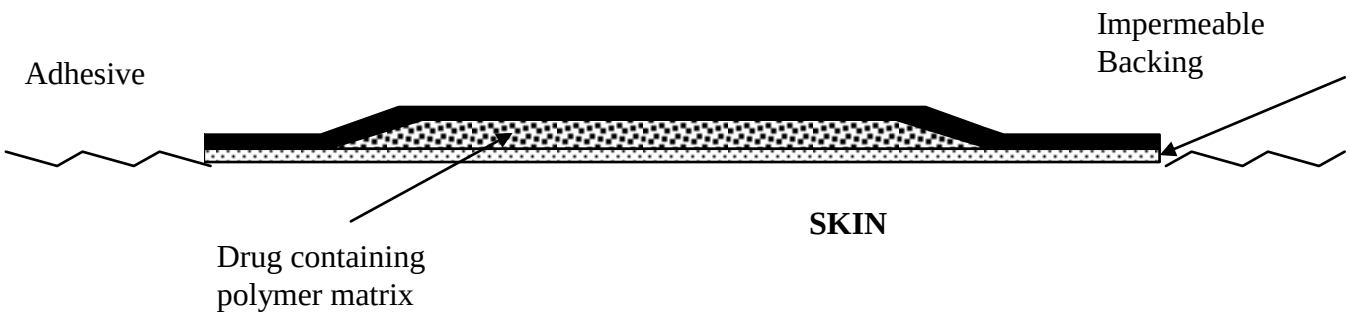
Transdermal drug delivery systems fall into two broad categories:

1) Monolithic systems and
2) Reservoir systems

Monolithic Transderm Therapeutic System:

A typical monolithic system is schematically represented in Fig. 5a. The therapeutic transderm system (TTS) has 3 layers, an impermeable backing, and an adhesive matrix that contains the drug. In this system, the matrix material controls the drug-diffusion rate from the device. Fig. 5b shows a typical drug-release profile from a monolithic system. Initially the drug contained in the device is uniformly distributed throughout the polymer matrix, when the system is placed on the skin, the drug contained in the surface layers permeates into the skin first at a relatively rapid rate. As the surface layers of the polymer matrix become depleted of drug, the drug-release rate falls as the drug is removed from the interior of the device and must diffuse progressively further to reach the device surface.

