

UNIVERSITY OF JOS



**“SELF-THINKING MEDICINES”: AUTOMATING
PHARMACOTHERAPY FOR ELIMINATING UNWANTED
EFFECTS.**

INAUGURAL LECTURE

BY

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“SELF-THINKING MEDICINES”: AUTOMATING PHARMACOTHERAPY FOR ELIMINATING UNWANTED EFFECTS.

The Chairman, Prof. Hayward Babale Mafuyai – Vice-Chancellor, University of Jos

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Members of staff of the University

Distinguished invited Guests

Great Josites and other students

Great Pansites

Distinguished Ladies and Gentlemen

Gentlemen of the Press

This lecture is aimed at enlightening the public about some of the modern technologies and developments in my area of specialisation. In doing that, I have tried to highlight some of my work relevant to such developments.

I wish to start with an overview which I believe will make us understand the lecture better.

1.0: OVERVIEW

The physiologic and pathologic profiles in an individual vary from one time of the day to another, thus the blood sugar level of a diabetic patient for example varies at different times of the day. The administration of anti diabetics like insulin to such a patient should therefore be continuously adjusted accordingly (Figure 1.1). The best physician and even the best pharmacist treating themselves, have no way of knowing the exact amount of drug their bodies need at any particular time, or controlling the site of drug release in their bodies. Medicines should therefore be designed and formulated to release their active ingredients according to the body's needs at precisely the affected site.

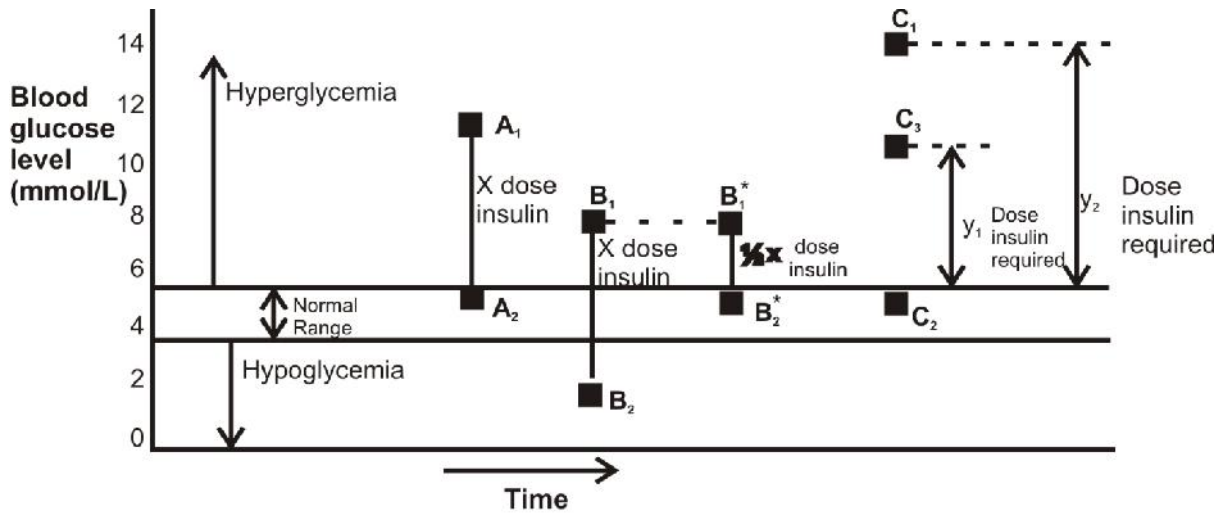


Figure 1.1: Illustration of the need for adjustment of dosage of Insulin with time, depending on the blood glucose level of a diabetic patient.

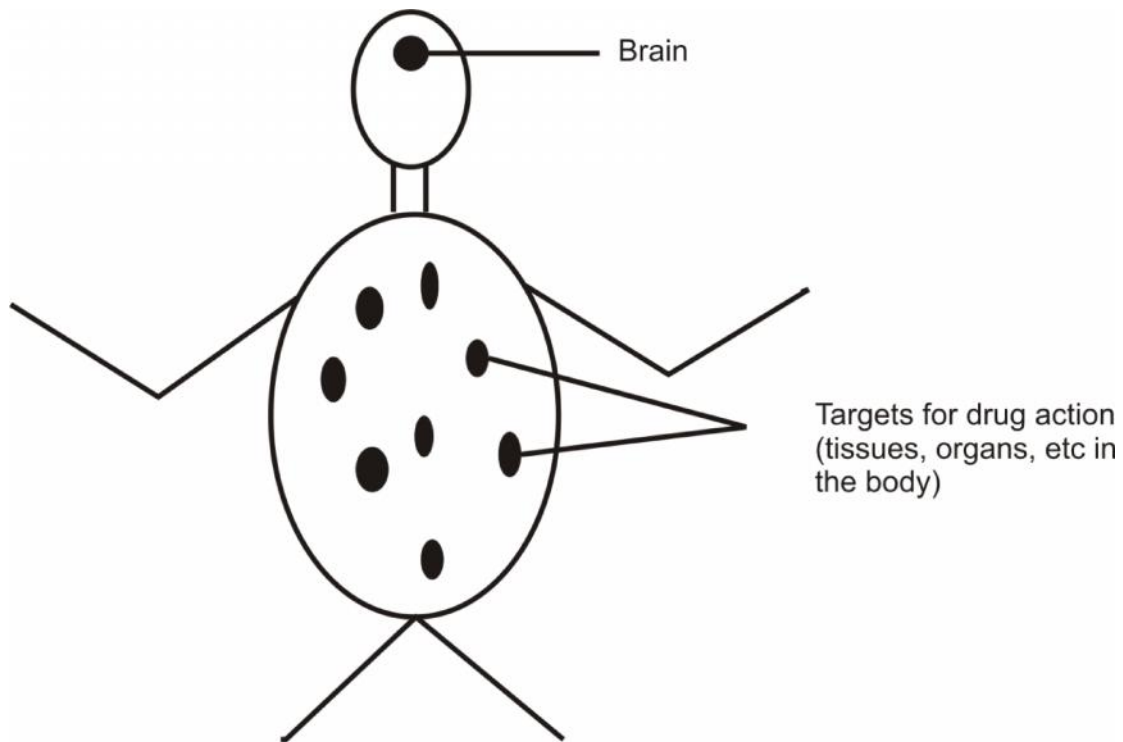


Figure 1.2: Illustration of the idea of targeting drugs to specific sites in the body.

New technologies and Information Communication Technology (ICT) are increasingly playing crucial roles in drug product manufacture and **automation** of drug administration.

“**Self-thinking medicines**” are now available that can continuously sense a patient’s response to a drug and through some **feedback system** like physiologic, physicochemical, pharmacologic signals, or pathologic parameters, or electronic, thermal, magnetic, ultrasonic signals, **automatically adjust drug release by themselves** to meet the patients’ needs (**temporal control**). This is similar to an air conditioner in a room that will be on when the temperature of the room is higher than a preset temperature, but the thermostat switches off by itself when the temperature falls to the preset temperature and gets actuated again when the temperature rises. Drug administration technology has gone to the extent of having the capability of learning the organised time-structured rhythm of ailments (**chronobiology**) and after an initial recurring sequence can anticipate the severity of ailments, and automatically adjust the doses of drugs administered to patients by such a “**self-learning**” process

Similarly, technologies like “**drug targeting**” (Figure 1.2) have been developed to enable medicines control the site in the body of drug release by themselves (**spatial control**), using some unique properties of the site for identification (as exemplified by the concept of the “**magic bullet**” for cancer therapy). Such automation optimises the administration of drugs to the sick (**pharmacotherapy**) in many cases.

Nigerian pharmaceutical researchers need to extend the frontiers of the use of our locally available raw materials by chemically, biologically, enzymatically or physically modifying them to transform them to “**designer**” **bioresponsive excipients**, for self-automation and targeting of drug release

In this presentation, the term **medicines** will be used interchangeably with the terms **drugs, drug products, dosage forms, drug delivery/medicine administration systems** and **pharmaceuticals**.

THE PRESENTATION WILL CAREFULLY MINIMISE DETAILS OF TECHNICAL NATURE

2.0: INTRODUCTION

When people fall sick, they require therapeutic or surgical intervention or both to get well again. The therapeutic intervention could be in the form of **pharmacotherapy** (the administration of drugs to the sick), in contradistinction to physiotherapy or psychotherapy that do not involve the use of drugs. From the therapeutic point of view, pharmacotherapy has made an outstanding contribution to healthcare, and a former World Health Organisation (WHO) Director General, Dr. Hiroshi Nakajima once pointed out that, **“Without drugs, a health service has no substance and no credibility”**.

2.1: PHARMACOTHERAPY

2.1.1: IMPORTANCE OF MEDICINES

As explained by Ansel (1978), certainly the vast array of effective medicinal agents available today represents one of man's greatest scientific accomplishments. According to him, it would be frightening to perceive of our civilisation devoid of these remarkable and beneficial agents. Through their use, many of the diseases which have plagued mankind throughout history, such as smallpox and poliomyelitis, are now facing extinction. Illnesses such as diabetes, hypertension, and mental depression are effectively controlled with modern drugs. Today's surgical procedures would be virtually impossible without the benefit of general anaesthetics, analgesics, antibiotics, blood transfusions, and intravenous fluids and nutrients. Drugs may also be used to diagnose diseases like diabetes, liver malfunction, tuberculosis, or natural physiologic conditions like pregnancy; or they may be employed to replenish a body deficient in antibodies, vitamins, hormones, electrolytes, protein, enzymes, or blood; or be used to extend life. **Nigeria is richly blessed with abundant herbal medicines, which could make significant contributions to health care delivery like the existing orthodox medicines. They therefore need to be developed especially in terms of isolation of active ingredients and dosing, to make them safer for users.**

2.1.2: DRUG RELATED MORBIDITY (DRM)

Medicines are indispensable in modern healthcare delivery, but, at the same time, they most often have **unwanted effects** ranging from mild side effects to severe

harmful and even lethal effects. Drug therapy is indeed clearly an essential part of medical management for many patients, and unfortunately it is also a major contributor to preventable injury called **Drug Related Morbidity (DRM)** or even **mortality**. Let me be quick to add here that it is not only medicines that suffer this dilemma, as most other necessities and luxuries of life (e. g. drinking water, food, fire, cars and even the air we breathe) can both be useful and harmful. Unsafe drinking water for example is the cause of death of millions of people in the developing world.

Prevalence and cost of DRM

In 2001, Charles D. Hepler declared that “the causes of the widespread problem of **Preventable Drug-Related Morbidity (PDRM)** that have been identified in literature constitute system failure”. The author showed evidence that preventable adverse outcomes of drug therapy are prevalent in the United States and Europe. Preventable drug related morbidity represents on average about 3.2% of all hospital admissions. Johnson and Bootman in 1995 have put the total cost of ambulatory PDRM in the U. S. at \$76 billion per year. We cannot imagine what the cost would be in developing countries (like ours) where such data do not exist, **although many health institutions in Nigeria these days are involved in pharmacovigilance**, in which unwanted effects of drugs (expected and unexpected) are recorded for individual patients. PDRM as a cause of hospital admissions (4 per 1000 people) has been put by Hepler (2001) at par with myocardial infarctions (3.1 per 1000 of the populace), lower than cancer (5.2 per 1000 of the populace) and higher than diabetes mellitus (1.91 per 1000) and asthma (1.8 per 1000). Ironically, medicines are a crucial part of the management of these diseases, and an unknown percentage of admissions attributed to these diseases are in fact the result of PDRM. To varying degrees, the side effects or unwanted effects of drugs complicate the task of the therapist, tax the compliance of the patient with his/her regimen, and increase cost at the research and development stage as discovering a serious toxic effect late in the clinical testing stage can nullify years of research. **Thus unwanted effects of drugs are of serious concern to pharmacists, both during the design & formulation of medicines and during administration to patients. Pharmacists should take advantage of modern technology such as the powerful Information Communication Technology (ICT). For example, pharmacists can more easily**

and more reliably detect adverse drug interactions by the use of computerised drug interaction alert software.

2.1.3: PRIME CONSIDERATIONS IN PHARMACOTHERAPY

In pharmacotherapy, safety and efficacy are of prime importance as drugs are known to be potent substances that can cause serious harm or unwanted effects in patients and result in Drug Related Morbidity (DRM) or even mortality. It is now widely recognised that the pharmacological properties of a drug do not, in themselves, constitute safe and effective clinical therapy. The rate at which the drug is administered to the body can be equally important, if not more so (Cosgrove, 1985). Different formulations of the same drug can have varied safety and efficacy.

(a) Patient safety

Patient safety is a prominent theme in health care delivery, and “**first, do no harm**” has been the ethical watchword throughout the history of pharmacy, medicine and nursing (Schyve, 2005).

When supplying both prescribed and non-prescribed medicines to patients, pharmacists have a professional duty of care to ensure that products are both safe and appropriate for use as determined by current/latest therapeutic knowledge and legislation. For example, some drugs are either contraindicated or should be used with caution in certain clinical conditions like pregnancy and breast-feeding, etc.

The ever increasing safety requirements for newly introduced drugs and other factors have dramatically increased registration costs, the number of new drug entities introduced per year has therefore dropped considerably in years. The re-formulation of already known safe drugs into modern medicines has therefore become an attractive alternative.

(b) Efficacy

A drug product must overcome all obstacles diminishing its therapeutic performance and provide its intended action. When a drug from an administered medicine enters the body, it becomes part of a complex and dynamic system consisting of fluids, tissues, cells, chemicals, electrical charges, etc. The release of the active drug from the formulated medicine thus needs to be dynamic according to the needs of the

patient at varying times during therapy. Furthermore, inter patient variation calls for **individualisation of dose regimens** as response fluctuation is generally unpredictable. Efficacy can also be affected by faulty medication use (e.g. delayed medication, inappropriate prescribing, overdose/under-dose, patient non-compliance, unexpected adverse drug reactions, etc.).

