

**INTELLIGENT DRUG DELIVERY SYSTEMS**

**&**

**TAILOR MADE MEDICINES**

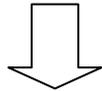
# INTELLIGENT DRUG DELIVERY SYSTEM (IDDS)

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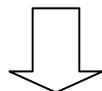
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## INTRODUCTION TO IDDS:-

- It **senses the signal** caused by disease  
(**SENSOR FUNCTION**)



- Judges the **magnitude of signal**  
(**PROCESSOR FUNCTION**)



- Then act to **release the drug** in direct response  
(**EFFECTOR FUNCTION**)

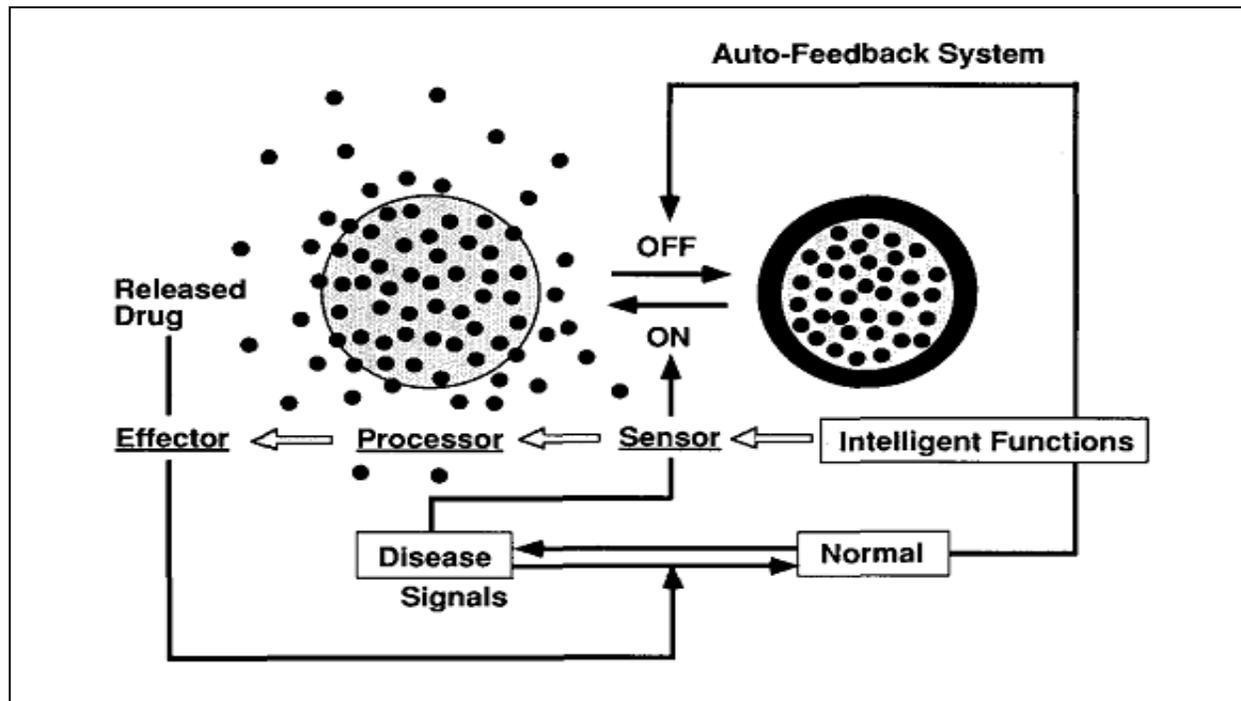


FIGURE-1 INTELLIGENT DRUG DELIVERY SYSTEM

- Intelligent DDS have been developed to deliver drug effectively to the targeting site (targeted, site-specific delivery) and release drug when drug is required (temporal control, self-regulating drug delivery).

# PULSATILE SYSTEMS

## **1. Single Unit Capsular System**

- Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body.
- Pulsincap<sup>®</sup> system is such a delivery in which a water insoluble body containing the drug formulation is closed with a swellable hydrogel and plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after a lag time. For rapid release of water insoluble drug effervescent or disintegrating agents are added.

## **2. Pulsatile Delivery by Osmosis**

- This system consists of a capsule coated with a semi permeable membrane. Inside the capsule is an insoluble plug consisting of osmotically active agent and the drug formulation. This system shows good in vivo and in vitro correlation in humans.
- The Port<sup>®</sup> System is a representative that consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate)

housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation.

- When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness.

### **3. Pulsatile Delivery by Solubilization (Erosion of Membrane)**

- These systems are based upon a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time.
- Time Clock<sup>®</sup> system consists of solid dosage form coated with lipid barriers such as carnauba wax and beeswax along with surfactants like polyoxyethylene sorbitan monooleate represents such a delivery.
- When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, pH, enzyme and gastric residence.