MONOLITHIC SYSTEM



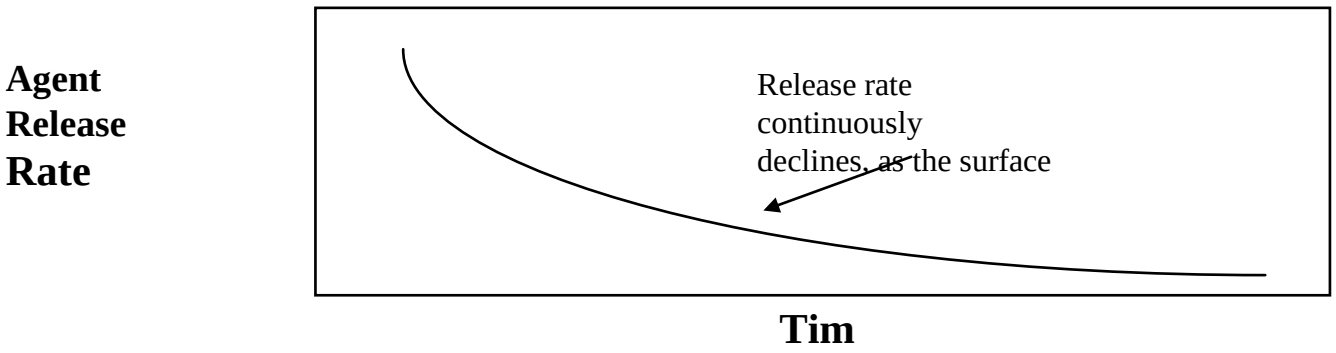


Fig. 5 : Schematic of a monolithic transdermal drug-delivery system (a) and

Reservoir Transdermal Therapeutic System :-

This type of a device also has a backing and adhesive layer, but the drug is now contained in a reservoir, from which its diffusion is controlled by a separate rate-controlling membrane layer. The drug is usually contained within the reservoir as a suspension in a liquid or gel carrier phase. On storage, a portion of the drug contained in the reservoir migrates into the membrane and adhesive layers. When the device is placed on the skin, this drug is released rapidly, giving an initial burst effect. Thereafter, drug release is controlled by the rule of drug diffusion through the membrane and adhesive layers to the skin. This release will be maintained at a constant value so long as the solution inside the device reservoir is saturated. i.e. excess undissolved drug is present. Drug diffusing from the reservoir solution is then immediately replenished by dissolution of some of the excess drug. When the last excess drug dissolves, the drug concentration drops below the saturation value and the drug-release rate falls. With this type of device, the release rate can be altered by changing the membrane thickness and permeability.

A final type of system, having drug-release kinesis intermediate between a monolithic and reservoir system, is obtained when a membrane is over coated onto a monolithic polymer matrix containing dispersed drug. The drug release is initially controlled by the membrane, but as the drug contained in the polymer matrix adjacent to the membrane is depleted the release rate falls because the drug must now diffuse through an increasingly thick layer of matrix.

Marketed Transdermal Therapeutic Systems: -

Table 13 enlists some of the commercially available Transdermal Therapeutic Systems.

Table 13 Commercial Transdermal Devices

Drug	System	Company (Reference)
Scopolamine	Reservoir	Alza/Ciba-Geigy (2-4)
Nitroglycerin	Reservoir Reservoir-monolithic Monolithic Monolithic Reservoir-monolithic	Alza/Ciba-Geigy (5,6) Pharma-Schwars (7) Key Pharmaceuticals (8,9) Searle Health-Chem/Bolar
Isosorbide	Monolithic	Nitto Electric
Dinitrate		
Clonidine	Reservoir	Alza/Boechringer Ingelheim (10)
Estradiol	Reservoir and Ethanol enhancer	Alza/Ciba (11-13)

Currently available marketed controlled TTS can be classified into 4 types as follows:

1) Membrane permeation-controlled system in which the drug permeation is controlled by a polymeric membrane. Transderm-Scop (scopolamine;Ciba-Geigy)
2) Adhesive dispersion-type system is similar to the foregoing but lacks the polymer membrane, instead the drug is dispersed into an adhesive polymer.
   Deponit (nitroglycerin; Wyeth)
3) Matrix diffusion-controlled system in which the drug is homogeneously dispersed in a hydrophilic polymer, diffusion from the matrix controls release rate.
   Nitrodur (nitroglycerin; Key)
4) Microreservoir dissolution-controlled system in which microscopic spheres of drug reservoir are dispersed in a polymer matrix.
   Nitrodisc (nitroglycerin; Searle)

Most marketed systems are of the polymeric membrane-controlled type, representative of these is Transderm-Scop. This product is designed to deliver scopolamine over a period of days, without the side effects commonly encountered when the drug is administered orally. The system consists of a reservoir containing the drug dispersed in a separate phase within a highly permeable matrix. This is laminated between the rate-controlling micro porous membrane and an external backing that is impermeable to drug and moisture. The pores of the rate-controlling membrane are filled with a fluid that is highly permeable to scopolamine. This allows delivery of the drug to be controlled by diffusion through the device and skin. Control is achieved because, at equibrium, the membrane is rate limiting for drug permeation. To initiate an immediate effect, a priming dose is contained in a gel on the membrane side of the device.

Another drug that is popular for controlled transdermal release is nitroglycerin. Conventionally, this drug is administered sublingually, although the duration of action by this route is quite short. This is acceptable for acute anginal attacks, but not for prophylactic treatment. Oral administration has the disadvantage that large fractions of the dose are lost to first-pass metabolism in the liver. Topical ointments have long been used for prophylactic treatment of angina, but their duration is only 4-8 hr and, in addition, are not aesthetically

acceptable. The trandermal nitroglycerin devices employ a variety of systems to provide 24 hr delivery.