Proper drug product design and formulation is paramount to the therapeutic performance of a drug. Differences in design and formulation can result in remarkable differences in performance between different brands of the same drug with regards to absorption, efficacy, duration of action and the suppression of unwanted effects, etc. For example, Tense and **Ibrahim (2002)** have reported the variation in bioavailability of the active ingredient in their study of the in-vitro bioequivalence of different brands of chloroquine phosphate syrups found in Jos, Nigeria. ANOVA treatment of the results showed significant differences in the in-vitro absorption profiles of the brands which can cause variations in their safety and efficacy. Similarly, the stability of different formulations of the same drug has been shown to vary. **Ibrahim and Magaji (1994)**, compared the stability of the formulation options of the liquid dosage forms of the poorly water soluble paracetamol. From the accelerated stability studies and the relevant extrapolations to room storage temperatures, these authors showed that the co-solvent solubilised form (elixir) was more stable than the suspension form which in turn was more stable than the surfactant solubilised form. This has safety and efficacy implications as deterioration influences these parameters. Remarkable improvements can be achieved by novel formulations of well-known and established drugs that even open up new fields for their application. Absorption can be facilitated, the necessary dose can be reduced, efficacy and/or the duration of the effect can be prolonged, undesirable side effects can be suppressed, etc. (Szejtli, 1985).

Optimisation of pharmacotherapy aims at eliminating or minimising unwanted effects (including toxicity, resistance/tolerance, etc.), and enhancing efficacy (achieving cure or relieve of disease conditions, etc.). We know that drugs would be more effective if we could deliver them to the desired site with an optimal concentration profile.

2.2: DEVELOPMENTS IN DRUG PRODUCT DESIGN AND FORMULATION

Drugs are rarely administered as pure substances, but are usually formulated into chemical, mechanical or electromechanical drug delivery systems (Smollen, 1985).

The **art of drug product design** has produced devices ranging from systems that totally **rely upon the healthcare professional** for dosing decisions and administration, to highly **automated systems** performing one or more tasks such as monitoring, analysing, and dosing. Automated control of administration utilises a measured patient variable as input information for the basis of action.

The ultimate drug delivery system is that, which would continuously sense the individual patient's response to a drug, and through **some feedback system continuously adjusts drug release by itself**. It would also be desirable if it could at the same time target the drug to the desired site of action. Such drug products are thus able to control the rate and location of drug delivery to the body by themselves in response to the patient's need without human intervention.

To that extent, these medicines/systems decide by themselves if a patient needs more, less, or no drug at any given time, without borrowing from other opinions or conforming to any prevailing opinion, i.e. they are "self-thinking".

The developments can be summarised as follows:

(a) CONVENTIONAL MEDICINES

In the beginning all medicines were formulated to release their entire drug content at once, these are commonly called **conventional medicines** (Figure 2.1). Although these medicines provide fast and prompt action, they have some disadvantages and their use does not optimise pharmacotherapy (in terms of **safety** and **efficacy**). This is because **they lack time course (temporal) and location (spatial) control of drug release resulting in preventable unwanted drug effects.**

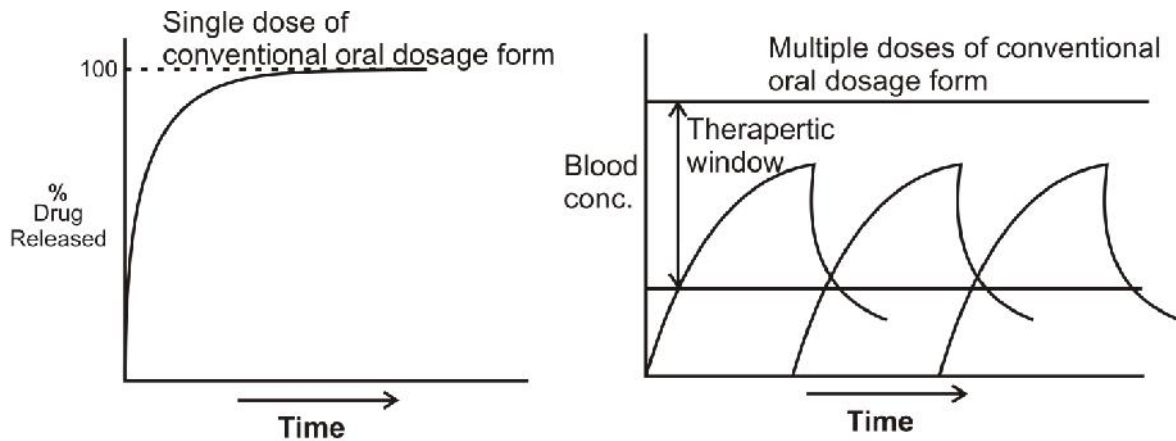


Figure 2.1: Release and Blood drug concentration profile of conventional oral dosage form

They therefore have two major disadvantages. First, they do not respond to a patient's dynamic physiologic process and the continuous change in pharmacologic response to a given drug input. Second, when administered, they get distributed throughout the body. This leads to wide spread action of the drug on both the desired and undesired tissues, resulting in therapeutic and toxic actions. Efforts to modify their release pattern therefore began and the first in the series was the introduction of prolonged-release products e.g. sustained-release medicines.

(b) SUSTAINED-RELEASE MEDICINES

These aim at releasing the drug slowly over a long period of time and maintaining a constant blood drug concentration within therapeutic range (Figure 2.2). This results in reduced dose frequency and reduced side effects. Consequently, patient compliance is enhanced, as the patient may for example need to take only one dose of the medication a day instead of three or four times a day. This is particularly useful for chronic clinical conditions like asthma, rheumatic arthritis, etc. Many reports abound in literature on sustained-release drug products, but their major short-come is that they release their drug content by first-order kinetics instead of the preferred zero-order kinetics that would produce constant blood level of the drug and avoid fluctuations that produce side effects.

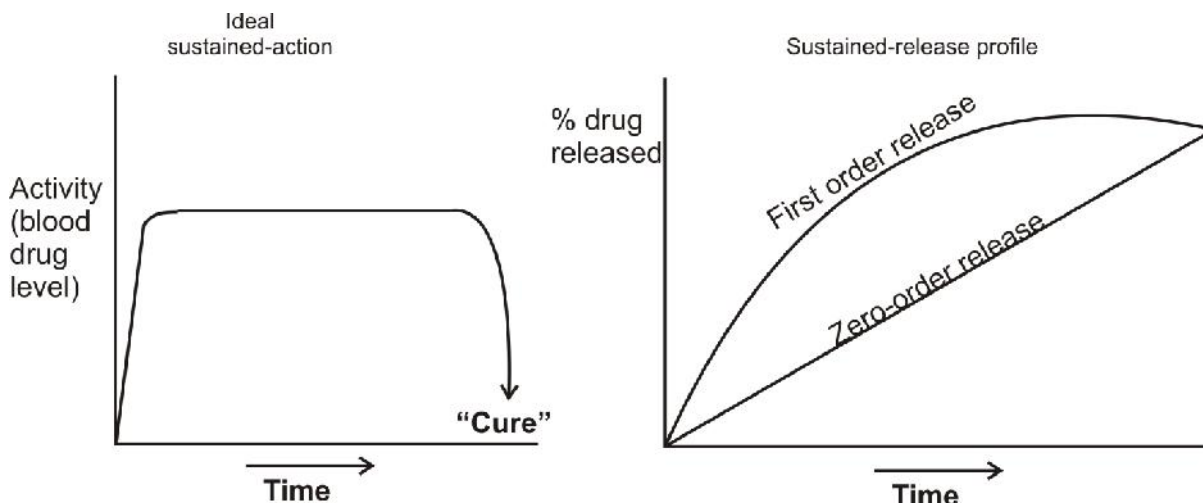


Figure 2.2: Ideal sustained-action profile, aimed by sustained-release drug products.

For theophylline (a bronchodilator for asthma management), the appearance of side effects of increasing severity with higher plasma concentration of the drug has been demonstrated by Hendeles *et al.* (1977). Such side effects vary from mild (GIT, CNS and cardiac) to potentially serious (tachycardia) to severe (grandma seizures and arrhythmia). It has been shown that the formulation materials greatly influence the drug release profile from the drug product. Some of us have worked on indigenous materials found in our local environments. *Cissus populnea* polymer (locally called “okoho”) has been shown to produce the desired zero-order release of anhydrous theophylline (Ibrahim *et al.*, 2000a). These authors evaluated *Cissus populnea* polymer - CPP (a polysaccharide hydrocolloid obtained from the stem bark of the plant *Cissus populnea* of the family *Amplidaceae* (*Vitaceae*)) as a matrix former for controlled drug release. Their study showed that CPP produced greater elongation of theophylline release and better correlation to zero-order release kinetics than well known polymers like methocel. The release profile was not significantly affected by pH, ionic strength and surfactant concentration, and may therefore be resistant to changes in the gastrointestinal tract (g.i.t.) conditions. Using this material, Ibrahim and Dawes (2000) were able to formulate “once-daily” theophylline tablets for enhancement of patient compliance. The use of computer simulation revealed a satisfactory pharmacokinetic performance of the product devoid of spike plasma levels or peak-trough variation in multiple dosing with the product.

There is a school of thought that argues in support of controlled release systems for administration of vaccines. Immunisation is the most cost effective weapon for disease prevention in developing countries where 80% of the world's population live and where 86% of all births and 96% of deaths occur (Bloom, 1989). Immunisation currently requires multiple injections and in developing countries drop-out rates from the first to the last doses of vaccine can be up to 70% (Aguado and Lambert 1992). An ideal vaccine would deliver the antigen in such a way that a long-lasting boosting effect is achieved with a single administration, that gives controlled release and pulsatile-release (Heller, 1993). The difficulty has been preserving biological activity while achieving the desired release kinetics. One technique was the use of a liposome system developed for pulsatile release and encapsulated within calcium alginate microspheres. Although encapsulation of the liposomes stabilised the protein initially, activity was greatly reduced after 30days at 37°C (Gibbon *et al.*, 1996). **The use of long lasting vaccines will go a long way in solving the problems causing high failure rates of vaccination programmes in our country, Nigeria.**

(c) NOVEL MEDICINES

The modern medicines that pharmacists prepare and dispense have now gone beyond the era that merely required them to contain the labelled amount of drug, be free of contaminants and be stable. Nowadays, the formulator's professional horizons have been extended to include responsibility for the performance of the drug product in the body and the **optimization** of therapy. This has led to the introduction of novel drug products that provide well controlled drug concentrations in a patient's bloodstream and eventually at the site of action, in its safe, effective and reliable form. **Drugs that were useless or of limited use due to very short duration of action, difficulty of control, unwanted effects, etc can gain expanded use via automation of administration.**

3.0: “SELF-THINKING MEDICINES”

Pharmaceutical scientists are now designing and formulating sophisticated medicine administration systems and medicines that **continuously monitor illness through some feedback mechanism and automatically adjust the amount of drug they release by themselves according to the patient’s requirement**. To have such control on drug delivery requires a means of sensing and responding to changes in biological stimuli. This can be achieved as shown in Figure 3.1 by the following options:

(i) Exogenous types (Section 3.1)

An external biosensor which electronically controls drug release, (A) in Figure.

Or

The use of external triggers for pulsed delivery e.g. sonic, magnetic, electrical signals, etc., (B) in Figure.

(ii) Endogenous types (Section 3.2)

An incorporated system in the delivery system, in which the stimulus has a direct effect on the release of drug, (C) in Figure.

Or

Endogenously triggered system.

At this stage I would like to give a “definition” of the term “self-thinking medicines” and I find the statement of McDonald *et al.* (1996) on closed loop systems most appropriate, which is slightly modified by inserting the word medicines as follows:

Systems/medicines that directly sense the state of the patient and then deliver an intervention without human action.

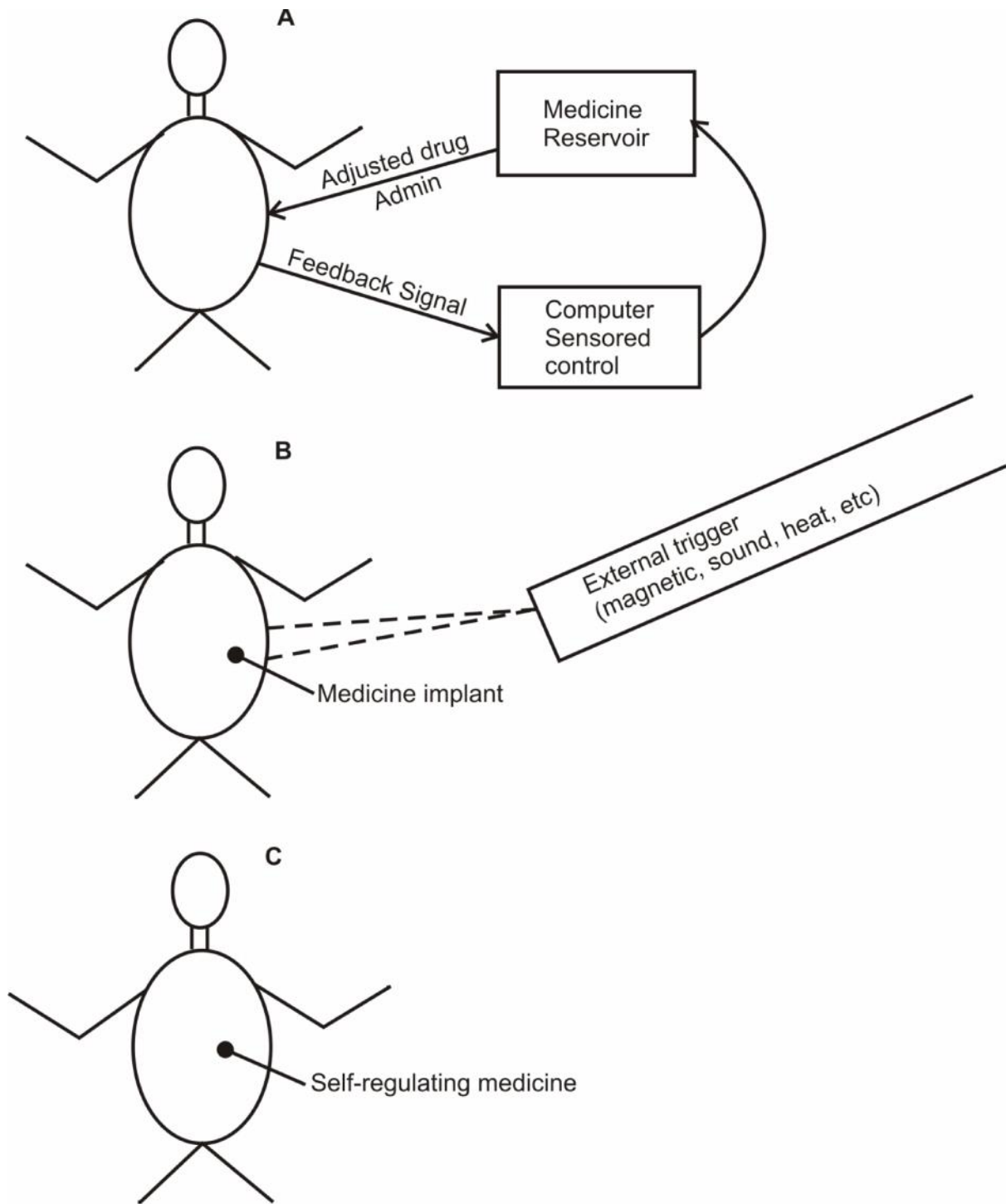


Figure 3.1: Types of “self-thinking medicines” showing drug release controlled by (a) external electronic devices (b) external trigger (c) self-regulating mechanism

This is particularly useful as the dosage that is optimally effective will necessarily differ among patients and from one time of the day to another in any particular

patient (Cosgrove, 1985). Self-thinking systems can be of the open or closed loop types as described under exogenous and endogenous types respectively.