#### **4. Pulsatile Delivery by Rupture of Membrane**

- These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent. Citric acid and sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose.
- When system comes in contact with water it produces carbon dioxide gas, which exerts pressure and after a lag time the membrane ruptures and rapid release of drug occurs.
- A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in vivo drug pattern similar to the administration of several immediate release doses crosscarmellose sodium, sodium starch glycolate or low substituted hydroxyl propyl cellulose were used as swelling substances, which results in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane.

#### **5. Electrically Regulated Systems:**

- ❖ These systems exhibits drug release under the effect of an applied electric field due to action of an applied electric field on rate limiting

membrane or directly on the solute thereby controlling its transport across the membrane.

- ❖ Electric field-sensitive polyelectrolyte hydrogels have been developed for use in solute permeation control, artificial muscles and actuators utilizing their swelling-deswelling behavior.
- ❖ Insulin was released from poly-(dimethyl aminopropyl acrylamide) (PDMAPAA) gel with chemo mechanical shape change (shrinking) under the influence of electric fields.
- ❖ Effect of electric current on solute release from cross-linked poly (2-acrylamido-2-methylpropane sulfonic acid co-n-butyl methacrylate) (BMA) loaded with a positively charged solute (edrophonium chloride) by an ion-exchange method. The drug was released only when an electric field was applied and 'on-off' drug release was achieved.
- ❖ The use of carbomer (poly acrylic acid) in conjugation with agarose enables the formulator to achieve zero order release with application of electric current. An increase in anisotropy of gel system was observed on application of electric current, which could alter effectiveness of drug delivery systems.

## **6. Photoresponsive Systems:**

- Photoresponsive gels change their physical or chemical characteristics reversibly upon exposure to photoradiation.

- A photoresponsive polymer consists of a photoreceptor usually a photochromic chromophore and a functional part. The photochromic molecules capture the optical signal and subsequent isomerisation of the chromophores in the photoreceptors converts it to a chemical signal.
- Copolymer gels of N-isopropyl acrylamide and a photosensitive molecule, bis(4-dimethyl amino phenyl)(4-vinyl phenyl) methyl leucocyanide, exhibited a discontinuous volume phase transition upon ultraviolet irradiation due to osmotic pressure of cyanide ions generated by irradiation.
- Phase transition in polymer gels is induced by visible light and the mechanism proposed was direct heading to the network polymer response to the light.

## **7. Ultrasonically Modulated Systems:**

- The feasibility of ultrasonic-controlled polymeric delivery systems in which release rates of substances can be repeatedly modulated externally.
- Both Non-erodible as well as Bioerodible polymers can be used for the preparation of drug carrier matrices.

- The bioerodible polymers: polylactide, polyglycolide, poly(bis(p-carboxyphenoxy) alkane anhydrides and their copolymers with sebacic acid.
- The bioactives used:- p-aminohippurate, p-nitroaniline, insulin and bovine serum albumin.
- On exposure to ultrasound an enhanced polymer erosion and drug release occurs. The response of system to the ultrasonic triggering is rapid (within 2 min) and reversible in nature.
- The enhanced release is also observed in Non-erodible systems exposed to ultrasound where the release is diffusion controlled.
- The release rates of zinc bovine insulin from ethylene vinyl acetate copolymer (AVAc) matrices are 15 times higher when exposed to ultrasound. It is also noted that the extent of enhancement can be regulated by the frequency, intensity or duty cycle of the applied ultrasound.

## **8. Magnetically Modulated Systems:**

- This approach involves incorporation of magnetic beads in elastic polymers. It has been shown that when oscillating magnetic field is applied, more drug will be released.

- Insulin and other macromolecular bioactives can be continuously released by embedding them in a carrier like ethylene vinyl acetate copolymer (EVAc).
- Another system utilizing EVAc-protein matrices containing magnetic beads exhibit enhanced releases rates when placed in oscillating magnetic field.

## **RESPONSIVE SYSTEMS:**

### **1. pH Sensitive Systems:-**

- The pH range of different parts of gastrointestinal tract may provide environmental stimuli for pH sensitive systems.
- The charge density of the polymers depends on the pH and ionic composition of the surrounding environment. Alteration in pH of the environment will cause swelling or deswelling of the polymer. Therefore, drug release from device made from such polymer will display release rates that are pH dependent.
- It should be noted that poly acidic polymers are unswollen at low pH as the acidic groups remains unswollen and hence unionized, with an increase in pH however these polymer will swell.
- In contrast, polybasic polymers swell with decreasing pH as the ionization of these polymers increases with dropping pH.
- By use of pH sensitive bio erodible polymer approach, enzyme substrate interaction produces a pH change that is utilized to modulate the erosion of pH sensitive polymer containing dispersed bioactive.
- Recently recombinant DNA proteins that undergo reversible gelation in response to pH or temperature change.

