ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

REVIEW ARTICLE

A Review on Novel Biochemical Mediator Triggered on Demand Drug Delivery System

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Abstract

Unavailability of drug in appropriate amounts on apt time at the desired site of action can lead to further complications in the diseases which can turn into more deadly condition. Timely delivery of right amount of drug is very crucial in proper therapy, thereby avoiding the adverse effects of the drug. Feedback regulated closed loop delivery system can controllably deliver the drug on demand which means the release rates can be increased, decreased or totally stopped, as a response towards physiochemical response produced by the body. The system can be designed in such a way that the concentration of the drug released from the system is proportional to the degree of stimuli produced by the body. Various diseases and disorders progress by feedback loop mechanisms, owing to which biochemical signal triggered delivery of drug can be achieved in such conditions. The system is also advantageous in case of some drugs whose fluctuation in plasma concentrations is unenviable. In the current work, self-regulated drug delivery devices designed for various conditions like diabetes mellitus, hypercoagulation, cancer, microbial infections and opioid poisoning are reviewed. Various combinations of smart polymers are employed to design such devices that work by responding to the feedback produced by the body.

Keywords: *Feedback regulated delivery systems, Diabetes mellitus, Hyper-coagulation, Cancer, Microbial infections, Opioid poisoning, and smart polymers.*

Introduction

Feedback means the system is triggering itself again and again whenever there is need, which means the output of the system are routed back as inputs to the same system. Human body produces either positive or negative feedback in order to maintain the homeostasis. Positive feedback means the output produced by the system will enhance the original stimulus; example: childbirth, lactation, blood clotting etc.

Negative feedback, the common type of feedback mechanism utilised by the body to regulate the normal physiological functions, means that the output of the system will supress the original stimulus, as in case of thermoregulation, blood sugar regulation, osmoregulation etc. Feedback regulated drug delivery systems, also known as closed loop drug delivery systems, and is the smarter version of modified drug releasing systems that deliver the drug based on the stimuli received from the body.

These stimuli may be any biochemical factor (alteration in pH, temperature, pressure, ion concentration etc.) produced in the body due to unusual physiological conditions. The system will release the drug as long as it detects the abnormal biochemical change and thus the drug will be delivered as and when required which means that the rate of drug delivery can be triggered, ceased, increased, reduced or maintained at desired levels in the body.

The system can be designed in such a way that the concentration of the drug released by the system is proportional to the intensity of stimulus [1]. This type of drug delivery is suitable for new generation of drugs like DNA, siRNA, nucleotides, proteins, peptides etc. which are specific in their action but are cytotoxic and hence fluctuations in their blood levels are undesirable. The side effects and cytotoxicity of these drugs can be

worsened by recurring administration which can be overcome by closed loop drug delivery. Moreover, many diseases and disorders follow regulatory feedback loops which control their progression [2].

Closed loop drug delivery has many advantages over the conventional drug delivery systems and is thus superior to the later.