3.1: EXOGENOUS TYPES

These have systems outside the body that control administration of drugs by the use of computers as interface between the patient and a drug containing device. The feedback signal can be a pharmacologic response like **blood pressure, heart rate, electrophysiological signals**, etc.; or **pathologic parameters** (Section 3.1.1). They could also be some **open-loop** control system in which information about the controlled variable is not automatically used to adjust the system inputs to compensate for the change in the process variables (pulsed or externally regulated). The externally controlled devices use external triggers for pulsed delivery e.g. magnetic, ultrasonic, thermal and electric forces.

A feedback controlled drug delivery system includes the automated sampling and analysis of a patient sample and dosing the patient based on the analysis (Gauthier *et al.*, 2000: U. S. Patent 19). The sampling may be performed by direct analysis of the patient sample, such as measurement of a blood sample coagulation state or a glucose level. In the Patent by Gauthier *et al.* (2000), the drug delivery system includes a sample set that has a bidirectional patient tube that allows for delivery of the patient sample to the analyser, and at another time, the infusion of a therapeutic drug. A controller receives a measurement from the analyser, and based on that measurement, adjusts the delivery of the therapeutic fluid.

3.1.1: SYSTEMS FOR AUTOMATIC FEEDBACK CONTROLLED ADMINISTRATION OF DRUGS (SAFCADs)

In pharmaceutical applications of control, as in any control system, there is some desired effect (called a **set point**) and an actual effect (**system output**), which is assessed or measured by a measurement element and compared with the desired effect (Cosgrove, 1985). According to this author, based on this comparison (the difference called the **error signal**), some corrective action is undertaken by someone or something (**the controller**) to manipulate an actuator to administer or stop the drug (**the input**) to the body (**the system**). The controlled process is as shown in Figure 3.2 below:

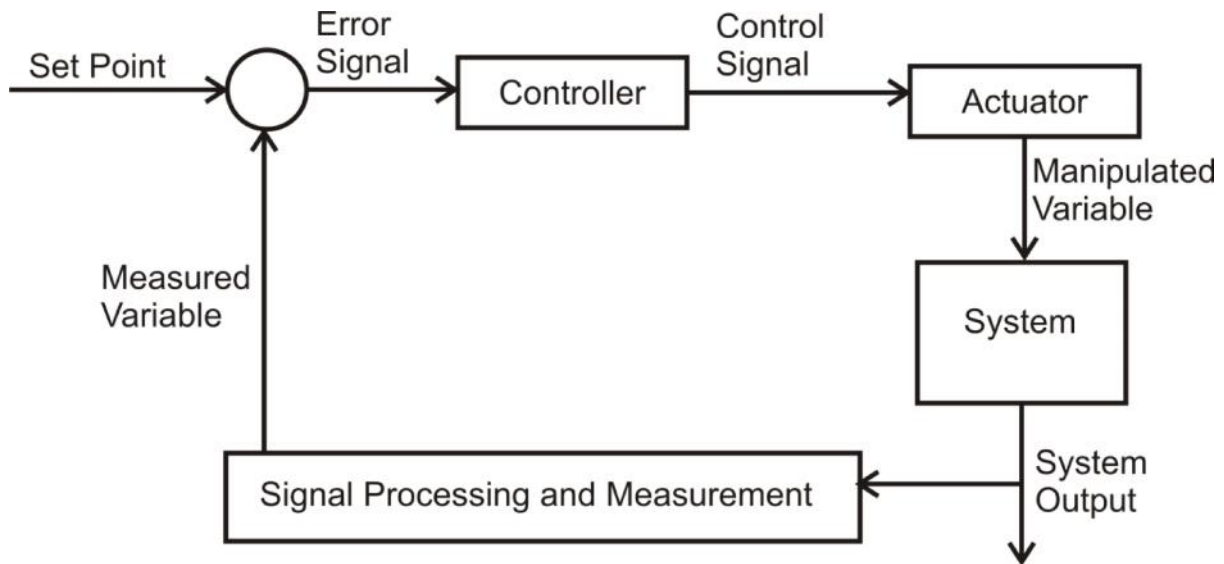


Figure 3.2: General Feedback Control System

Drug is infused at a preset rate until the patient's measured condition is in the desired range and then the infusion is temporally stopped. When the patient's condition enters or approaches the undesirable region (i.e crosses a predetermined threshold) the infusion is reinstated. This can improve substantially the patient's safety.

The pioneering work on SAFCADs started before 1950 with Bickford's work on anaesthetic SAFCADs. Kadish reported in 1974 his development of an insulin SAFCAD, thereafter many SAFCADs were developed for myorelaxants in 1966, blood infusion for postsurgical support of patients of open-heart operations in 1960s, control of acute hypertension and for inducing hypotension in 1973 and 1974, antiarrhythmics, cardiac stimulants and oxytocin during the 1970s, for insulin/glucose administration in 1980.

Examples of SAFCADs

(i) Insulin and glucose SAFCADs

Even the most carefully controlled and individualised injectable insulin regimens cannot prevent the progression of hyperglycaemic complications of diabetes. Insulin regimens are affected by activity, diet, etc. Kadish (1974) developed the first glucose controller, which was a dual on-off SAFCAD for insulin and glucose. The system utilised an analyzer®

(Technicon) for blood glucose monitoring. When the glucose concentration reached an upper threshold a standard dose of insulin is injected. If glucose fell below the glucose infuser threshold, a proportional controller action was instituted to administer glucose. Numerous other insulin SAFCADs have been developed by numerous investigators such as Kline et al (1967), Kraegan *et al.* (1977), etc.

(ii) Anaesthetics

One in one thousand surgical patients die from anaesthesia, which rises exponentially with age and with severity of underlying disease or injury. The use of barbiturates, primarily thiopental has reduced morbidity and mortality by up to 60% in acute cerebral anoxia. But thiopental therapy must be undertaken by highly trained personnel for the entire course of therapy, which may last for days. Bickford described a SAFCAD system which was used to control anaesthesia with thiopental and ether, and used the electroencephalograph (EEG) as a feedback signal (Figure 3.3).

When the EEG reached a certain value, a preset adjustable quantity of drug was administered. The SAFCAD was able to detect changes in the depth of anaesthesia much earlier than a trained anaesthetist. The most obvious effect of anaesthesia on EEG is on the EEG amplitude. At low doses of anaesthesia, and during induction of higher doses when the patient is in stages 1 and 2 anaesthesia, the amplitude is much greater than normal. As the depth of anaesthesia is increased through stage 3 anaesthesia, the EEG amplitude progressively diminishes until in stage 4 the EEG is virtually flat, indicative of greatly depressed electrical activity. The measured EEG is compared with the appropriate EEG set point as determined for the desired depth of anaesthesia. The difference is the error signal. The controller algorithm uses the error signal to generate an actuator signal which in turn drives the servo controlled syringe pump. The pump delivers thiopental at the rate specified by the actuator signal.

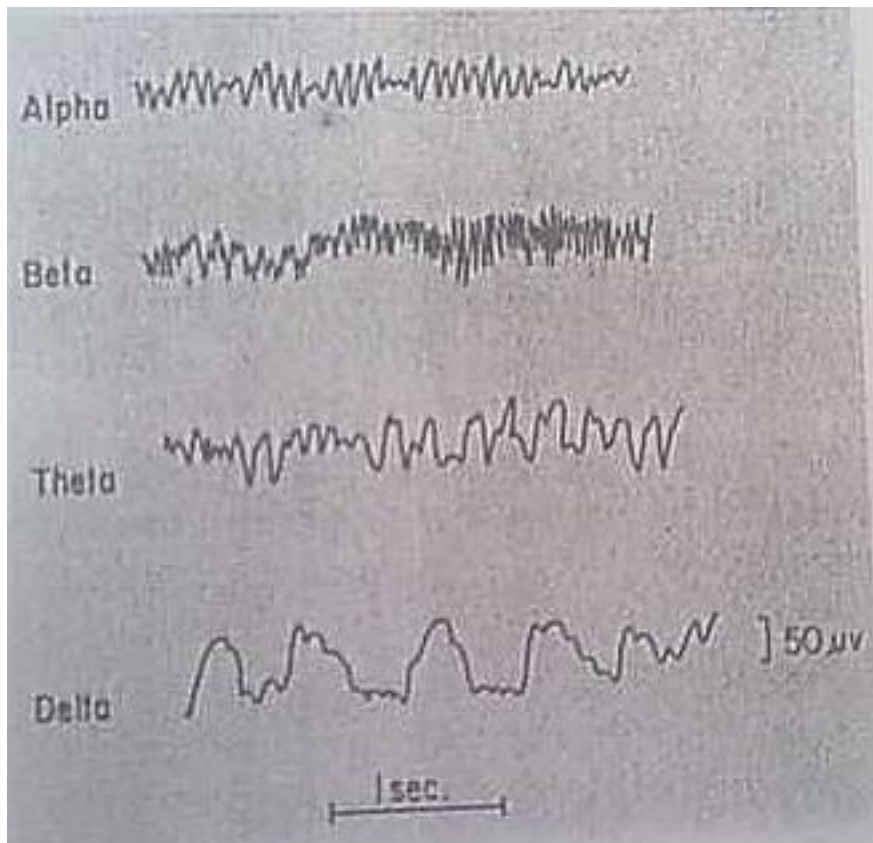


Figure: 3.3 Different types of normal electroencephalographic waves.

(iii) Oxytocin

Friedman (1978) described a feedback controlled infusion pump for improving the administration of oxytocin to induce or assist childbirth. The dose regimen mimics the physiological release of oxytocin to induce and regulate the intensity of contractions. Carter and Steer (1980) described a system to accelerate induced and spontaneous labours. The system uses intrauterine pressure as the measured variable. If the integrated pressure over 15 minute period exceeds 1500kPaS, the infusion rate of oxytocin is halved. If the integrated pressure is under 500kPaS, the infusion rate is incremented by 2mU/min.

Many other SAFCADs exist for the administration of drugs like neuromuscular blocking agents during surgery (using evoked myoelectric tension, etc. as feedback signal); antiarrhythmics and cardiac glycosides (using repetitive ventricular response as feedback signal); blood pressure – postsurgical hypertension (using mean arterial pressure as feedback signal); sodium bicarbonate, etc. The major obstacle to

SAFCAD development has been the availability of a reliable drug effect. Pharmacological response, especially as assessed by electrophysiological signals is generally a more suitable measurement variable for a SAFCAD than drug conc. (Cosgrove, 1985). Chemical assays, because they are generally time consuming compromise control system performance by adding a lag time to the feedback dynamics. Electrophysiological signals circumvent the problems of chemical assays. However, practical limitations prevent bioelectric signals from constituting a panacea for SAFCAD applications. Primary among these limitations is the lack of measurable effect of many drugs on bioelectric signals. Even if a drug affects a bioelectric signal, it may be very difficult to extract a quantitative measure of drug response from the signal (Cosgrove, 1985).

3.1.2: Exogenously Triggered systems

Implantable hydrogels can be made to be responsive to external stimuli like electrical, electromagnetic, sonic, stimuli, etc.. If the hydrogel is fabricated into a porous membrane having plugs fixed in place, the application or removal of the electrical stimulus would start or stop the exchange of a drug with body fluids. When the hydrogel implant is exposed to the stimulus, pores in the hydrogel membrane become wide-open and the contents of the implant are discharged at the site of implantation. The removal of the stimulus shuts off the valve as the membrane pores contract thereby stopping the flow of the contents. Thus the release of drug from such a device is at the operator's control according to patient's needs. This has been investigated for delivery of insulin in response to changes in glucose levels.

3.2: ENDOGENOUS TYPES

3.2.1: Self-regulating Modulated drug delivery devices

These have drug products within a patient using some other forms of sensors to regulate drug release. This is mainly by modifying the properties of pharmaceutical additives (excipients) like gums, starches, etc., or of the active ingredients to make them responsive to one physicochemical property or another like **blood glucose level, chemical responses of body fluids e.g pH, hydrostatic/osmotic pressures, temperature, enzyme-substrate reactions, metal concentration-dependent hydrolysis, ionic strength**, etc. These are discussed under self-

regulating, self-learning and targeted medicines in section 3.2. – 3.4). These are **closed-loop** control systems in which the controlled variable is detected, and as a result the system output is adjusted accordingly (self-regulated). In the self-regulated devices the release rate is controlled by feedback information without any external intervention.

God Almighty Himself is the greatest designer of self-regulating delivery systems: A healthy pancreas is a classical continuous feedback control system which monitors the concentrations of various metabolites and secretes three hormones at appropriate rates (i) insulin, (ii) its antagonist glucagon & (iii) somatostatin which inhibits the secretion of the other two.

(a) pH controlled self-regulating delivery devices

One means of achieving self-regulation in drug delivery is to use enzymes (enzyme-substrate interaction) or antibodies that can interact with specific molecules to produce a pH change which modifies the erosion rate of a pH sensitive polymer and the consequent release rate of an incorporated therapeutic agent.