- pH-sensitive hydrogels have been synthesized by the addition of ionic monomers to the gel such as acrylic acid (AAc) or aminoethyl methacrylate (AEMA).
- Heterogeneous hydrogels with both pH- and temperature-sensitivity from N-isopropyl acrylamide (IPAAm), acrylic acid and vinyl terminated polydimethylsiloxane (VTPDMS) loaded with indomethacin into the gels. (At gastric condition pH is 1.4 & 37°C, gel doesn't swell due to its LCST (Lower Critical Solution Temperature) is below 37°C and enteric condition: pH 6.8-7.4 & gel swells due to its LCST is above 37°C, ionization & repulsion of AAc groups.)
- pH-sensitive hydrogels having ionizable groups from hydrophobic N-alkyl methacrylate (AMA) and N,N-dimethyl aminoethyl methacrylate (DMA). (pH 3 or 5)
- Effect of pH and swelling on drug release behavior using graft copolymers of poly(ethylene glycol) (PEG) with poly(methacrylic acid) (PMAA).

## **2. Thermoresponsive Systems:-**

- Thermosensitive polymers can be classified broadly into two classes based on the origin of the temperature sensitivity in aqueous media.
- The first is based on polymer water interaction and the other is based on polymer-polymer interaction along with polymer water interaction.

- Usually a negligible or small positive enthalpy of mixing occurs when polymer network swell in solvent. Though a positive enthalpy change opposes the process, while the large gain in the entropy drives it. The opposite is often observed in aqueous polymer solution. This unusual behaviour is associated with a phenomenon of phase separation as the temperature increased to a critical value known as the Lower Critical Solution Temperature (LCST).
- Cross linking polymers which exhibit an LCST, such as polyethylene oxide (PEO), HPC, PVA and derivatives of poly(N-substituted acrylamides).
- Polymers showing LCST usually shrink, as the temperature is increased above the LCST, while reducing the temperature below LCST results in the swelling of the polymer.
- Poly(acrylamide) gels **swell** with increasing temperature, while poly(N-alkyl substituted acrylamide) gels **deswell**. The thermo-sensitivity is attributed to the delicate hydrophilic/hydrophobic balance of polymer chains and is readily affected by the size, configuration, and mobility of alkyl side groups.

### 3. Inflammation Responsive Systems:-

- It is based on the biodegradable hydrogels of cross-linked hyaluronic acid.

- This approach is used to treat patients with inflammatory diseases like rheumatoid arthritis using anti-inflammatory drug. This approach involves dispersion of drug loaded lipid microspheres in to degradable matrices of cross linked hyaluronic acid.
- Hyaluronic Acid gel is injected at inflammatory sites which are specifically degraded by hydroxyl radicals produced from inflammation-responsive cells during inflammation. Hyaluronic acid is a linear mucopolysaccharide composed of repeating disaccharide subunits of N-acetyl-D-glucosamine and D-gluconic acid.
- Hyaluronic acid has been extensively used in vivo as a therapeutic agent for ophthalmic surgery and arthritis. In the living body, hyaluronic acid is known to be degraded by two mechanisms: (1) via hyaluronidase as a specific enzyme and (2) via hydroxyl radicals as a source of active oxygen.
- The degradation of hyaluronic acid by hydroxyl radicals may be dominant and rapid as compared to that by hyaluronidase if hyaluronic acid is injected in the proximity of inflammatory reactions.

#### **4. Glucose and Other Saccharide Sensitive Systems:-**

- ★ Based on the principle of competitive and complementary binding behavior of **Concanavalin A (CON-A)** with Glucose & Glycosylated Insulin (G-INSULIN).

- ★ CON-A is immobilized to on sepharose beads and G-INSULIN, which is biologically active is displaced from the CON-A by glucose in proportion to the amount of glucose present, which competes for the same binding sites.
- ★ Encapsulation of glycosylated insulin bound CON-A in a suitable polymer membrane that is permeable to both glucose and insulin, the glucose influx and insulin efflux can be controlled.
- ★ **POLY(HYDROXYETHYL METHACRYLATE) POUCHES (PHEMA)** which contain a G-INSULIN-CON A complex suspension  
Drawback: **Exhibit lag time** due to exchange of G-INSULIN & GLUCOSE.
- ★ **Hydrophobic Nylon Microcapsule** showed quick 'ON-OFF' response of insulin release.
- ★ Glucose sensitive insulin delivery system based on a sol-gel transition:-  
A **Phenyl boronic acid (PBA)** moiety incorporated in poly (N-vinyl-2-pyrrolidone) using radical copolymerization of N-vinyl-2-pyrrolidone with m-acrylamido phenyl boronic acid {poly(NVP-Co-PBA)}. Insulin was entrapped into the polymer gel formed by a complex of poly(vinyl alcohol) with poly (NVP-Co-PBA). PBA forms reversible covalent complexes with molecule having a diol units, like PVA or glucose. When glucose is added, PVA from the PVA-boronate complex is replaced by glucose. This lead to the transformation of the system from gel to sol state facilitating the release of insulin from the polymeric complex.