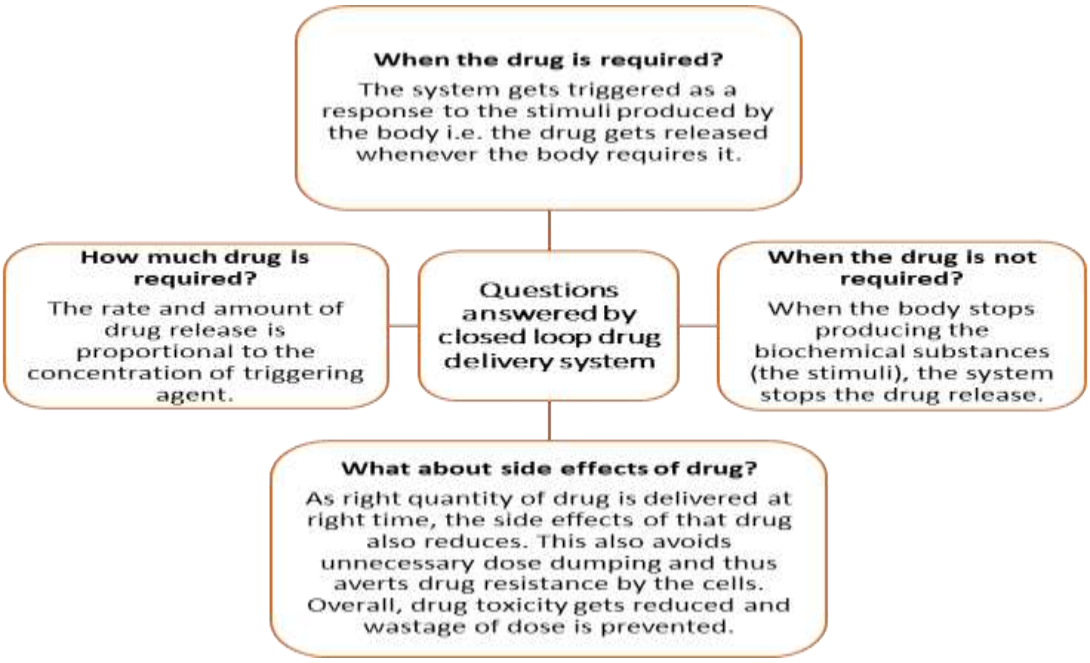

Figure 1: Rationale behind Feedback Regulated drug Delivery Systems

The basic design of this system consists of three components: a drug reservoir, a rate controlling membrane and a sensor that responds to the biochemical triggering agent.

This basic design can then be modified depending on the need and complexity of the disorder.