These devices use hydrolytically labile, pH-sensitive polymer containing dispersed therapeutic agent that can vary erosion rate in response and in proportion to the pH change. **Ibrahim et al. (2000b)** have shown that the rate of theophylline release from *Cissus populnea* polymer (CPP) is more controlled by matrix erosion, while linearity (zero-order release) is more controlled by matrix swelling as given by the zero-order slopes and correlation coefficients of the release profiles. Employing a simple 2^n factorial experimental design, some functional relationship was established between erosion, swelling and porosity of CPP for theophylline release.

The ability to control the degree of swelling of polymers by varying the pH of the outer solutions presents several opportunities for self-regulated drug delivery. The most obvious application of this approach is in gastrointestinal tract where there is division into regions of differing pH. Oral delivery systems based on pH-sensitive gels that will release drugs in regions of the gut according to the pHs are thus possible. Erosion and swelling of gels remain relatively low when placed in media near the physiological pH of 7, but when placed in a highly acidic medium, they will swell at a rate that is sensitive to the pH and ionic environment. This could be

exploited to produce oral drug delivery systems that will not release their contents until they reach the stomach. Also drugs for treating peptic ulcers could be released at a rate determined by the pH of the stomach.

Examples

(i) Urea-Urease modulated system

Urease converts urea to NH_4HCO_3 and NH_4OH , thus a polymer that increases erosion rate with increasing pH is needed. An ideal polymer for this is a partially esterified copolymer of methyl vinyl ether and maleic anhydride which has been shown to undergo surface erosion with concomitant release of an incorporated therapeutic agent. The pH sensitivity of the polymer was demonstrated by Heller (1990) when he dispersed hydrocortisone (HC) in a hexyl half ester copolymer and the device surrounded by a hydrogel containing urease immobilized by glutaraldehyde cross-linking (Figure 3.4). This device has no therapeutic relevance, but established the feasibility of the concept as placing the device in solutions containing varying amounts of urea resulted in urea concentration dependent release of HC.

(ii) Glucose Oxidase – Glucose Modulated System

The need for improved diabetes therapy over the simple replacement of insulin by periodic injections is well recognized. Some polymers dissolve or swell more at low pHs by the reduction of their cross-linking. Addition of glucose in the presence of glucose oxidase produces gluconic acid thus lowering the pH of the environment. The increased swelling leads to release of more insulin as glucose concentration increases (Figure 3.5).

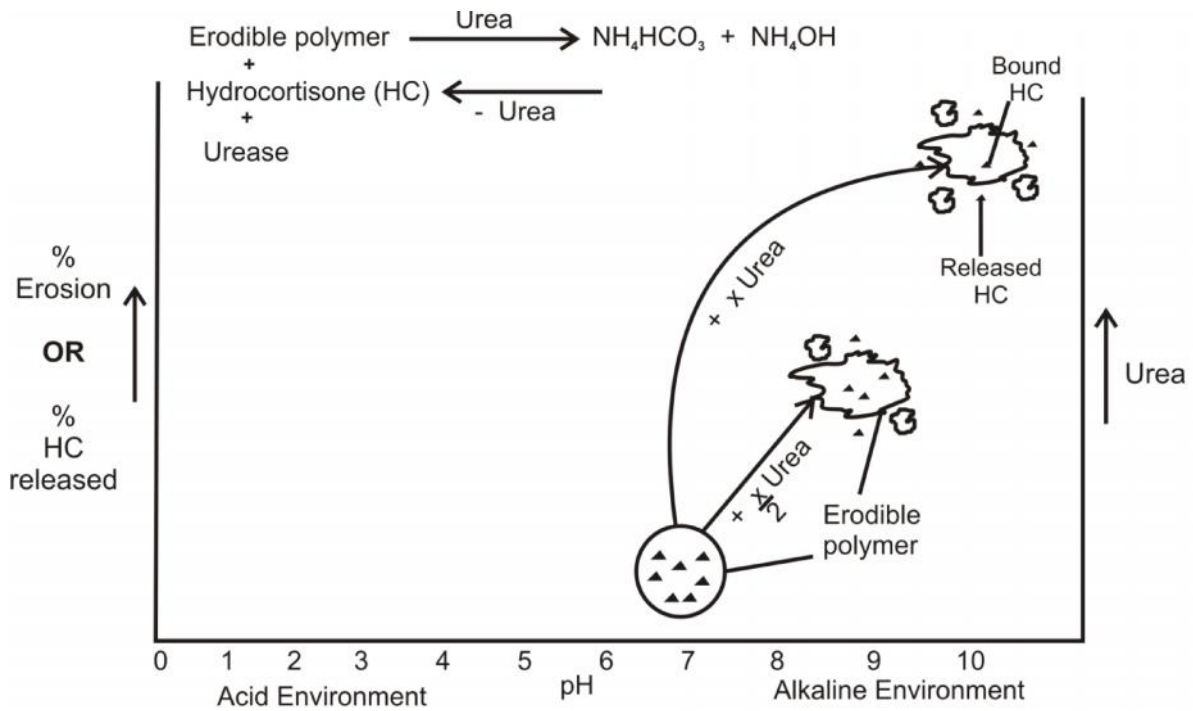


Figure 3.4: As urea level increases the environment becomes more alkaline (increased pH) according to chemical equation above. This increases the erosion of the polymer resulting in increased release of HC.

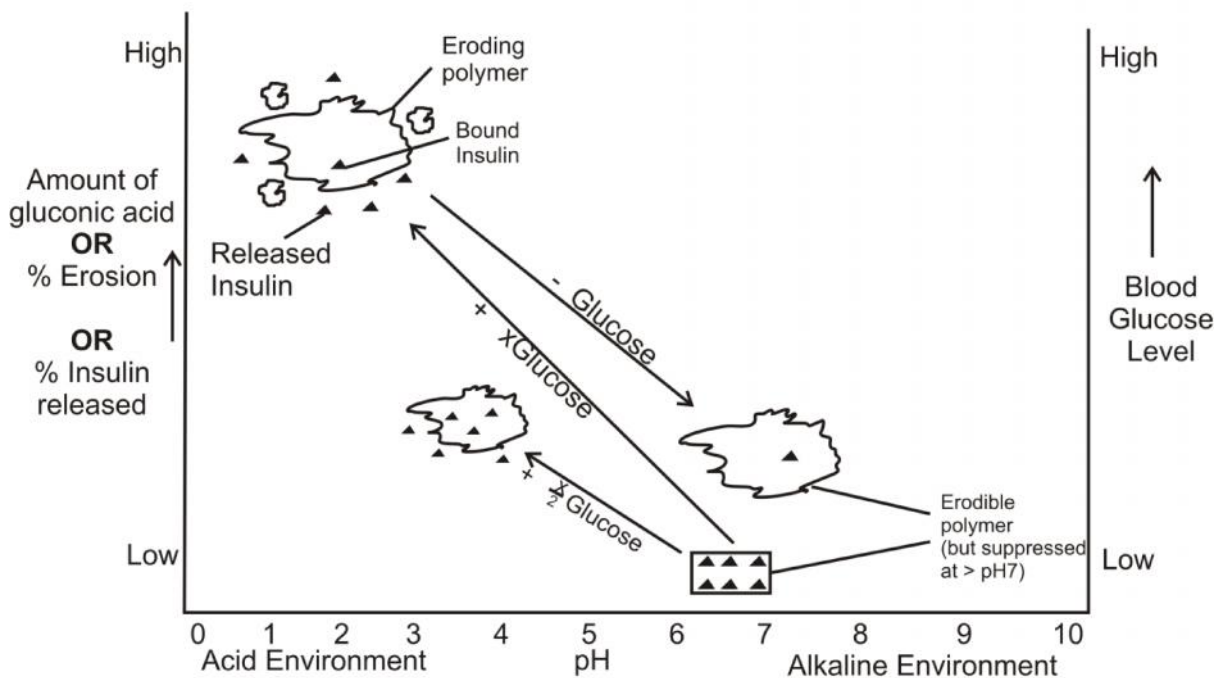


Figure 3.5: As blood level glucose increases, more gluconic acid is produced according to chemical equation above. This lowers pH, increases erosion of polymer, resulting in increased release of insulin.

An erodible polymer system containing insulin that is modulated by glucose-glucose oxidase reaction is clearly of considerable interest.

The reaction between glucose and glucose oxidase produces gluconic acid, thus this application requires a polymer that increases erosion rate with decreasing pH. A likely polymer candidate system is the poly (ortho esters) which contain a pH-sensitive linkage in the polymer backbone and which have been shown to undergo surface erosion with concomitant release of physically incorporated drugs (Heller *et al*, 1980). The evaluation of our CPP (**Ibrahim *et al*, 2000a**), showed that the material is not pH sensitive. While it is a very good material for sustained-release drug products, it would have to be modified to be considered for use in self-regulating products. The need for such modification is discussed in section 4.0 of this lecture.

(iii) Glucose – Dependent Reorganization of Phospholipid Membranes

Phospholipids can be made to release their drug contents in response to elevated concentrations of organic solutes of physiological interest. The approach uses an enzyme or mixture of enzymes to convert the solute of interest into a source of H⁺. The elevated local concentration of H⁺ is then exploited as previously described. An example is the use of the glucose oxidase to provide H⁺ in proportion of the local concentration of glucose.

Also, hydration of phosphatidylcholines in mixed solutions of PEAA and glucose oxidase provides vesicular dispersions. On adding physiological concentrations of glucose to the solutions, a depression of pH results with a consequent membrane reorganization from vesicular to micellar forms resulting in loss of turbidity.

The application of this approach for developing self-regulated insulin delivery systems is clear, which can also be applied to other substrate of medical interest.

Another approach is to use a modified insulin whose solubility depends on pH. When glucose is enzymatically converted to gluconic acid it causes a pH sensitive polymer to release the insulin in a pH dependent manner.

Interactions of poly (2-ethylacrylic acid) – PEAA with natural or synthetic phosphatidcholines

Tirreli (1990) in his work employed the interactions of poly (2-ethylacrylic acid) – PEAA with natural or synthetic phosphatidcholines. PEAA in water undergoes a sharp conformational transition near physiological pH, from an expanded coil in basic solutions to a compact globule upon acidification (Nachinkin *et al.*, 1967; Hay and Clark, 1977). This causes the PEAA chain to adsorb strongly to the lipid membrane (and other surfaces as well). Reorganization of the bilayer occurs in order to accommodate the adsorbed chains, this results in micellar, rather than vesicular arrangement (Figure 3.6).

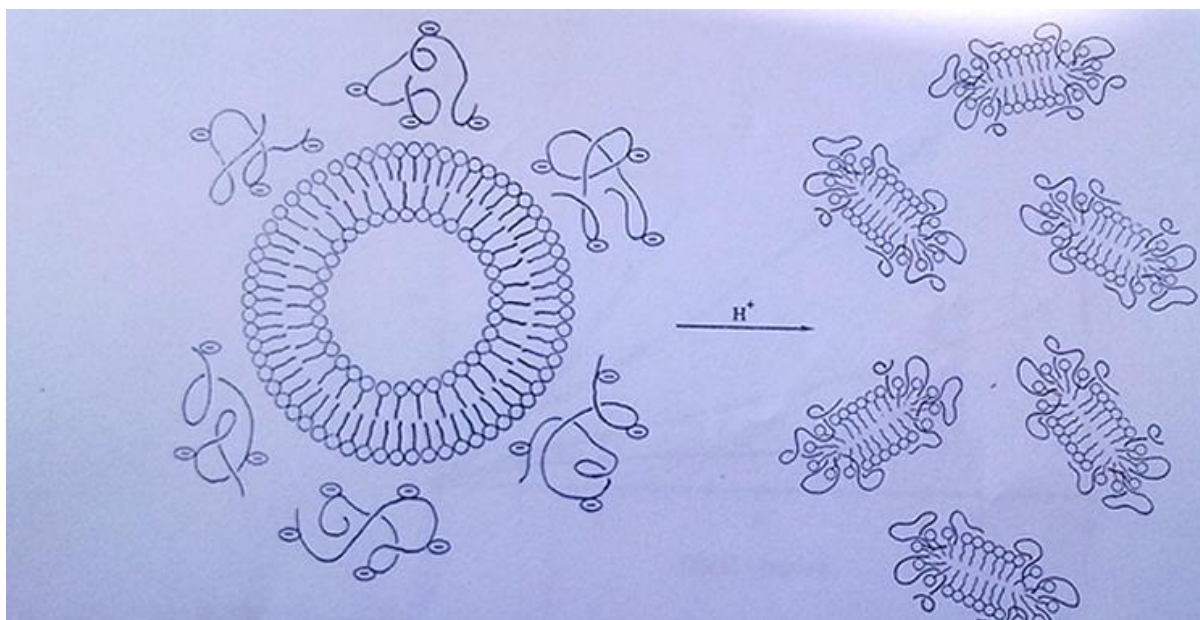


Figure 3.6: pH-Dependent reorganization of phospholipid vesicle membranes by PEAA (Tirrell, 1990).

The conversion from vesicles to micelles compromises the barrier properties of the membrane and allows rapid quantitative release of contents. PEAA has been found to provide high sensitivity to pH in the physiological range and in causing membrane reorganization. The phosphatidylcholines serve as convenient bilayer-forming surfactants of systematically variable structure. The phosphatidylcholines are the predominant lipids in the outer monolayer of mammalian cell membranes and are therefore non-toxic, non-immunogenic. The binding of PEAA to the bilayer is

required to ensure very small levels of free polyelectrolyte in systemic circulation. Tirreli (1990) was able to experimentally show the rapid release of the fluorescent dye calcein from vesicles of conjugated PEAA achieved by changing the pH of the system from 7.0 to 6.5. Sensitivity to pH in this range (7.4 to 6.5) is potentially useful in several areas of drug delivery in pathologic conditions that cause abnormal acidity such as inflammation or infection, certain tumor tissues, or ischemia. The precise pH response of PEAA – modified vesicles can be optimized by variations in polymer molecular weight, composition and stereochemistry.

(iv) Mechanochemical pump

The volume of a pH sensitive polymer gel will depend on blood glucose concentration due to lowering of pH as a result of formation of glucuronic acid by glucose oxidase which will charge up the gel. This principle has been used in the construction of a mechanochemical pump, which acts by the direct conversion of chemical energy due to changes in blood glucose activity, to a hydraulic force.