V) VAGINAL AND UTERINE SYSTEMS :

Sustained and controlled-release devices for drug delivery in the vaginal and uterine areas are most often for the delivery of contraceptive steroid hormones. The advantages in administration by this route--prolonged release, minimal systemic side effects, and an increase in bioavailability-- allow for less total drug than with an oral dose. First-pass metabolism that inactivates many steroids hormones can be avoided.

One such application is the medicated vaginal ring. Therapeutic levels of medroxy progesterone have been achieved at a total dose that was one-sixth the required oral dose and ring expulsion, to name a few. Microcapsules have also recently been useful for vaginal and cervical delivery. Local progesterone release from this dosage form can alter cervical mucus to interfere with sperm migration. Other steroids have also attained sustained delivery by an intracervical system. The sustained release of progesterone from various polymers given vaginally have also been found useful in cervical opening and induction of labor.

A more common contraceptive device is the intrauterine device (IUD). The first intrauterine devices used were of the unmedicated type. These have received increased attention since the use of polythylene plastics and silicone rubbers. These materials had the ability to resume their shape following distortion. Because they are unmedicated, these IUDs cannot be classified as sustained release products. It is believed their mechanism of action is due to local endometrial responses, both cellular and cytosecretory. Initial investigations of these devices led to the conclusions that the larger the device, the more effective it was in preventing pregnancy. Large devices, however, increased the possibility of uterine cramps, bleeding, and expulsion of the device.

Efforts to improve IUD's have led to the use of medicated devices. Two types of agents are generally used, contraceptive metals and steroid hormones. The metal device is exemplified by the CU-7, a polypropylene plastic device in the shape of number 7. Copper is released by a combination of ionization and chelation from a copper wire wrapped around the vertical limb. This system is effective for up to 40 months.

The hormone-releasing devices have a closer resemblance to standard methods of sustained release because they involve the release of a steroid compound by diffusion. The progestasert, a reservoir system. Shown in Fig.6.

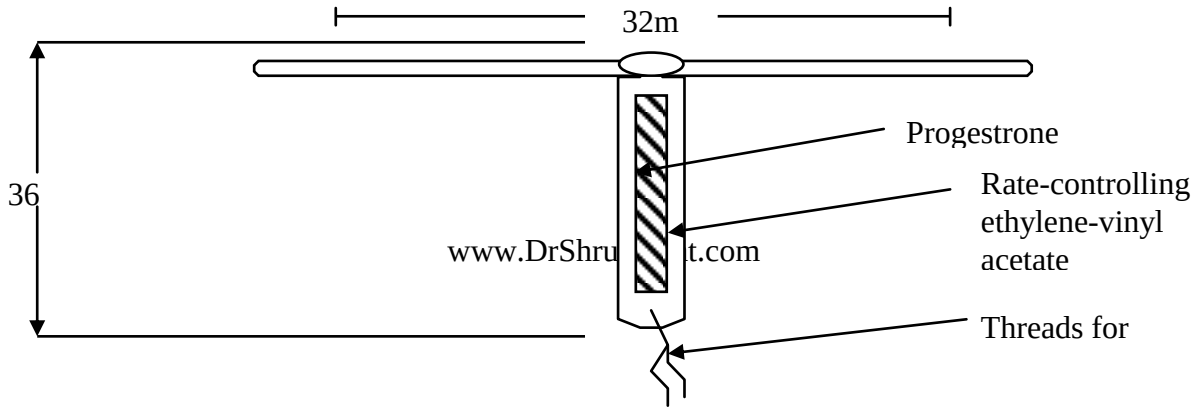


Fig. 6 : Schematic diagram of the Progestasert intra uterine device for the release of progesterone

Progesterone, the active ingredient, is dispersed in the inner reservoir, surrounded by an ethylene/vinyl acetate copolymer membrane. The release of progesterone from this system is maintained almost constant for 1 year.

Conclusion:

The space limitations of a written work such as this do not permit a complete discourse on all of the sustained and controlled mechanism available for possible drug delivery. Hence controlled release injections, implant delivery systems, quality control of CRDDS, Regulatory considerations and Novel CRDDS are being been dealt with in Part II of this article.

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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.

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