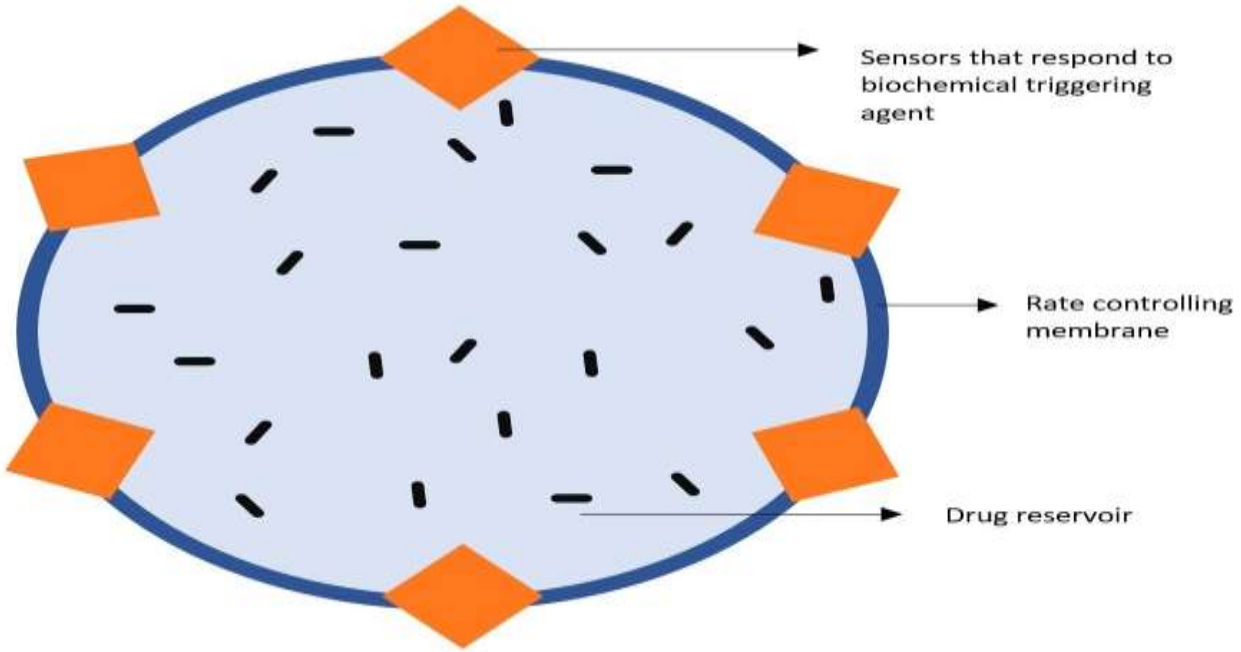

Figure 2: Basic design of feedback regulated drug delivery system

There are different mechanisms by which the drug is released from the reservoir and accordingly they are classified as:

- Bioerosion regulated drug delivery system: The biochemical agent triggers the biodegradable polymer of the membrane, after which it gets eroded to release the drug.
- Bioresponsive drug delivery system: The membrane is made up of bioresponsive

polymer which controls the membrane permeation as a response to the triggering agent.

- Self-regulating drug delivery system: Drug reservoir is encapsulated within a semipermeable polymeric membrane. The system is activated by the permeation of triggering agent and the drug is released depending on the reversible competitive binding of the triggering agent with the biosensor [3].

Diabetes Mellitus

Insulin therapy is a requisite in case of Insulin Dependent Diabetes Mellitus (IDDM), also known as Type-I Diabetes Mellitus (T1DM), wherein the pancreas is unable to produce insulin. It also becomes a crucial therapy in the grave stage of Type-II Diabetes Mellitus (T2DM) [4,5]. Today, around 100,000 Indian children are the victims of T1DM, whereas in United States 40,000 people are diagnosed with the same every year. This number is expected to cross 5 million by 2050 [6].

This population needs insulin administration every day and the most common route is a subcutaneous injection which is given via syringes, injecting pens and infusion pumps. However, these methods are invasive, inaccurate and inconvenient [7]. The invasive nature of insulin therapy promotes skin complications such as subcutaneous inflammation, scars, pain, infection and erythema at infusion site which requires antibiotic treatment or surgery [8].

Conventional methods being pulsatile have greater risks of hypoglycaemia than continuous infusion [9]. Repeated insulin injections at a particular site causes local amyloidosis [10] resulting into resistance to insulin doses [11]. The wounds and reuse of syringes cause gas gangrene [12]. Moreover, the patients are ignorant towards the fluctuations precipitated by the conventional insulin delivery.

Excessive and perpetual hyperglycaemia leads to the gruesome conditions like angina pectoris, coronary thrombosis, peripheral gangrene, myocardial infarction [13], chorea [14], arteriosclerosis and enhanced blood pressure [13, 15, 16]. Also, long term intensified conventional insulin doses cause severe episodes of hypoglycaemia which may be fatal [17]. It is also found that patients with chronic insulin dependent diabetes mellitus are scarcely aware of hypoglycaemia and its relative symptoms [18]. Therefore, deliberate insulin therapy is essential and can be attained only by continuous glucose monitoring (CGM) that ensures minimal fluctuations in the blood glucose levels. CGM can achieve precise regimen with respect to the duration, frequency of the administration and the strength of the insulin dose [19]. To achieve this, insulin pumps are designed which provide continuous subcutaneous insulin infusion that is mostly used for T1DM patients.

These pumps promise to give continuous insulin delivery but come with their own limitations such as; pump failure, occlusion, insulin instability, infusion site related difficulties and user errors which may enable the pump to deliver either higher insulin doses, provoking intensive hypoglycaemia or lower doses giving rise to hyperglycaemia [20]. Closed loop delivery of insulin overcomes such issues. Following are some glucose responsive chemicals which are under employed for designing closed loop insulin delivering systems:

- GOx -Glucose Oxidase
- GBPs -Glucose Binding Proteins, mainly Concanavalin A
- PBA -Phenyl Boronic Acid

Glucose Oxidase (GOx) Based Systems

Glucose oxidase enzyme (also known as GOx or GOD) is a flavoprotein that metabolises ß-D-glucose to D-glucono-1, 5-lactone, which further undergoes hydrolysis to get gluconic acid with hydrogen peroxide (H_2O_2) as biproduct [21]. GOD can be extracted from many sources like red algae, bacteria, insects, citrus fruits and various fungi [22]. At large scale it is obtained from fungi of genus *Aspergillus* and *Penicillium*, of which *Aspergillus Niger* is the common source for commercial production of GOx [21-23]. There are certain other enzymes which can sensitize glucose along with some other monosaccharides.