(b) Temperature controlled self-regulating delivery devices

Some hydrogels are viscoelastic soft gels at room temperature but become much firmer at body temperature.

Examples

(i) poly (N-isopropylacrylamide)

An aqueous solution of poly (N-isopropylacrylamide) has a critical transition temperature at 32 – 37°C. This gellation tendency is utilized to immobilize cells inside the gel matrix. A polymeric solution containing islets of Langerhans (insulin-releasing pancreatic cells) is loaded into a pouch with a semi-permeable membrane. When the pouch is implanted, the solution becomes a gel which immobilizes the cells. As glucose levels rise in diabetic patients, the islets would secrete insulin to maintain a normal glycemic level. It was demonstrated that free islets of Langerhans dispersed in a solution tended to aggregate and lost their viability quickly, while the cells immobilized in the gel matrix remained intact and viable much longer.

(ii) Temperature Sensitivity of Polyelectrolytes

The rate of the polyelectrolyte-driven reorganization of phosphatidylcholine membranes is dependent on temperature and passes through a maximum at the main melting transition of the lipid bilayer. This provides a potential basis for development of temperature-sensitive vesicles for use in delivery of therapeutic agents to targets characterized by local hyperthermia.

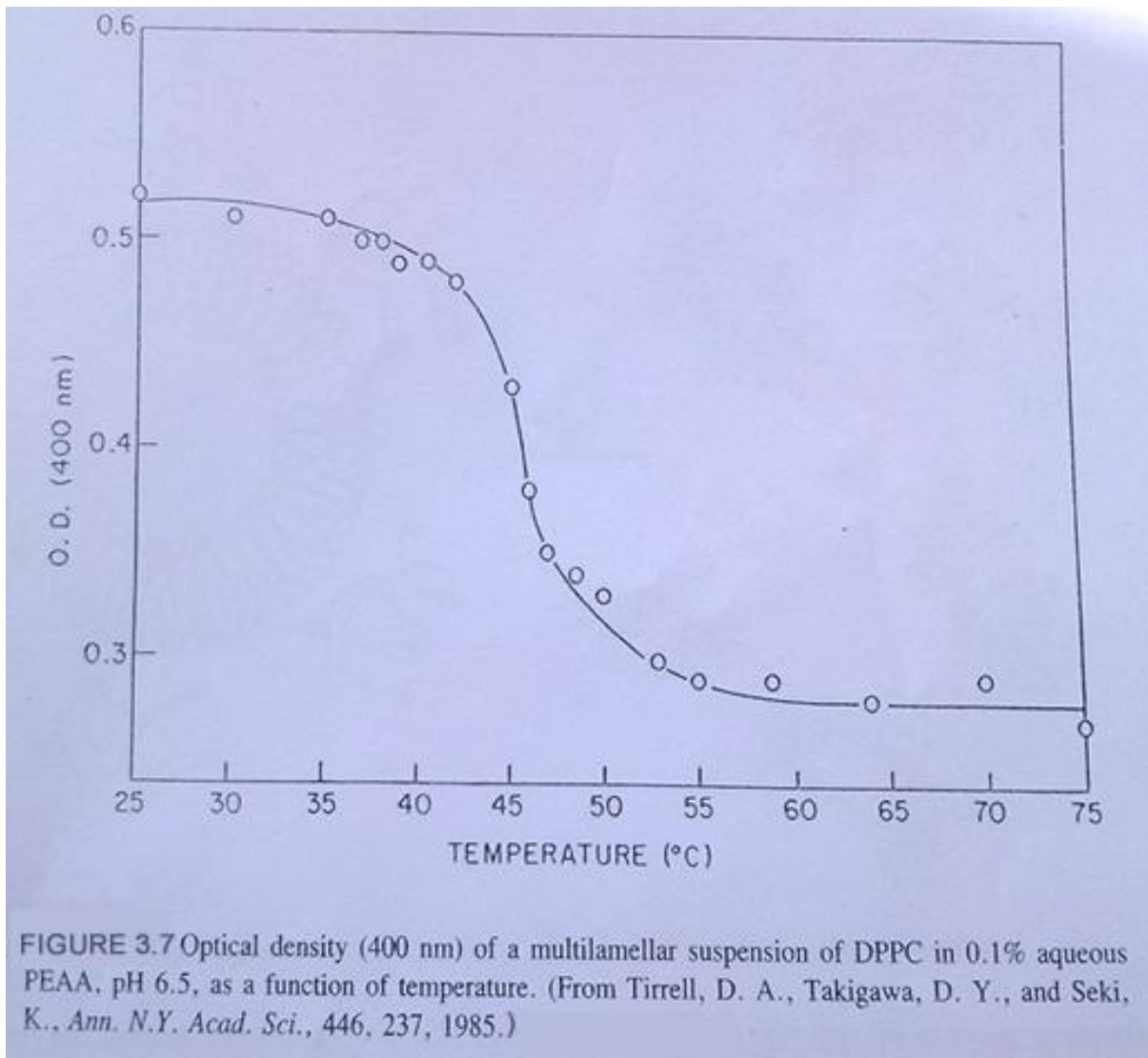
(iii) Dipalmitoylphosphatidylcholine (DPPC)

This melts at 41°C. Hydration of DPPC followed by addition of PEAA at room temperature and pH 6.5 produces a stable, turbid vesicular dispersion. On warming through the phase transition, the turbidity of the suspension rapidly disappears as a consequence of the PEAA-driven vesicle-to-micelle transition (Figure 3.7).

(iv) Devices for the eye, nasal and vaginal cavities

Poloxamer F127 undergoes phase transition induced by changes in temperature. At room temperature it remains a solution, but when instilled onto the eye surface (34 °C), or in the nasal cavity, or the vaginal cavity, the solution becomes a gel, thereby prolonging its contact time with the site of administration. However, the issue of ocular tolerability is a major concern due to the high polymer concentration (25% poloxamer) and the surfactant properties. Other temperature sensitive materials include ethyl(hydroxyethyl) cellulose, poly(acrylic acid). Gellan gum (an anionic polysaccharide) which forms clear gels with increased ionic strength due to sodium content of the human tears following instillation into the conjunctival sac (Wilson *et al*, 2001) has also been used for controlling drug release.

Ibrahim et al (2000c) in their studies using Differential Scanning Calorimetry (DSC), have shown that granulation and magnesium stearate influenced the plasticization of CPP as shown by their influence on the glass transition temperature (T_g) and softening point temperature (T_s). This in turn influenced the penetration of water into the CPP matrices and consequently, the rate of matrix swelling and release profile. The release characteristics of a directly compressed theophylline : CPP (3 : 1) matrix changed from rapid release to a good linear sustained-release characteristics when granulated, indicating thermal influence on CPP performance.



(c) Glucose-sensing hydrogels (Reversible cross-linking interaction)

Hydrogels can also be made to undergo sol-gel phase transformation depending on the glucose concentration in the environment using glucose-specific and reversible cross-linking interaction. Concanavalin A (Con A) provides this reversible interaction between chains of glucose containing hydrogels. A gel is formed by mixing glucose-containing polymers with Con A in the absence of external glucose. In the presence of elevated glucose levels, the gel becomes sol. The competition of free glucose against the polymer-bound glucose determines the gel-sol-gel transformations. It has been shown that diffusion of insulin is much slower in the gel state (low external glucose concentration) than in the sol state (high external glucose concentration).

This in effect gives a controlled release of insulin as a function of the glucose concentration in the environment.

3.2.2: Endogeneously triggered systems

Triggered drug delivery system can also be a device containing the active agent placed subdermally or in other appropriate body sites where it remains passive until a specific molecule appears in the tissues surrounding the device. The molecule then enters the device and triggers a programmed release of the therapeutic agent from the device. The device must recognize the presence of a specific trigger molecule in a complex mixture of physiological fluids, it is therefore essential that a highly selective sensing mechanism is used. This high selectivity can be provided by antibodies to the trigger molecule and thus current development of triggered devices is based on hapten-antibody interactions (Delvin and Tirrell, 1986; Borden *et al.*, 1987).

One important application of such a device is the rehabilitation of individuals that have developed an opiate dependence. In the application, after withdrawal therapy, the individual would be implanted with a device containing the narcotic antagonist naltrexone, and the device would be designed so that it can be triggered by morphine. As long as the rehabilitated addicts refrain from heroin, the device will remain passive and no naltrexone will be released. However, upon heroin intake which is rapidly metabolized to morphine (Ellis, 1948; Wright, 1942; and Way *et al.*, 1965), the device will trigger the release of naltrexone in amounts sufficient to displace morphine from its receptors and to thus neutralize the pleasurable heroin-induced effects. Another important application is contraception where a device could be triggered by the first indication of pregnancy (the appearance of human chorionic gonadotropin).

3.3: SELF-LEARNING DRUG SYSTEMS

3.3.1: Chronobiology

The cosmic environment and the temporal-spatial organization of life are time dependent resulting in rhythmic processes that are relevant to individuals/organisms as well as population dynamics and ecosystem development. From this

understanding developed the concept of chronobiology (time structured biology). The time structure of life include among others, tidal rhythms of about half a day (circa hemidian); daily rhythms (circadian) such as body temperature, systolic and diastolic blood pressure, heart rate, renal functions and plasma concentrations of various hormones; lunar rhythms about monthly (circa triguitan) such as the menstrual cycle; seasonal rhythms (3 monthly); annual rhythms (circannual) and life cycle rhythms (which differ between organisms but always include some variation on gestation, infancy, childhood, adolescence, adulthood, reproductive prime, decline and death). Certain diseases exhibit circadian time dependent profiles, thus drug delivery patterns can be further optimized by pulsed or self-regulated delivery, adjusted to the biological rhythms (Hrushesky, 2000).

Many endogenous peptides and proteins (including insulin) are naturally released in a pulsatile fashion and subject to complex feedback control mechanisms; consequently drug timing plays a crucial role in determining the observed effect (Hillery, 2001). According to this author, luteinizing hormone releasing hormone (LHRH) for example can give completely opposite effects depending on the timing of the administration. Pulsatile administration mimics the endogenous hypothalamic secretion and can be used to restore fertility in women with hypothalamic amenorrhea. However, chronic administration (e.g. a depot injection) evokes an initial release of up to several days to weeks, followed by suppression of gonadotrophin secretion. Chronic administration is used clinically in the treatment of sex-hormone responsive prostate and breast cancer.

3.3.2: Dosage adjustment based on chronobiology

Different timing of drug administration can cause variations in the pharmacokinetics (chronopharmacokinetics) and in pharmacologic response (chronopharmacodynamics). These variations can result in altered efficacy and/or intensity of side effects. Efforts are in progress to modify drug input to march these complex time courses. Self learning process for automatically adjusting a dosage of a drug administration to a person by drug delivery device has been developed.

Example (Pain relief medication)

Reports in literature exist for the timed administration of theophylline and corticosteroids to asthmatics, antihypertensive drugs, antiarthritic, anticancer, and anti-diabetic drugs, etc.

Pain is experienced differently at certain times of the day, therefore the administration of pain relievers should be adjusted accordingly. An invention by Krijnsen, *et al.* (2010) is claimed to anticipate the **pain experience** and to deliver pain relief medication by appropriate timing of the right amount of medication and by appropriate timing of turning off the medication to reduce side effects. The drug delivery device administers the drug in accordance with at least one recurring sequence resulting in adjustment of dosage of drug in successive cycles of the sequence in accordance with some feedback. The feedback is a demand on the delivery device to increase, decrease or maintain the dosage of the drug on the evaluation of the effect of the previous dose on the recurring sequence. Many diseases have a certain time period during which pain is worse than at other times (Krijnsen *et al.*, 2010). According to these authors, arthritis for example (a common inflammatory disease of the joints) runs on a biological clock. Rheumatoid arthritis is caused by immune system disorders which attacks components of the joints, while non-rheumatic arthritis (e.g. osteoarthritis) includes a wide range of degenerative diseases like the formation of crystals in the joints, wear and tear, trauma, or infection. The pain, swelling and stiffness of the joint in rheumatoid arthritis is more severe in the morning, whereas pain and stiffness in osteoarthritis is typically less intense in the morning than in the afternoon or evening. Ankylosing spondylitis is characterised by swelling and discomfort in the joints of the back. Studies have shown that the pain intensity in this disease condition is greatest between 6.00am and 9.00am, and least bothersome between noon and 3.00pm (Krijnsen *et al.*, 2010). The invention of these workers provides a process to prevent commonly occurring episodes of pain. This is achieved by a self-learning process for adjusting the dosage of substance administered to a person by a drug delivery device. The administration is in accordance to at least one recurring sequence, adjusting the at least one recurring sequence in response to a feedback. The dosing responds to variations of the individual in for example, experiencing pain. The recurring sequence is any rhythmic cycle such as circadian, ultradian, and infradian sequences. The

process according to the invention learns from the person's feedback and is able to prevent the person from feeling pain by appropriate dosing, through the use of microcomputers, micro-pumps, valves, flow channels, reservoirs, etc.

3.4: TARGETED DRUG DELIVERY

3.4.1: The need for selectivity in drug action

Drug action selectivity ranges from modest to nil, and lack of selectivity is a major obstacle in optimising drug action. The usefulness of drugs will be enhanced if they can exert their effects selectively on target sites. The therapeutic potential for certain cells and tissues coincides in most cases with toxicity of the same agents for other cells and tissues. The most striking example of this dilemma is shown by anticancer drugs, which in general match a cytotoxic effect with severe side effect on unaffected organs. The concept of "magic bullet" as developed by Paul Ehrlich in the early 20th century proposed that drugs reach the right site in the body, at the right time, at the right concentration. The potentials of novel peptide and protein drugs, vaccines, genes and oligonucleotide therapies (biotherapeutics) to revolutionize the treatment or prevention of disease is severely compromised by the significant delivery and targeting obstacles which prevail in the body, such as zero or minimal drug absorption, unwanted distribution, and premature inactivation and elimination (pharmacokinetic obstacles). The drug should not exert side-effects, neither on its way to the therapeutic target, nor at the target site nor during the clearance process.