## 5. Ionic Cross-linking In Situ Gelling System

- Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive in situ gel. Cross-linking ions can be provided in formulation in complexed form.
- Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of divalent cations, including  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ . The formulation consists of gellan gum solution with calcium chloride and sodium citrate complex.
- When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan gum thus forming a gel in situ. Dilute aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions.

## 6. Enzymatic Cross-linking In Situ Gelling System

- In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Xanthan gum has capacity to form gel with the enzyme 'lysozyme' which is present in the tear fluid

## SYSTEMS UTILIZING ENZYMES

### **1. Urea Responsive Delivery Systems:-**

- \* The alteration in local pH by immobilization of enzymes that lead to changes in polymer erosion rates. This system is based on the conversion of urea to  $\text{NH}_4\text{HCO}_3$  and  $\text{NH}_4\text{OH}$  by the action of urease that increases the pH.
- \* A partially esterified copolymer of methyl vinyl ether and maleic anhydride developed that displayed a pH dependent drug release. This polymer dissolves by ionization of the carboxylic groups.
- \* This pH sensitive polymer containing dispersed hydrocortisone is surrounded with urease immobilised in a hydrogel prepared by cross-linking of a mixture of urease and bovine serum albumin with gluteraldehyde.
- \* Diffusion of urea into the hydrogel and its subsequent interaction with the enzyme leads to a pH increase thereby enhancing erosion of the pH sensitive polymer with concomitant release of hydrocortisone.

## 2. Glucose Responsive Insulin Delivery:-

- Glucose responsive delivery systems utilizing enzymes are based on the glucose oxidase mediated reaction converting glucose into the gluconic acid.
- System based on pH sensitive polymers consist of immobilized glucose oxidase in a pH responsive hydrogel encapsulating a saturated insulin solution. With the diffusion of glucose into the hydrogel, glucose oxidase converts it into gluconic acid resulting in lowering of pH in the microenvironment of the hydrogel and subsequently causing swelling. As insulin permeates the swelled hydrogel more rapidly; relatively faster delivery of insulin in presence of glucose is anticipated. As the glucose concentration decreases in response to the released insulin, the hydrogel due to pH rise contract and collapse to impede the rate of insulin delivery.
- System using a porous cellulose membrane with surface grafted poly (acrylic acid) as a pH sensitive membrane.
- On immobilization of glucose oxidase onto the poly(acrylic acid) grafted cellulose membrane, it becomes responsive to glucose concentration.
- Basically in absence of glucose, the chains of poly(acrylic acid) grafts are rod like, that reduce the porosity of the membrane and suppress insulin permeation, however in the presence of glucose, gluconic acid produced by glucose oxidase (GOD) promotes the poly(acrylic acid), making the

graft chains coil like and opening the pores to enhance insulin permeation and release.

- **Glucose dependent insulin release:**

This approach is based on the fact that insulin solubility is pH dependent. Insulin entrapped into EVAc matrices in solid form, hence the release is dictated by its dissolution and subsequent diffusion. Glucose oxidase was immobilized into sepharose beads that were in turn incorporated along with insulin into EVAc matrices. When glucose entered to the matrix, gluconic acid is produced that caused a rise in insulin solubility and hence enhanced release.

### **3. Morphine Triggered Naltrexone Delivery System:-**

- Naltrexone is a long acting opiate antagonist that blocks opiate-induced euphoria and thus used for treatment of heroin addiction.
- Activation of the device is based on the reversible inactivation of enzymes obtained by the covalent attachment of hapten close to the active site of the enzyme-hapten conjugate with the hapten antibody.
- As the antibodies are large molecules, access of the substrate to the enzyme active site is sterically prevented thus rendering the enzyme inactive.
- Drug release is initiated by the appearance of morphine (hapten) in the vicinity and dissociation of the enzyme-hapten-antibody complex

rendering the enzyme active. This system was developed by entrapping Naltrexone in a bioerodible polymer.