Thus, GOx is used as a biosensor for glucose it is very specific and highly reactive towards glucose [23]. Since many years GOx it has been used in glucose detection tests and now

in recent years it is studied as an ideal glucose biosensor in designing closed loop drug delivery system for diabetes [22]. The GOx based delivery systems work on certain mechanisms and accordingly they are divided as:

PH Triggered GOx Based Systems

Formation of gluconic acid from GOx catalysed metabolism of glucose decreases the pH of the surrounding medium. This change in pH is utilised as a triggering agent for the system to release insulin through a membrane. For this purpose, the system is made up of pH sensitive polymers like chitosan and carbopols. The insulin release from the system is directly proportional to the amount of gluconic acid formed depending on the concentration of glucose present in surrounding medium.

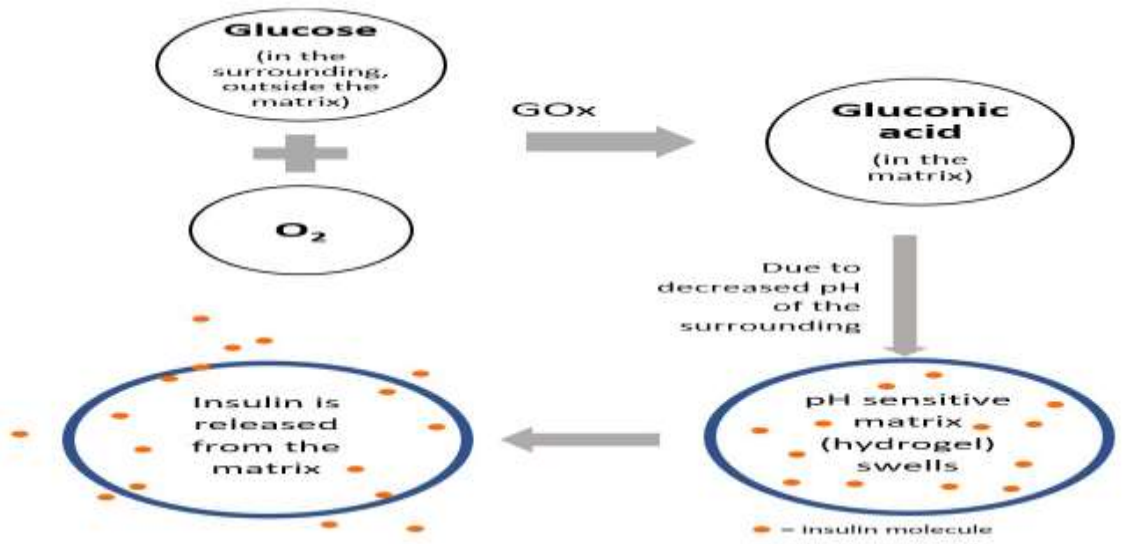

Figure 3: Working of pH triggered GOx based systems

The other type of formulation is injectable GOx loaded acid degradable nanoparticles which are prepared using pH sensitive polymers. Acetal modified dextran is employed as pH sensitive polymer in which mixture of insulin and GOx enzyme is encased. These dextran nanoparticles are then coated with oppositely charged polymer to form an injectable gel. This gel releases insulin under acidic conditions [24].