3.4.2: Identifying therapeutic targets

Progress in molecular biology and biotechnology give better understanding of receptor sites and allows the engineering of protein structures that will target the receptors. Proteomics and genomics provide means of identifying differences between normal and diseased tissue which may be used for targeting of drugs to particular tissues. Genomics is the systematic study of the structure and function of mammalian genetic information, e.g. the systemic analysis of the genes and proteins that encode drug target receptors reveal the molecular architecture and molecular mechanisms by which the receptor proteins work. The rapidly growing field of genomics will in the future be used to identify specific receptors for targeting

purposes using robust molecular approaches for building specific delivery and activation characteristics into broad classes of drugs (Karsa and Stephenson, 1996).

3.4.3: Administration routes

(a) Direct application

In the simplest form, drug targeting can be achieved by local application of creams, ointments, lotion on the affected area of the skin; or the direct injection of an anti-inflammatory agent into a joint.

Sophisticated drug targeting systems are also available particularly for oral and parenteral delivery.

(b) Oral route

Oral delivery systems are available to achieve site-specific delivery within the g.i.t; for example targeting the drug to the small intestine, colon, or gut lymphatics using enteric coated tablets, prodrugs, osmotic pumps, colloidal carriers and hydrogels.

Targeted Drug Delivery to the Colon

Colon-specific delivery of drugs may be required for local disorders of the colon e.g. ulcerative colitis, Crohn's disease and carcinoma of the colon. The colon can also be used as an absorption site. Strategies for colon-specific drug delivery include the use of sustained-release formulation, enteric-coated dosage forms and osmotic pumps (Lee and Yang, 2001). Another approach is the use of a prodrug which is metabolized by enzymes found in the colon, e.g. menthol- β -glucuronide, which is stable at various pHs and in other parts of the rat gut, but undergoes accelerated hydrolysis in the rat cecum and colon. Other examples are the glucoside and glucuronide prodrugs of dexamethasone. These prodrugs are relatively poorly absorbed in the upper gastrointestinal tract but are rapidly hydrolyzed into dexamethasone and glucuronic acid once in the colon. Other classical examples include prontosil and sulphasalazine, on reaching the colon anaerobic bacteria reductively cleave the azo bonds and release the active agents (sulphanilamide and 5-aminosalicylic acid) respectively, and a carrier moiety (Lee and Yang, 2001). This principle of azo reduction has led to the introduction of azo coating which has been shown to promote the oral administration of insulin and desmopressin in rats, while

some other azo polymer systems have demonstrated potential for the systemic delivery of vitamin B12 and ibuprofen.

Enteric-coated tablets

Some tablet coatings are resistant to gastric juices, but readily dissolve in the alkaline environment of the small intestine. Common polymers used for enteric coating include methacrylic acid plus ethyl acrylate copolymers (Eudragit L 30D), cellulose acetate phthalate (Aquateric) and polyvinyl acetate phthalate (Coateric). These polymers exhibit pH dependent solubility, being insoluble in gastric acid but soluble at intestinal pH. They are able to prevent gastric irritation of drugs or protect drugs from destruction by gastric acid or enzymes. Other applications of targeted oral delivery include drug targeting to the **Peyer's patches** and to the **lymphatics**.

(c) Parenteral administration

Technologies for parenteral targeted drug delivery are most advanced. The technologies are concerned with delivering drugs to specific targets in the body and also to protect drugs from degradation and premature elimination.

Targeting of drugs to tissues can be of two types, namely, passive and active targeting.

(a) Passive Targeting

This exploits the "natural" passive distribution of a drug carrier in the body, and no homing device is required. For example, particulate carriers tend to be phagocytosed by cells of the mononuclear phagocyte systems (MPS), thus the drug will tend to accumulate in the liver and the spleen. After phagocytosis, the carrier and the associated drug are transported to lysosomes, and the drug is released upon disintegration of the carrier in the cellular compartment. Such targeting to the liver has some clinical applications in the treatment of macrophage associated microbial, viral or bacterial diseases like leishmaniasis, the treatment of some lysosomal enzyme deficiencies, the immunopotentialization of vaccines, etc. Passive targeting can also deliver drugs to site of inflammation or tumor cells.

(b) Active Targeting

A homing device is attached to the carrier system to effect delivery to a specific cell, tissue or organ. Receptors on Target sites under physiological conditions can differ and have different cell-specific ligands. For example, galactose can be used to target a drug carrier to parenchymal liver cells. Other receptors may become available under pathological conditions which include:

- (i) Antigenic sites on pathogens (bacteria, viruses, parasites)
- (ii) Infected host cells expressing specific antigenic structures
- (iii) Tumor-associated antigens (i.e. antigenic structures specifically occurring at the surface of tumor cells).

Drugs used in the treatment of diseases that are life threatening or that dramatically affect the quality of life are prime candidates for formulation into Drug Delivery and Targeting Systems (DDTS). Such drugs include those used in the treatment of cancer, life-threatening microbial, viral and fungal diseases, chronic diseases such as arthritis, etc.

A DDTS generally comprises of three functional units, namely:

- (i) The active moiety: to achieve therapeutic effect
- (ii) The carrier system (soluble or particulate): to effect a favourable distribution of the drug, prevent the drug from metabolism, protect the drug from early clearance
- (iii) A “homing device”: to specifically target the drug to the target cells or target tissue.

3.4.3: Drug Carrier Systems

The body is highly compartmentalized, and the ability of a macromolecule or particulate carrier to move around depends on its physiochemical properties like molecular weight/size, charge, surface hydrophobicity and the presence of homing devices. The smaller the size, the easier a molecule can passively move from one compartment to another. If a therapeutic target is located outside the blood circulation and if normal anatomical conditions (continuous endothelial lining on a

basal membrane) exist around the target site, a small-sized macromolecular carrier must be selected for possible endothelium penetration.

Furthermore, the effect of macrophages in blood circulation (e.g. kupffer cells in the liver) can easily clear particulate carriers by phagocytosis. Typically, the phagocytic uptake by the cells of the reticuloendothelial system (RES), existing in the liver, spleen, lung, bone marrow, lymph nodes (fixed cells) and blood monocytes, and tissue macrophages (molecule cells) must be considered and precautions taken against it.

Technology is available to reduce uptake by macrophages. The process of “steric stabilization” (Crommelin *et al*, 2001) involves the coating of the delivery system with synthetic or biological materials, which makes it energetically unfavourable for other macromolecules to approach. A standard approach is to graft hydrophilic, flexible poly(ethylene glycol) - PEG chains to the surface of the particulate carrier. The PEG forms a repulsive steric layer which reduces adsorption to the macrophages.

A further consideration is that under pathological conditions, endothelium exhibits modified characteristics. Permeability fenestration is generally enhanced, for example, the endothelial permeability in inflammation sites can be increased. Also necrotic tissue affects tumor cell permeability.

(a) Soluble Carriers for targeted drug delivery

These include antibodies and soluble synthetic polymers such as poly (hydroxypropyl methacrylate) poly (lysine, Poly(aspartic acid), poly (vinylpyrrolidone), poly(N-vinyl-2pyrrolidone-co-vinylamide) and poly(styrene co-maleic acid/anhydride).

These carriers permeate the body compartmental barriers better than particulate carriers. The relatively simple homing device e.g galactose is attached for targeting to the liver, alternatively, more complicated devices such as antibodies, or antibody fragments can be used.

(b) Soluble Polymeric Carriers

Soluble carriers together with homing devices aim to improve drug disposition and also protect the system against premature inactivation. The system enters target cells by the process of pinocytosis and reaches the lysosomes where it is exposed to the actions of degradative enzymes, resulting in the release of the active drug into the cytoplasm and other parts of the cell. Examples of soluble macromolecular carriers include poly(N-(2-hydroxypropyl) methacrylamide (pHPMA), cytotoxic neocarzinostatin (NCS) which is transformed to styrene-maleic-anhydride-neocarzinostatin (SMANCS).

(c) Particulate carriers for drug targeting

These have size range of 0.02 μm to about 10-30 μm . The drug is physically associated to the carrier and drug release kinetics are generally controlled either by diffusion transportation or matrix degradation.

The advantages of this type of carriers include:

- (i) The high drug loading
- (ii) The drug does not have to be chemically attached to the carrier
- (iii) A considerable degree of protection may be conferred on the drug.

However, they have the limitation of inability to cross intact endothelial barriers of cells. Microparticulate carriers are phagocytised by the macrophages of the RES thereby rapidly concentrating in the liver and spleen. Examples of particulate carriers include liposomes (conventional liposomes, immunoliposomes, cationic liposomes), polymeric micelles poly(alkyl cyanoacrylate) nanoparticles, lipoproteins, etc.

3.4.4: Homing devices

Antibodies raised against a selected receptor are extensively used as homing devices and modern molecular biotechnology permits the production of large amounts of tailor-made "homing" devices, such as the 1gG antibody. Antibodies (monoclonal-mouse derived and humanized or human antibodies) have received the

most attention as potential homing devices, while other potential candidates like cytokine and growth hormone are emerging.

Theoretically, an endless number of antibodies can be formed by inducing the body with suitable antigens (Figure 3.8). Non protein materials or haptens may be conjugated to a protein to form an antigen. Monoclonal antibodies are highly specific and recognize only one antigenic determinant or receptor site.

EXAMPLES

(i) Plasmid-based Gene Therapy

Genes are segments of DNA that provide information to cells for protein production. Gene therapy is a method for the treatment or prevention of disease by using genes to provide the patient's somatic cells with genetic information necessary to produce specific therapeutic proteins needed to correct or modulate a disease (Mahato and Tomlinson, 2001). The gene delivery system distributes plasmids to the desired target cell. Once inside the cytoplasm, the plasmid translocate to the nucleus, where gene expression begins leading to the production of therapeutic proteins.

(ii) Prodrugs

Prodrug-based technologies for cell-specific drug delivery offer an alternative approach to enhance therapeutic activity through chemical modification of known compounds. After administration or absorption of a prodrug, the active drug is usually released by either chemical or enzymatic, hydrolytic or reductive processes (Figure 3.9). Prodrugs can be targeted to particular sites in the body through mechanisms given in (a) – (d).

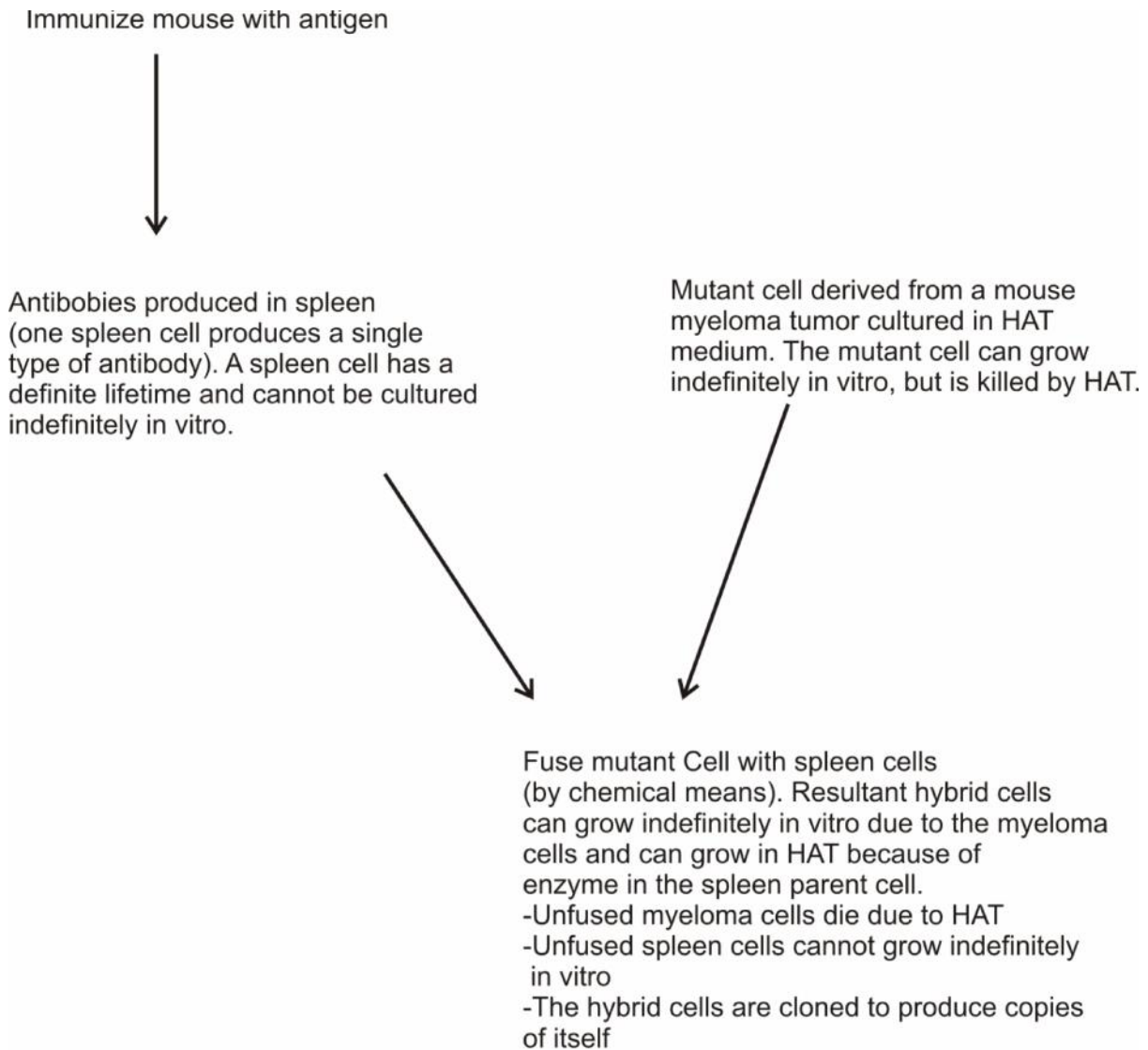


Figure 3.8: Production of Specific monoclonal antibodies that act as homing devices for targeting cancer cells.

(a) Site-specific enzyme-based delivery systems

These utilize enhanced enzyme or chemical activity of a particular cell type. Prodrugs are designed to ensure that the release of the active drug only occurs at its site of action. Improved selective localization of anticancer agents to neoplastic tissue may be using non-toxic prodrugs which release the active drug within the tumor cell as a result of enhanced activity in the cell, (A) in Figure. For example, the prodrug cyclophosphamide is initially activated by hepatic cell enzymes to 4-

hydroxycyclophosphamide which is then specifically converted to the alkylating cytotoxic phosphoramidate mustard in the target cell.