- This polymer matrix is in turn covered by a lipid layer that prevents water entry into the matrix and thereby retards its degradation and subsequent Naltrexone release.
- The system is placed in dialysis bag, which contains lipase enzyme that is covalently attached to morphine and reversibly inactivated by antimorphine complexation.
- Therefore, when morphine is present in vicinity of the device, morphine diffuses into the dialysis bag and displaces the lipase-morphine conjugate from the antibody allowing now activated enzyme to degrade the protective lipid layer that permits the polymeric core degradation and release Naltrexone into the body.

### **SYSTEMS UTILIZING ANTIBODY INTERACTIONS:-**

- This approach has proposed antibody mediated release of contraceptive agent.
- The  $\beta$  subunit of Human Chronic Gonadotropin (HCG) is grafted on to the surface of the polymer, which in turn is exposed to antibodies to  $\beta$  -HCG. The appearance of HCG in the blood (indication of pregnancy) will cause

release of contraceptive drug as HCG competes for the polymer bound antibodies to HCG and initiates the drug release.

- Another reversible antibody system for controlled release of Ethinyl Estradiol (EE):- EE stimulates biosynthesis of sex hormone binding globulin (SHBG). It has been observed that high serum levels of EE stimulates the production of SHBG, which increases the concentration of SHBG attached to the polymer surface and reduces the EE release rate.
- In case of fall in serum EE levels the SHBG level falls as does binding of the SHBG to the polymer surface leads to an automatic increase in EE release rate.

### **SYSTEMS UTILIZING CHELATION**

- These include some antibodies vis-à-vis chelates used for treatment of metal poisoning.
- The concept is based on the property of metals to accelerate the hydrolysis of carboxylate or phosphate esters and amides.
- Tagging of the chelator to a polymer chain by a covalent ester or amide link prevents its premature loss by excretion and reduces its toxic effects.

In the presence of specific ion, the bound chelating agent forms a complex followed by metal accelerated hydrolysis and subsequent elimination of the metal chelate.