Hypoxia Triggered GOx Based Systems

Oxidation of glucose by GOx utilizes huge amounts of oxygen that causes local hypoxic conditions in that particular tissue. Hypoxia is utilised as a signal for triggering the release of insulin from the formulation or the device.

To prepare such formulations hypoxia sensitive materials like 2-nitroimidazole (NI) and its derivatives such as pimonidazole are used. Being very sensitive to hypoxia, NI and its derivatives are used as hypoxia markers and are commonly used in hypoxia imaging technology in tumor tissue. These substances have strong electron affinity which contributes to their sensitivity for hypoxic conditions [25, 26].

NI is bound to the branches of Hyaluronic acid (HA) to form a conjugated amphiphilic molecule. These conjugates arrange themselves in order to encapsulate insulin and GOX mixture. In a manner to make the delivery of the formulation less painful, these NI-HA vesicles are formulated as microneedles. As the level of glucose in the blood raises, so will the oxidation rate, the oxygen consumption in that particular tissue will also increase.

As a result, there is rapid depletion of oxygen levels and as a consequence hypoxia occurs. Hypoxia sensitizes NI and it undergoes reduction to form 2-amino imidazole which has hydrophilic nature.

This process dismantles the NI-HA vesicles that allow release of insulin in the tissue. Although this system is sensitive to hypoxia, its mechanism is not same as that of pH sensitive polymers, hence these vesicles have capacity to reduce hyperglycaemia and bring it down to standard blood glucose levels within 20 minutes and upholds it for many hours, when tested in mice induced with type I diabetes mellitus [24].

H_2O_2 Triggered GOx Based Systems

When GOx oxidises glucose, H_2O_2 is formed as a biproduct which can be used as a triggering agent to design a closed loop system that delivers insulin. A block polymer of Phenyl boronic ester (PBE) modified serine and polyethylene glycol (PEG) is prepared which is amphiphilic and can self-assemble to form nano sized vesicles that encapsulate insulin and GOx mixture. When these vesicles are exposed to H_2O_2, PBE gets degraded and becomes water soluble. In the course of time, the polymer gets eroded and the vesicles are dismantled to release insulin.

This formulation is also formulated as painless microneedle patch. The other advantage of this formulation is that it consumes peroxide formed locally in the tissue and thus curtails the skin inflammation ensuring enhanced biocompatibility of the device. H_2O_2 sensitive polymers can also be integrated with hypoxia sensitive polymers to form a dual sensitive polymer that enhances the sensitivity of formulation towards slight changes in glucose concentration.

This can be done by conjugating NI with PEG polyserine structure by peroxide sensitive thioether as a linker moiety. Linking these two will form an amphiphilic molecule whose vesicles can encapsulate insulin as well as GOx enzyme. At higher blood glucose levels, the copolymer will be degraded and will solubilize in water, thereby disabling the vesicles to liberate insulin from the formulation. These vesicles can also be loaded on microneedles to abate the pain during its delivery [24].

Glucose Binding Proteins (GBPs) Based Systems

Many proteins have capacity to bind with other biomolecules like carbohydrates (lectins), proteins, amino acids and some ions. These binding proteins can be easily extracted from natural sources like animals, microorganism, plants etc [27, 28]. Binding of proteins with these molecules changes their conformation, which also changes their properties. Glucose sensitive proteins (GBPs) are special polypeptides that have high affinity towards glucose. They are very sensitive as well as selective and are able to detect very minute change in the glucose concentration; and when they do, they bind to that particular sugar molecule and undergo conformational change [28]. Taking advantage of this behaviour of GBPs they are employed as glucose biosensors to monitor patients' blood glucose level [27], moreover, in recent years they are being excessively studied as efficient biosensors in closed loop insulin delivery devices that get triggered when the blood glucose concentration is altered. Concanavalin A (con A) is the most studied lectin, obtained from *Canavalia ensiformis*, having specificity to bind with nonreducing part of the sugars, specifically α-D-mannosyl and α-D-glucosyl moieties [29].