An alternative approach is based on the fact that blood supply to large solid tumors is disturbed and the internal regions are often non-vascularized. The cells become deprived of oxygen (hypoxic), which enhances the reductase activity in these hypoxic tissues which act on selective chemical prodrug-delivery system. Certain aromatic, heterocyclic nitro-containing compounds (e.g. the 2-nitro-imidazole compound misonidazole) can be reduced in hypoxic environment to produce intermediates which then fragment into cytotoxic alkylating species, (B) in Figure.

More recently, hypoxia in rheumatoid arthritis has been thought to also offer opportunities to specifically deliver anti-inflammatory agents to arthritic joints using bio-reductive prodrugs. It is hoped that the development of genomics differential expression of enzymes in diseased and normal tissues, will allow the future development of prodrug-based delivery systems to specific targets.

(b) Redox-based drug delivery (“Trapping”)

This approach has been used in delivering drugs across blood-brain barrier (BBB). Usually, the BBB is impenetrable to highly polar drugs. This may be overcome by using lipophilic prodrugs, however, the increased lipid solubility may enhance uptake in other tissues that can result in increase in toxicity. Furthermore, therapeutic levels of lipophilic prodrugs in the brain can only be maintained if there is an equivalent constant plasma concentration. These problems may be overcome by utilizing a drug delivery system which relies on “trapping” a prodrug in the brain by oxidizing the prodrug to a less membrane permeable derivative, (C) in Figure. This approach has been used to enhance the CNS penetration of the nerve gas antagonist pralidoxime using a non-polar prodrug that crosses the blood-brain barrier but is then rapidly oxidized to the active but less membrane penetrating form and therefore gets trapped in the CNS. In the periphery (i.e. outside the CNS) metabolism and elimination removes excess drug and metabolic products, thus reducing systemic side effects.

(c) Antibody-directed enzyme prodrug therapy(ADEPT)

It is possible to target drugs to specific cells through their surface ligands using antibody-directed enzyme prodrug therapy (ADEPT). In its application to targeting tumor cells, an enzyme is conjugated to an antitumor antibody which localizes in the tumor by an antibody-antigen interaction, (D) in Figure. The bound enzyme-antibody conjugate ensures that an administered prodrug is converted to the cytotoxic compound only at the tumor site. For example, cytosine deaminase has been used to generate 5-fluorouracil from the 5-fluorocytosine prodrug at tumor sites which increases drug delivery to the tumor 17 fold.

Recently, a β -lactamase enzyme antitumor antibody conjugate and a cepham sulfoxide derivative of taxol (Protax) has been investigated for treating breast cancer. The localized β -lactamase enzyme, which is not normally found in any other tissues, ensures selective release of taxol from protax at the tumor site.

(d) Gene-directed enzyme prodrug therapy (GDEPT) – “Suicide genes”

Suicide genes can be encoded for nonmammalian enzymes which can convert a prodrug into cytotoxic agent. Cells which are genetically modified to express such genes essentially commit metabolic suicide on the administration of the appropriate prodrug. Viral vectors have been used to deliver suicide genes like herpes simplex thymidine kinase and *Escherichia coli* cytosine deaminase, (E) in Figure.

(iii) Mechanised nanoparticles

These are nano-sized drug delivery systems that only release their payloads in specific pH condition for targeting cancer cells as developed by some United States researchers (Angelos *et al*, 2009). The particles have nanovalves which are “stalks” carrying rings and control the release of their payloads. At a pH lower than 5.4 all the nitrogen groups on the stalk are protonated and the ring sits in the “open position” letting molecules leave or enter the nanoparticles.

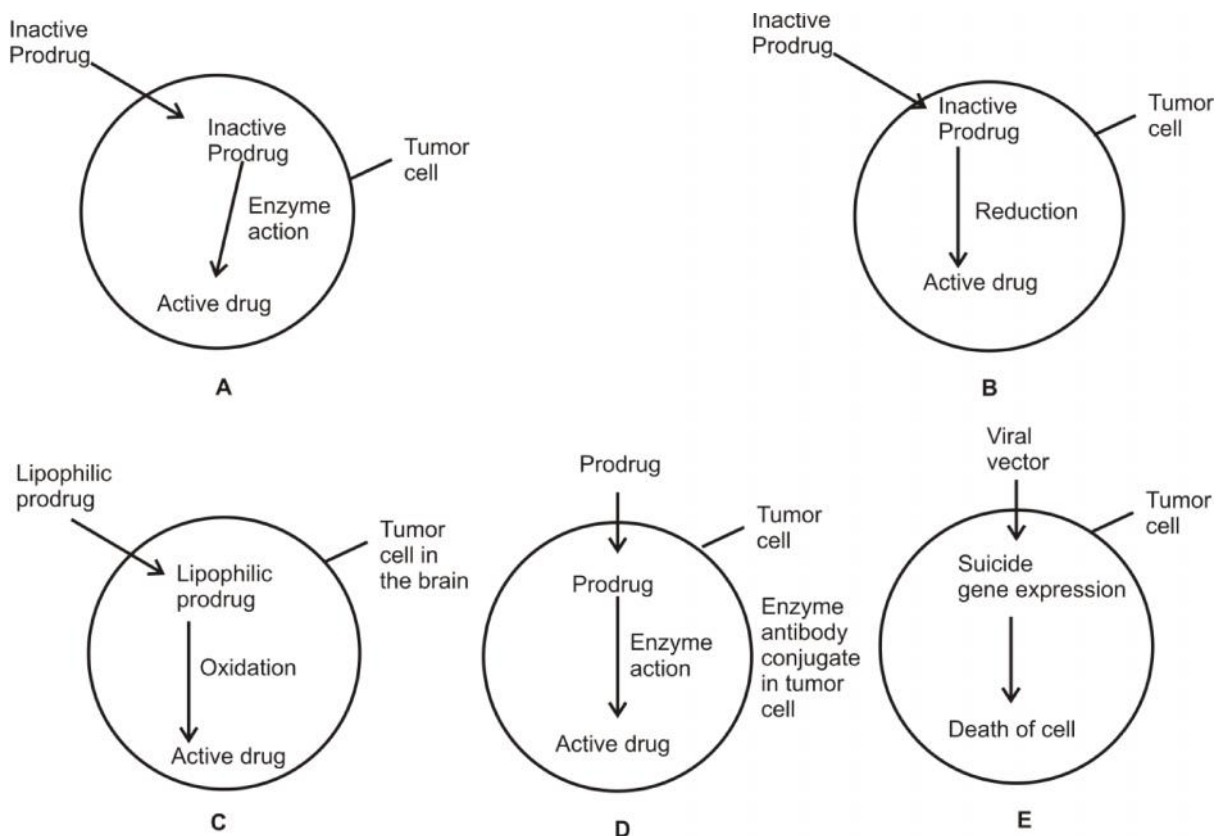


Figure 3.9: Examples of Prodrug applications in the killing of Cancer cells

When the nanoparticles become less acidic ($\text{pH} > 5.4$) the ring moves over two ammonium groups into the “closed position” due to the deprotonation of anilinium groups. This stops any molecules escaping from the nanoparticles. If the solution is adjusted to $\text{pH}10$, both the ammonium and anilinium groups are deprotonated causing the rings to fall off the stalks and releasing the entire payloads (Figure 3.10).

The pH at which the nanoparticle opens and closes can be tuned by adjusting the substituent on the aniline in the para position to the nitrogen. An expert in this field (Alberto Credi of the University of Bologna, Italy) believes that this system is particularly important as the pH in tumour cells is very different from that of healthy cells, making pH a very good trigger for delivering anticancer drugs.

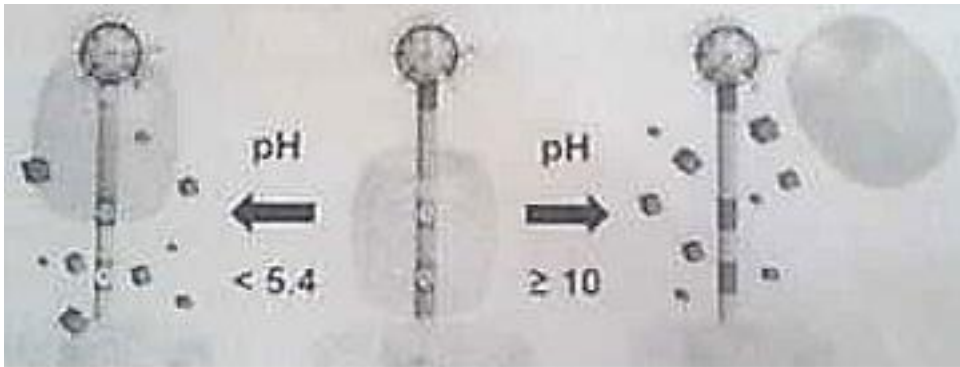


Figure 3.10: The mechanised nanoparticles respond to particular pH conditions, either releasing their payload or 'closing' to prevent molecules leaving or entering

Again, the modification of our CPP may produce a pH sensitive material that can find application in drug targeting.

(iv) Liposomes

These lipid vesicles have recently been used as drug carriers in the therapy of infectious diseases (antibacterial, antifungal, antiparasitic, anticancer – immunomodulation, and antiviral drugs). Liposomes are closed structures composed of lipid membranes surrounding closed water-filled compartments. The membrane structure can be a variety of substances including natural or synthetic phospholipids, sterols, fatty acids, glucolipids or even proteins (Szoka and Papahadjopoulos, 1980; Cullis *et al.*, 1987). The most promising applications (a) – (e) below are:

* Liposomal drug delivery to the Reticulo endothelial System (RES) the site of pathogenic infections afflicting the RES.

* The therapy of systemic fungal infections which prevents host toxicity by permitting selective transfer of the drug to the fungal pathogens but not to the host cells.

(a) Antibacterial Actions

Many important classes of antibiotics such as the amino-glucosides and the beta lactam antibiotics penetrate poorly into the intra cellular environment (called pharmacological sanctuary – Juliano, 1989). A number of investigators have demonstrated increased effectiveness of several different antibiotics against intracellular pathogens during in vitro experiments when the drugs were given in liposomal form probably due to improved uptake by pathogens. Nacucchio *et al.*

(1985) showed that the incorporation or bonding of piperacillin to liposomes protected the drug against beta lactamases and thus enhanced in vitro anti *staphylococcal* activity.

(b) Antifungal Actions

The main stay of antifungal therapy is amphotericin B (a polyene antibiotic). It is an extremely effective, broad spectrum anti-fungal agent, but it is also extremely toxic (Juliano, 1989). Studies indicate that liposomal amphotericin B (AMB) can rapidly and effectively transfer from the liposomal carrier to fungal cell membranes, but not to mammalian cell membranes thereby reducing unwanted effects.

(c) Antiparasitic Actions

Leishmaniasis is a parasitic disease that is common in the tropical and subtropical regions. The organisms colonize the phagocytic vacuole of macrophages and related cells (one of the body's key host defense cells). The drugs most used against leishmaniasis have been pentavalent antimony compounds like sodium stibogluconate, while aminoquinolines and amphotericin B have been used as secondary drugs (Pratt and Fekety, 1986). Alving *et al.* (1978) have shown that the incorporation of antimonial compounds into liposomes produced a remarkable enhancement of their potency against Leishmaniasis in an animal model. Liposomes have also been used as carriers for antimalarial drugs. The toxicity of primaquine was reduced about 4 fold when the drug was incorporated into lipid vesicles, with no loss of therapeutic efficacy (Pirson *et al.*, 1980).

(d) Immunomodulation (for infections and cancer therapy)

Macrophages are key cells in the host defense systems against cancer and infectious diseases. In-vivo activation of macrophages by the administration of soluble immunomodulators (like lymphokines and muramyl dipeptide bacterial cell wall product) has had a limited success due to rapid degradation and/or excretion. Some investigators have demonstrated that the macrophage activating effects of lymphokines and muramyl dipeptide could be markedly enhanced by incorporation into liposomes (Fidler, 1987). The lipid vesicles tend to promote uptake and binding of the immunomodulators. There is evidence that activated macrophages are able to

distinguish between tumor and non-tumor cells, and to selectively kill tumor cells (Fidler, 1981; 1982).

(e) Antiviral Actions

Work in this area have aimed at incorporating drugs into liposomes to inhibit the replicative cycle of virus, and the use of liposomal immunomodulators to enhance the host response to viral infection through macrophage activation. There is a realization that macrophages may be a major reservoir of HIV (Streicher and Joynt, 1986) and thus they may contribute significantly to the pathogenesis of AIDS. This suggests that there may be numerous attempts to use liposomes to target anti-HIV drugs to macrophages.

4.0: BRINGING IT ALL HOME

Having looked at these advanced drug delivery systems and medicines, I would want to now briefly look at the role that our local pharmaceutical raw materials should play. Natural and synthetic polymeric materials have been used frequently in the development of advanced drug systems.

4.1: Locally available raw materials

Nigeria is blessed with abundant sources of natural polymers such as:

- (i) Polysaccharides: gums and mucilages - many of which are used as edible soups like okra, ogbono, okoho, etc.
- (ii) Carbohydrates: starch, glucogen - from our food materials like the tubers, grains, etc;
- (iii) Cellulose: from many fibrous materials and their wastes like sugar cane, groundnut and rice husks, etc;
- (iv) proteins (Gelatin): from animal skin and bones;
- (v) polyelectrolytes: such as sulfonate and carboxymethyl cellulose, poly(vinyl alcohol), poly(ethylene oxide), polyvinyl pyrrolidone (PVP), polyelectrolyte complexes (like gelatin-gum arabic complex), etc.

4.2: Cross linking and degradation of hydrogels

Water-soluble, natural polymers can form gels by cross linking individual polymer molecules. These types of polymers are cross-linked with biodegradable cross-linking agents. The choice of cross linking agents depends on the functional groups available on the polymer chain. Hydrogels are usually made up of hydrophilic polymer molecules which are cross linked either by chemical bonds or other cohesion forces like ionic interaction, hydrogen bonding or hydrophobic interaction.

Many proteins and polysaccharides are able to form physical gels (three-dimensional network), which are usually mechanically weak. To enhance the mechanical strength, physical gels can be modified by chemical cross linking.

Polyelectrolytes can have ionic interactions between two oppositely charged polyelectrolytes which lead to a complex having properties quite different from the individual components. . Nonequimolar polyelectrolytes complexes are usually pH sensitive (Park *et al*, 1993) that can be good biosensors for self-regulation of drug release.