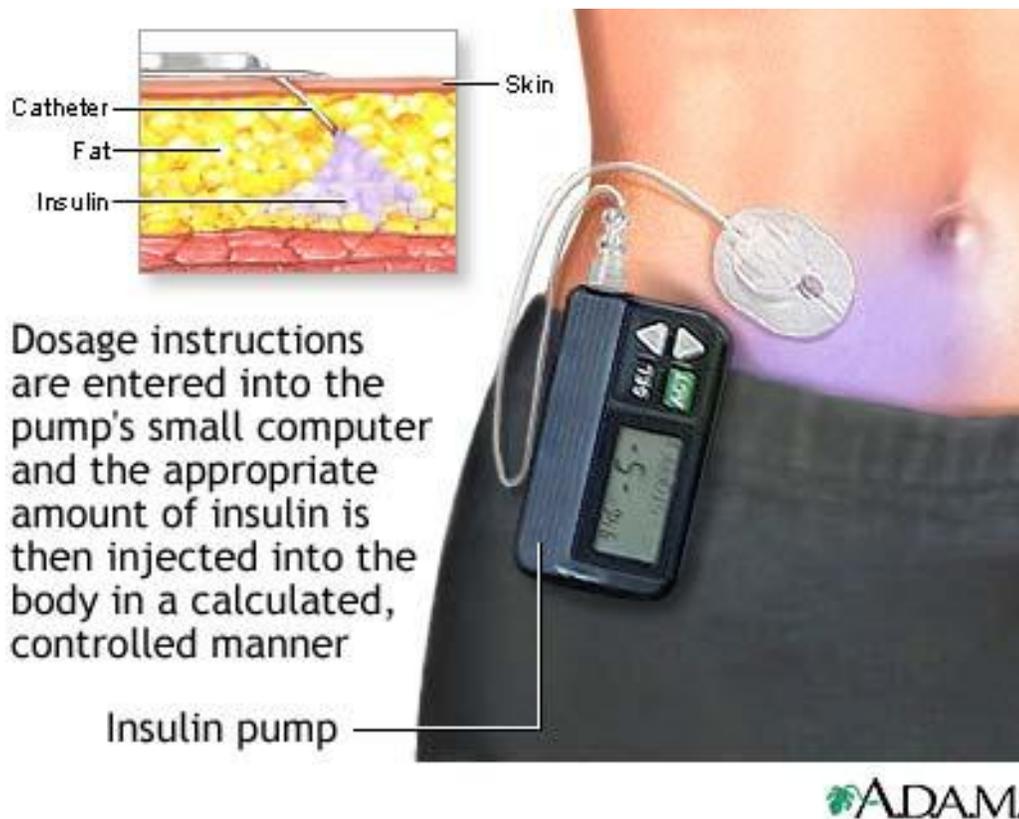
## **RECENT ADVANCES**

### **INSULIN PUMP**

- ★ The ultimate goal of insulin treatment in diabetes mellitus is to control the blood glucose level and prevent or stabilize long-term diabetic complications.
- ★ Administration of insulin through subcutaneous injection is currently the major therapy of diabetes. Two or three injections are required a day to maintain the normal blood glucose level. Because this method is burdensome and invasive to living organisms, the patient's situation would not be good regarding the quality of life. Therefore, an electrical and mechanical controlled insulin pump that injects insulin automatically into the bloodstream has been developed.
- ★ An insulin pump constructed with polymer materials has been studied. Wang developed an insulin reservoir consisting of silicone rubber, which releases insulin stored inside by generation of a pressure gradient by compression.

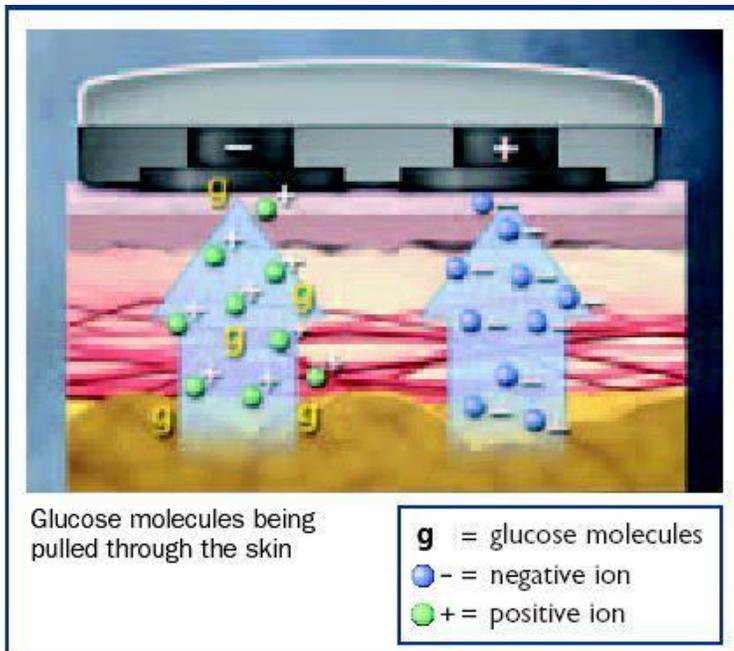
- ★ Siegel and Firestone designed an insulin release device using a polymer material as an actuator, which generates the pressure gradient for insulin release. The actuator is made from enzyme glucose oxidase and cationic hydrogel, whose swelling would change in response to glucose concentration through an enzymatic reaction. Insulin is released from these devices through the orifice.
- ★ Polymer materials used for insulin pumps should have superior biocompatibility. For this purpose, polymer membrane should have biocompatibility, insulin permeability, mechanical properties, and processability.
- ★ **Segmented polyurethane (SPU)** can be used as an elastic material for preparation of the insulin reservoir. For enhancement of insulin permeability and biocompatibility, a novel **copolymer composed of 2-methacryloyloxyethyl phosphorylcholine (MPC) and 2-EthylHexyl MethAcrylate (EHMA)** can be designed. Addition of the MPC polymer to other polymers enhances the biocompatibility to the original polymer.
- ★ In the insulin pump systems, the insulin permeability is controlled by a pressure gradient. Thus, the materials for this system need to have a pressure-responsive insulin release function. The amount of the insulin release is controlled by an applied pressure. The main problem of intraperitoneal insulin infusion from implantable pumps is the occurrence of under delivery of insulin.

★ Two main mechanisms are generally involved in under delivery events: **insulin aggregation** in the pump insulin pathway and **catheter occlusions**. Moreover, these aggregates, which are likely to be generated by hydrophobic interactions with the pump circuits, seem to promote an increased production of anti-insulin antibodies in many patients treated by implantable pumps. Concomitant improvements of catheter design also contributed to the reduction of under delivery. Despite these problems, implantable pumps currently provide the most effective and physiological insulin delivery.



## GLUCO WATCH

- GlucoWatch™ biographer is non-invasive, watchlike device that measures glucose. A plastic part of Gluco watch that snaps into the biographer and sticks to the skin. Automatic reading every 10 min up to 13 hrs is taken by it.
- Gluco watch presently takes the lead among user-friendly techniques aimed at glucose monitoring. This system is based upon the principle of reverse iontophoresis.



- A low electric current pulls glucose through the skin. Glucose is accumulated in two gel collection discs in the auto sensor. Another electrode in the auto sensor measures the glucose. A signal in proportion to interstitial glucose level can thus be generated. A good linearity between the recorded signal and blood glucose level has been shown.