However, con A do not undergo any vital conformational change when it binds to glucose, rather it detects the alterations in glucose concentration through its competitive binding with glucose and other competing ligand [30]. On a whole, con A have four binding sites that bind reversibly to D-mannose and D- glucose sugars. Insulin, after its glycosylation (gluconic acid bound insulin) is bound to con A which serves as a potent competent of free glucose. Further integration of con A with polymers like dextran, chitosan, poly (hydroxyethyl methacrylate) (PHEMA), N-(2-(dimethylamino) ethyl)-methacrylamide (DMAEMA), glucosyloxyethyl methacrylate (GEMA) forms glucose sensitive hydrogels [24, 31-34].

When the glucose concentration in the blood will rise, free glucose molecules will compete with the glycosylated insulin which is already bound to con A. As con A has higher affinity towards glucose, it will readily replace glycosylated insulin which will lead to liberation of insulin from the hydrogel. This hydrogel can be placed in microneedles or guarded by a semipermeable membrane encased in a polymeric device [24].

The red blood cells (RBCs) are also used as carriers to procure glucose responsive delivery of insulin. An amino sugar, glucosamine modified insulin (Glu-insulin) can effortlessly bind to glucose transporter (GLUT) which is copiously found in RBCs. Only one intravenous dose of this formulation is able to bring down blood glucose level to normal for three days. One of the key advantages of this formulation is that the life cycle of RBCs is upto 120 days; therefore, the

RBCs loaded with insulin have ability to deliver insulin for longer duration when sensitized by glucose [24].

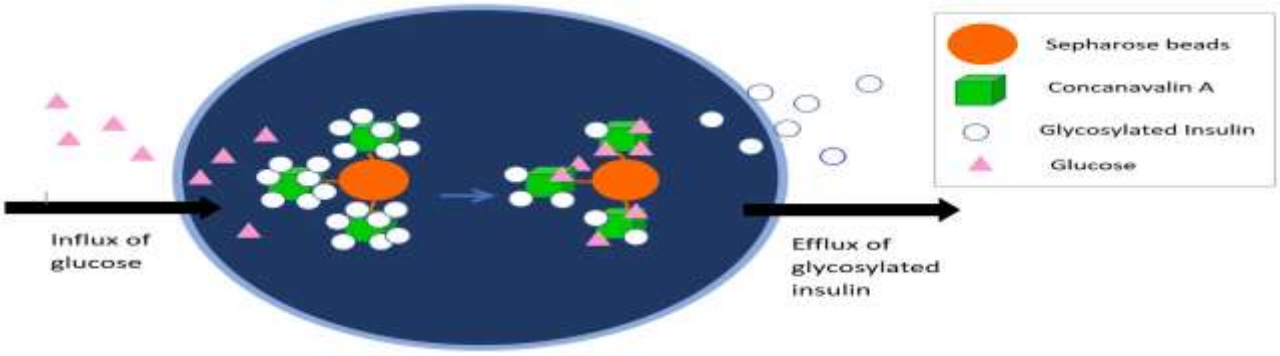

Figure 4: Working of Glucose Binding Proteins (GBPs) based systems

Phenyl Boronic acid (PBA) Based Systems

PBA have capacity to form covalent bonds with 1, 2- or 1, 3-diols and rearrange itself to form 5-6 membered water soluble cyclic boronate esters. Sugars have *cis*- diols which are capable of forming powerful but reversible ring structure with PBA and these conjugates form absolute glucose sensitive biosensors that are routinely employed in diagnosis of diabetes and in recent years they are extensively studied under closed loop insulin delivery [24, 35, 36].

Glycosylated insulin is formulated as gel beads by its esterification with PBA. Nanoparticles of PBA conjugated mesoporous silica (PBA-MSNs) are also been studied, surface of which is loaded by glycosylated insulin via PBA linkage. The release of insulin is triggered by cAMP which can also be entrapped in MSNs.