Hydrogels obtained from these polymers could be classed into three different categories:

- (i) The polymer backbone chain can be degraded by either hydrolysis or enzymatic degradation.
- (ii) The cross linking agent can be degraded while the backbone may remain intact.
- (iii) The pendant groups attached to the polymer may be cleaved while the polymer backbone and the cross linking agent remain unchanged.

The mode of degradation affects the release pattern of drugs from the polymeric matrix and their suitability as biomaterials. It is known that natural polymers such as proteins and polysaccharides undergo degradation by hydrolysis and are therefore suitable as biomaterials.

4.3: The need to develop our locally available raw materials

Many of our researchers have studied the formulation functions of locally available materials including the present author as follows:

- (i) Binding Properties: Using tablet properties associated with cohesiveness (binding) such as hardness, friability and to a lesser extent disintegration time, **Ibrahim** and Onyejekwe (**2003**) showed rapid changes in these parameters as *Cissus populnea* polymer (CPP) concentration increased over a low range of 1.0 – 2.94%w/w. This could be used to advantage over gelatine and acacia, as the rapid changes could improve hardness and reduce friability with little increase in CPP concentration. However, disintegration time would have to be monitored to ensure that it stays within the official limit. Similarly, Isah *et al.* (2008); Musa Autamashin, *et al.* (2011) have studied binding properties of maize starch mucilage, etc.
- (ii) Disintegrant/Diluent properties: **Ibrahim et al. (2000a)** have reported that at high concentration (20%w/w and higher) CPP matrices do not disintegrate, but rather swell and erode over periods of 24 hours and more. Isah *et al.* (2006); Autamashin *et al.* (2011) have reported effect of diluents type on formulation.
- (iii) Direct Compression Properties: Olowosulu *et al.* (2011a, b); Shittu *et al.* (2012) have reported their work on locally sourced coprocessed maize starch and acacia gum(StarAc), 3-composite “Micrcrystarcillac” for direct compression tableting.
- (iv) Thermal Properties (**Ibrahim et al., 2000c**): This has been presented earlier in section 3.2.1(b).
- (v) Microbial qualities: For CPP to be industrially acceptable for manufacturing medicines, its microbial quality must meet official specifications. **Ibrahim** and Olorunfemi (**2002**) in their studies showed that CPP gave microbial counts that were within acceptable limits for starting materials of plant source, and the absence of pathogens like *Staphylococcus aureus*, *Salmonella spp.*, *Pseudomonas aeruginosa* and *Escherichia coli* when cultured in respective selective enrichment media. The study showed that the method of extraction of CPP appeared to allow the introduction of

gram-positive Bacilli from the air into the product. However, CPP's low water activity did not allow the multiplication of these organisms.

- (vi) Stability studies: **Ibrahim et al. (2003b)** studied the sustained-release and potency stabilities of theophylline tablets formulated with CPP both under shelf and accelerated storage conditions of elevated temperature and humidity. The tablets did not exhibit changes in release profile and potency, but were highly affected by elevated temperature and humidity. The elevated temperature appeared to be enhancing some chemical changes/interaction in the tablet as shown by the unexplained high spectrophotometric absorbances that could not even be measured.
- (vii) Suspending properties: **Ibrahim and Dawes (2004)** studied a synthetic hectorite protective colloid and viscosity stabilizer (Laponite) alone and in a blend with sodium carboxymethylcellulose (SCMC) which exhibits shear thinning characteristics for suspending sulphamerazine. From the rheograms, the blend had higher viscosity and yield value in the presence of sulphamerazine than either material alone. The blend was resistant to change in the presence of sulphamerazine and was therefore an efficient suspending agent, in contrast to laponite alone whose rheogram changed from pseudoplastic to Newtonian patterns, but gave a flocculated suspension with large sedimentation volume and clear supernatant. The sediment was also easily redispersed. SCMC alone on the other hand allowed the sedimentation of sulphamerazine with low sedimentation volume, misty supernatant and difficult to redisperse sediment (a deflocculated system).

We now need to push the frontiers of our research on these materials to make them “designer” materials for self-regulation of drug release and drug targeting. We should try to produce hydrogels that can display sudden changes in properties in response to environmental stimuli including pH, temperature, ionic strength, electromagnetic radiation, electric field, shear, sonic radiation, enzyme substrates or affinity ligands. This calls for chemical, physical and enzymatic modification of the materials for which there are already known methods. **Hydrogels can be made to respond (shrink or expand or undergo erosion) to changes in environmental conditions** like pH (Siegel *et al.*, 1988; Pradny and Kopecek, 1990), temperature (Otake *et al.*,

1990; Bae *et al.*, 1991), electric field (Osada *et al.*, 1992), ionic strength (Hooper *et al.*, 1990) salt type (Hughlin and Rego, 1991), solvent (Tanaka, 1981; Ilavsky, 1982), external stress (Sawahata *et al.*, 1990), and combinations of these.

4.5: Examples of hydrogels used as biosensors

- (i) Heller *et al.* (1990) developed a chemically self-regulated drug delivery device using a pH-sensitive, bioerodible polymer. The pH sensitive, bioerodible polymer was surrounded by an albumin hydrogel containing an immobilized enzyme.
- (ii) Cellulose ethers have been used in a variety of formulations including topical and ophthalmic preparations, enteric polymer film coats, microcapsules, and matrix systems. The release of water-soluble drugs through for example uncrossed-linked hydroxypropylmethylcellulose (HPMC) occurs by a combination of diffusion and dissolution of the matrix (erosion) – Chapman and Chapman (1980). Diffusion, however, may not be significant to the release of hydrophobic drugs.
- (iii) Drug targeting has been achieved using water-soluble polymer chains or polymeric microparticles containing drugs and specific homing devices such as antibodies (Duncan and Kopecek, 1984; Brich *et al.*, 1992). Hydrogels are used in the preparation of synthetic membranes for biosensors (Aizawa, 1985; Oliver *et al.*, 1990) which may become a critical component of signal-response.
- (iv) Starch has been widely used as a drug delivery system e.g. by modifying it with glycidyl acrylate (Park, 1988; Shalaby and Park, 1990), drug targeting to RES (Artursson *et al.*, 1984; Degling *et al.*, 1991).

Also Heller *et al.* (1980) used starch to prepare a self-regulating naltrexone delivery system.

Soluble starch was modified by alkylation using glycidyl acrylate or by acylation using acryloyl chloride. The delivery of high (Artursson *et al.*, 1984) and low molecular weight (Laakso *et al.*, 1987; Stjarnkvist *et al.*, 1991) agents to tissues of the reticuloendothelial system using the glycidyl acrylate – modified starch microspheres has been shown to be quite promising.

- (v) Gelatin (a natural, biocompatible, nontoxic, edible and inexpensive macromolecule) has been used for the delivery of gene therapeutic entities like plasmid DNA. Complexes of therapeutic DNA with modified gelatin has been shown to possibly offer a safe and efficient strategy for systemic administration of therapeutic genes to solid tumors compared to naked plasmid DNA (Nezhadi, *et al.*, 2009)

Mixing hydrogels allows the resultant product to have properties that may be hybrids of the component macromolecules (Visscher *et al.*, 1990). For example, a pH-sensitive hydrogel can also be made temperature-sensitive by combining it with a temperature sensitive polymer. Hydrogels of natural polymers can be cross linked in the presence of a synthetic polymer which may modify the properties of the hydrogels, e.g its mechanical strength. The advantage of a two component hydrogel matrix is that it can perform like synthetic polymers and yet degrade like natural polymers.

5.0: CONCLUSIONS AND RECOMMENDATIONS

The optimisation of pharmacotherapy (in terms of safety and efficacy) can best be achieved when drug products (medicines) exert effective control on the rate of drug release (**temporal control**) and on the site of drug release (**spatial control**). This can be achieved by **taking advantage of the body's natural physiology, pathology itself, biology, and chemistry, together with the physicochemical properties of pharmaceutical raw materials (to transform them to "smart" materials) and information communication technology (ICT) advances**. This calls for extensive multidisciplinary collaboration involving pharmacists, medical doctors, chemists, biologists, biochemists, chemical engineers, physicists, engineers, etc.

The pharmacovigilance initiative in our country must be taken seriously and from a holistic point of view. Every pharmaceutical manufacturer in Nigeria should take the responsibility of monitoring the cases of unwanted reactions regarding their products. Such monitoring should be sincere and honest, whereby they should compile and report such cases with a view to engaging experts in the field of drug product design and formulation to modify their drug formulae. This is because the formulation of medicines has a profound effect on the temporal and spatial release profiles of

medicines which in turn affect safety and efficacy. The experts in this area should on their part extend the frontiers of research on our locally available pharmaceutical raw materials. Such expanded research may be able to transform our raw materials to “**designer smart**” raw materials for the self-regulation and targeting of drug release. Furthermore, the government must be ready to sponsor our pharmaceutical scientists to well equipped advanced laboratories of the developed nations to acquire the needed skills for these tasks. After all, our populace should be entitled to these modern sophisticated medicines for the numerous ailments confronting our people. Even if such medicines may be quite expensive, they should at least be available for people that can afford them.

With such sophisticated drug products, the problems of spurious drugs (fake and adulterated drugs) facing the pharmaceutical environment in developing countries must be wiped out. This is because spurious drug products that can fail and release their drug contents unpredictably would be disastrous and fatal. The NAFDAC Decree number 15 of 1993 has to be implemented fully in collaboration with the Pharmacists’ Council of Nigeria (PCN), to protect, promote and gurantee public health through effective control of the business of manufacture, distribution, sale and advertisement of pharmaceuticals.

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CITATION ON PROFESSOR M. A. IBRAHIM

Prof. Musa Andrew Ibrahim hails from Wusasa in Zaria of Kaduna State, Nigeria. He attended both primary and secondary schools in Wusasa and proceeded to Ahmadu Bello University, Zaria. On obtaining his **B.Sc. Pharmacy degree in 1976**, he joined the Institute of Health, A.B.U., Zaria as an intern Pharmacist, and later proceeded to Maiduguri (the then Borno State Capital) for his N.Y.S.C. in 1977.

On returning to A.B.U. in 1978, he joined the Institute of Health's Department of Industrial Pharmacy and Quality Control as a Production and Quality Control Pharmacist. In 1979, he became the Head of the Production section and in 1980 he proceeded for a postgraduate study at Kings' College, University of London. In **1982**, he obtained an **M.Sc. Pharmaceutical Technology degree** of that university and returned to the Institute of Health, A. B. U. Zaria. In **1985**, He became the **Head of the Department** of Industrial Pharmacy and Quality Control, Institute of Health, A.B.U., Zaria. By 1986, when F.C.D.A. Abuja wanted to establish a drug-manufacturing outfit, Prof. Ibrahim was hired as an **Assistant Chief Pharmacist** to implement the project. However, in 1988 when the Faculty of Pharmaceutical Sciences, University of Jos, moved from Makurdi to Jos, Prof. Ibrahim opted to join academics as a **Lecturer I**. In 1993, he returned to the University of London to carry out the bench work of his Ph.D. programme, which he obtained in **1997** from A. B. U., Zaria and thereafter rose to the rank of **Professor in 2003**.

In the University of Jos, Prof. Ibrahim has served in many capacities both in the Faculty and in the University in general including the following:

1. **Deputy Vice-Chancellor**, University of Jos (2010 to date). He is currently serving a second term.
2. **Ag. Vice-Chancellor**, University of Jos, Nigeria (June 2011).
3. **Ag. Head of the Department** of Pharmaceutics and Pharmaceutical Technology (1990 – 1992 and 1995 – 1997).
4. **Deputy Dean** of the Faculty of Pharmaceutical Sciences (1997 – 2001)
5. **Ag. Dean** of the Faculty of Pharmaceutical Sciences (2001 to 2003)
6. **Dean** of the Faculty of Pharmaceutical Sciences (2003 to 2006)
7. Member of the University Computer Committee (1996 to 2001)
8. Chairman, Faculty Computer Committee (1998 to 2001)

9. Departmental Postgraduate Co-coordinator (2000 – 2002)
10. Co-coordinator of the Pharmacists' Council of Nigeria's (PCN's) Mandatory Continuing Professional Education for recertification of Pharmacists, University of Jos Centre (1997 to 2002)
11. Others: like faculty registration, examination officer, etc.

Prof. Ibrahim has also served outside the University of Jos since joining academics.

He has served in the following capacities:

1. **External Examiner** for Master's degrees in University of Nigeria, Nsukka, University of Benin and Ahmadu Bello University, Zaria.
2. **External Assessor** for the promotion of Senior Lecturers to the ranks of Associate Professor (Reader) and Professor (2008 - date).
3. **Manuscript reviewer** for over 7 Nigerian Journals
4. **Member of the Pharmacists' Council of Nigeria.**
5. **Zonal Co-coordinator**, Expert Committee on the development of National Pharmacopoeia
6. External Examiner for overseas trained pharmacists
7. Resource person for Zaria Pharmaceutical's training programme.
8. **External supervisor** for some Postgraduate students of A. B. U. Zaria.
9. **Visiting Professor** to A. B. U. Zaria (2006 to 2007)
10. **Chairman, PCN accreditation teams** to Niger Delta University (NDU), Bayelsa state (2009), Madonna University, Rivers state (2009).
11. Member, **Governing Board of St. Luke's Hospital**, Wusasa Zaria. Nigeria.

Prof. Ibrahim has delivered many papers at various workshops and seminars. He also has many publications (**over 45**) in national and international journals to his credit. These publications cover various themes in pharmacy such as use of locally available pharmaceutical raw materials (largely covered in this lecture). Other themes outside the scope of this lecture include packaging, unit operations, pharmacokinetic studies, reliability/generalizability studies, etc. In recognition of his publications output, the International Biographical Centre (IBC), Cambridge, England, gave the following awards to Prof. Ibrahim in 2002:

1. Man of Achievement
2. Insignia of recognition, and
3. 2000 Outstanding Intellectuals of the 21st Century

Prof. Ibrahim has travelled to a number of countries of the world, **namely Britain, the United States of America, France, Belgium, Denmark and Tanzania. He is married and blessed with a daughter**, an alumnus of the University of Jos and currently undertaking a postgraduate course abroad.