## MICROFABRICATED DRUG DELIVERY SYSTEMS

Microelectronic devices have become integral part of our lives. They are present in our automobiles, cellular phones and computers. Here we discuss application of microfabrication technologies to the development of devices for the controlled release of drugs. Possible applications include micromachined silicon membranes to create implantable biocapsules for

the immunoisolation of pancreatic islet cells as a possible treatment for diabetes and sustained release of injectable drugs needed over long time periods. The use of microtechnology to tailor the size, shape, reservoir number, reservoir volume, unidirectional openings and surface characteristics of the drug delivery vehicle in conjunction with appropriate surface chemistry is potentially influential in the area of controlled release. The development of microneedles for transdermal drug delivery came about as an approach to enhance the poor permeability of the skin by creating microscale conduits for transport across the stratum corneum. To fabricate microneedles, a deep reactive ion etching process is commonly used. In this process, a chromium masking material is deposited on to silicon wafers and patterned into dots that have a diameter approximately equal to that of the base of the desired needles. When placed in the reactive ion etcher, the wafers are exposed to carefully controlled plasma of fluorine and oxygen, which causes a deep vertical, etch and slight lateral under etching. The regions on the wafer that are protected by chromium remain and eventually form the microneedles. Etching is allowed to proceed until the masks are undercut and fall off, leaving behind an array of silicon spikes.

Microfabrication technology has also created a new class of controlled release systems for drug delivery based on programmable devices called microchips. Microchips are particularly intriguing due to their small size, potential for integration with microelectronics and their ability to store and release chemicals on demand. With the recent advancements in biosensors and micromachining, implanted responsive drug release systems are becoming more plausible. The ultimate goal is to develop a microfabricated device devoid of moving parts, but with the ability to store and release multiple chemical substances. The device is fabricated by the sequential processing of a silicon wafer using microelectronic processing techniques including UV photolithography, chemical vapour deposition, electron beam evaporation and reactive ion etching. The experimental prototype is a 17

mm×17 mm×10 mm square silicon device containing an array of 34 square pyramidal reservoirs etched completely through the wafer.

# TAILOR-MADE MEDICINE

## Introduction:

- Scientific achievements have had an immeasurable influence on the uses of innovative biopharmaceuticals and methods in medicine. These breakthrough discoveries have contributed to an irreversible change in the perception and use of diagnostics in contemporary treatment of many illnesses.
- Today, in addition to the well-established types of physical and chemical examination and our growing understanding of biochemical processes occurring in the body, we now have at our fingertips state-of-the-art diagnostics and therapies based on the molecular pathomechanisms of illnesses.
- A gradual change is occurring in the treatment strategies that have been used for years, based on the format: specific → pathogenic → factor pathogenesis illness.
- Although the discovery of specific pathogens revolutionized medicine in the 19th and 20th centuries, making it possible to create pharmaceuticals essential to treat certain illnesses, generally improve health, or extend patients' lives, nowadays more attention is being paid to the lower than expected success of those medications. Their efficacy tends to fall between 25–62%. Such variation may result from different,

difficult to predict responses to the same therapy within a population of patients with the same illness, hence in cases that are seemingly the same.

- Significant differences are also noted with regard to the safety of administered pharmaceuticals. Intrapopulation variation, which determines the different responses to the same dose of a given drug, can lead to dangerous and undesirable side effects. In 1994 there were 1.8 million hospitalizations and over 100 deaths caused by such side effects in the US alone. Changing this will require implementing a fully innovative, individualized approach to illness and its treatment in patients.

### **Personalized Medication:**

For a long time researchers sought to fit one drug to as large a population of patients as possible, and identify the opportunities of using it to treat several different illnesses.

Put simply, they aimed for the broadest possible application for each drug. Today it is standard practice to place more weight on selecting the most appropriate drug and setting an optimal dose not just for each illness, but also for each given patient. Following selection based on sex, age, race and general health condition it is now the norm to carry out laboratory tests to establish individual risk factors (such as cholesterol levels and blood

pressure in suspected heart and circulatory disorders) as well as an analysis of family history of illness.

However, all these factors only help in establishing the patient's susceptibility to certain illnesses, rather than providing more specific information. They can be defined as making best use of the readily-available, routinely-used biochemical methods for precise diagnosis.

This practice can be extended further into the concept of personalized medicine: **selecting and administering a precise medication at an appropriate time to each patient.**

This is becoming possible thanks to the latest diagnostic tools that utilize molecular biology techniques to analyze genomes of bacteria or humans.

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## **Using Biomarkers**

- Biomarkers are essential for defining the progress of an illness in a given patient and predicting its likely course, as well as individual response to treatment. Biomarkers are indicators of biological or pathogenic processes or pharmacological responses to therapeutic intervention (Biomarkers Definitions Working Group).