When PBA forms bonds with glucose, it experiences charge transition, this phenomenon is used to design glucose sensitive vesicles. These vesicles are designed by synthetically preparing an amphiphilic block copolymer of poly (styreneboroxole) (PBOx) which is sensitive towards monosaccharides and PEG.

The resultant copolymer gets self-assembled to form polymersomes that entraps insulin. When body experiences hyperglycaemia, PBOx will react with glucose, it dissociated into its anionic form that caused deconstruction of polymersomes and insulin is released from the formulation. In another type of formulation, a glucose responsive thermosensitive gel is formulated employing PBA. When charge transition will occur in PBA, its anionic form will experience electrostatic repulsion that will cause expansion of the gel. This will result in brisk insulin liberation from the gel which will be again intensified due to the dehydrated skin [24].

Hypercoagulation

As a part of homeostasis, blood coagulation mechanism is the primary aid by which our body ensures that there is no excessive blood loss during bleeding. Key elements in thrombosis are platelets, plasma proteins and other clotting factors that interact with one another to form a clot. However, sometimes excessive clotting also known as Hypercoagulation or Thrombotic disorders can also occur which can even lead to thromboembolism and cause other severe complications like strokes, pulmonary embolism, venous thromboembolism, peripheral artery disease, pregnancy related problems, deep vein thrombosis etc [37,38].

The principle element in clotting mechanism is thrombin, also known as factor IIa or fibrinogenase, which interacts with its naturally occurring substrate fibrinogen to break it down to fibrins that polymerises to form a stable clot [39, 40, 47]. Scientists have been working on designing such a system that will target and cease the thrombin action and delivering anticoagulant therein.

Heparin is a clinically significant anticoagulant having polysaccharide backbone that is normally delivered by either intravenous or subcutaneous route because of its poor bioavailability through gastrointestinal tract [41-44].

Heparin can be used as a prophylaxis for thrombosis as well as to dissolve already formed clots. Accurate dosing of heparin should be ensured as it has many adverse effects like haemorrhage (especially during intermittent intravenous administration), thrombocytopenia, skin necrosis and transaminitis which is characterised by high levels of transaminases class of enzymes [45]; which is only feasible through feedback regulated drug delivery system.

These systems are designed by utilising thrombin levels in blood as a signal that will regulate heparin release from the formulation. A peptide which can be degraded by thrombin is used as a linker that will link heparin with branched PEG; this will form a hydrogel which will be sensitive towards thrombin levels. When the level of thrombin rises in blood, thrombin will cleave the linker peptide due to which heparin will be set free from the hydrogel. The free form of heparin will cause interaction between thrombin and antithrombin III [45], which is also known as heparin cofactor necessary for the heparin's anticoagulant action, to form a complex.

This wills supress the action of thrombin which will avail later as a feedback signal to halt the delivery of heparin from the formulation. When compared with the heparin loaded conventional hydrogel, this closed loop system could avert clot formation for longer duration [24, 46]. Bhat *et al.* utilised this concept to deliver acenocoumarol, another anticoagulant from MSNs [22, 43, 47].

Zhang *et al.* conjugated heparin to hyaluronic acid through thrombin cleavable peptide linker to form as thrombin responsive hydrogel and this formulation was loaded on transcutaneous microneedle array patch that provided prolonged but uninterrupted, pain-free administration and could detect little variations in capillary thrombin levels [24, 48, 49].

Cancer

Cancer is an enormous class of diseases which is identified by uncontrollable rapid multiplication of cells far higher than their normal number and these abnormal cells can be spread to any site of the body. Major concerns are associated with cancer as it is second foremost cause of death and has killed nearly 9.6 million people in 2018 according to the survey conducted by WHO [50, 51]. Chemotherapeutic agents are highly toxic [52] and hence it is important to target only cancer cells for their activity. It is essential to study the distinguishing parameters between normal cells and tumour cells. The malignant tissue has newly formed vasculature associated with certain abnormalities like incomplete or missing endothelial linings and basement membrane, absence of pericytes and pharmacological receptors [53, 54].