- In oncology the most commonly used biomarkers are enzymes and hormones linked with tumors. They can be detected using biochemical tests, although their presence is not always indicative of the presence of a specific tumor. For example, an increase in the levels of the prostate-specific antigen (PSA) indicates a high likelihood of a prostate tumor being present, but it can also be a result of a mild hyperplasia. Similarly, raised levels of the carcinoembryonic antigen (CEA) are characteristic in between 60–90% of colon cancer cases and 50–80% of pancreatic cancers.
- Thanks to the rapid development of molecular diagnostic techniques, it is possible to monitor the course of many illnesses by studying differences in the structures of nucleic acids. DNA biomarkers include chromosome abnormality, single nucleotide polymorphisms (SNPs), a change in the number of copied DNA fragments, or differences in the degree of methylation of promoter regions. RNA biomarkers include differences in the transcription levels, or RNA molecules that take part in regulation.
- Research shows that using a biomarker that defines the degree of DNA methylation may be a factor in differentiating between prostate cancer from mild hyperplasia.

## **Bringing Biomarkers to Market:**

Bringing biomarkers into general use must be preceded by thorough analyses of their safety in patients, reliability, efficacy, and the financial implications of their use in diagnostics. In the US, the steps involved in introducing a new biomarker include: identification of relevant information in the patient's biological material (using DNA microarrays, gene chips, restriction fragment length polymorphisms (RFLP) and others, depending on type), establishing possible applications, and finally clinical and analytical validation. The final stage must be carried out if the biomarker is to be approved by the FDA for clinical use, although it can be bypassed if it is to be used purely for research. The final decision regarding bringing a biomarker to market lies with the Center for Medicaid & Medicare Services (CMS), responsible for carrying out an analysis of costs versus benefits including social aspects.

## **Future of Theranostics:**

- Personalized medicine is closely linked with several clinical applications, and is most advanced in oncology and infectious diseases. In the latter case, defining the genotype of the virus (HIV, hepatitis B and C) and establishing the viremic concentration play a crucial role in selecting an

appropriate therapy, predicting its efficacy, discovering any drug resistance and any necessary modifications of the treatment.

- Researchers have even suggested introducing a new term “Theranostics,” which stresses the close links between therapy and diagnostics when the course of treatment is being determined for individual patients. Effort to promote this new coin-age show how far advanced the introduction of personalized medicine is in various branches of medicine. Some scientists are no longer debating whether such medicines are will be used at all, but when its use will become widespread in clinical practice.

### **Societal Benefits and Costs:**

Alongside the high hopes and optimism brought by the prospect of “made to measure” medicine, there are also some ethical concerns. The most frequently cited examples revolve around personal data protection, potential discrimination by insurance firms or employers against people who have a tendency towards certain illnesses, or personal stigma. These may become deciding factors in whether this novel treatment strategy ultimately gains societal acceptance, therefore they should be put forward for thorough discussion, eventually leading to concrete legislative measures. Doubts may also arise because of the potential costs of

introducing personalized medicine. In this instance it is essential to take a close look at the problems of efficacy and safety of current therapies, and the intentions and options in investing in innovative technologies. In this specific instance it is very important to stress that a significant part of the diagnostic costs should be recompensed through targeted and effective therapeutics. Contemporary biopharmaceuticals (hormones, interferons and interleukins) are very expensive, and yet ineffective, and therefore unnecessary (or badly dosed) use of expensive drugs is wasteful. The application of proteomics and transcriptomics to personalized medicine will make it possible to optimize the possibilities of medicine in both economic and social aspects.

### **Medicine 2050:**

The personalization of medicine is an irreversible process whose benefits can already be observed, and whose potential benefits cannot be overstated. This is excellently illustrated by a communication from the European Commission on 10 December 2008, which includes a declaration of support for scientific research in pharmaceutical development: “With the emergence of new technologies like **pharmacogenomics and patient-specific modeling and disease simulators**, personalized medicine is now on the horizon. In the long term, doctors may be able to use genetic information to determine the right medicines, at the right dose and time.

This field is already affecting companies' business strategies, the design of clinical trials and the way medicines are prescribed. Although it is too early to say whether 'omics' technologies will indeed revolutionize the sector, the Commission closely monitors the area and will reflect on how it can support its development.”

As one of its main aims, the Commission set 2010 as a deadline for presenting a report on possible applications of “-omics” technologies in scientific research and in the development of novel pharmaceuticals. We cannot predict what medicine will be like in 2020 or 2050, although we can be certain that it will be quite different from what it is today. The scientific, economic, and social circumstances all indicate that “tailor-made” medicine is likely the way of the future.