In addition to this, there is elongation of blood vessels, uneven distribution of vascularisation which gives rise to physiological abnormalities like platelet aggregation, blood cell extravasation, and haemorrhage etc [53]. All of these events cause enhanced permeation and retention (EPR) effect particularly for lipids and other macromolecules [55, 56].

The metabolism rate is found considerably higher in rapidly dividing malignant cells to that of normal cells, due to which there is higher rate of oxygen consumption that is not satisfied by the impaired tumour vasculature. It has been observed that the partial pressure of oxygen in normal cells lies within the range of 24-66 mm Hg, and in cancer cells it is found to be $\leq$ 20 mm Hg [55]. This gives rise to anaerobic respiration of cells that leads to lactic acid formation which further reduces the pH thereby [55, 57, 58].Tumour metabolism occurs by three mechanisms [58]:

- Glucose oxidation
- Aerobic glycolysis (lactic acid is formed in presence of oxygen)
- Anaerobic glycolysis (lactic acid is formed in absence of oxygen)

The nutrient supply is deficient due to inadequate blood flow as well as waste products particularly lactic acid gets accumulated in the tissue resulting in tissue acidosis. The pH of tumour venous blood falls to 7.1.

Moreover, the glycolysis and ATP hydrolysis generates huge amounts of H^+ ions which accumulates in the tissue and further intensifies the acidic conditions. However, in certain malignancies like mammary carcinoma and skin cancer, the arterial blood

pH shifts towards alkaline side [59]. Also, there is an abnormal distribution of certain enzymes in tumour tissue such as phospholipases [60, 61]. A drug delivery system can be designed which will sense these abnormalities and release the drug accordingly. The feedback regulated drug delivery can be achieved using pH sensitive polymers like poly [N, N-dimethylaminoethyl methacrylate (DMAEMA)/2-hydroxyethyl methacrylate (HEMA)]. This polymer swells when exposed to acidic pH and the volume swelling ratio determines the amount of paclitaxel to be released from the formulation.

The pH dependent release of paclitaxel from DMAEMA/HEMA nanoparticles was studied by Auguste et.al. The study demonstrated that, at pH 7.4, 16% paclitaxel was delivered by the DMAEMA/HEMA nanoparticles to the local tissue for 6 hours duration. When the pH was 7.0 it was increased upto 30% for 6 hours. Around 45% of drug was released over 6 hours when pH was about 6.8. Thus, the drug delivery from the DMAEMA/HEMA nanoparticles showed controlled feedback regulated drug delivery [62].

Infections

Lipases are the enzymes that primarily hydrolyse triglycerides and are produced by many living organisms like bacteria, protists, fungi, animals and plants of which only bacteria are used for commercial production of lipases [63-65]. These microbial lipases have capacity to accelerate both biosynthesis as well as hydrolysis of ester bonding of triglycerols [66-67]. The lipases produced by microorganisms are referred to as extracellular lipases. Lipases cleave ester bonds in presence of water to discharge organic acids and glycerol moieties. These enzymes also exhibit substrate specific activity which means lipases formed by a particular strain of organism will hydrolyse specific ester bonds of triglycerols. Not all microorganisms produce lipases that are virulent, but only some strains produce pathogenic lipases [65]. For example:

Table 1: Genus of bacteria and fungi producing extracellular lipases that cause respective diseases. *Bacterial genus, #fungal genus

Genus that produce pathogenic lipases	Disease
**Staphylococci (S. aureus)* [65]	Abscesses, meningitis, infectious wounds, sepsis etc.
**Pseudomonas aeruginosa* [65]	Cancer, wound infections, cystic fibrosis, lung infections etc.
#Aspergillus [68,69]	Aspergillus pneumonia, pulmonary aspergillosis, Allergic Bronchopulmonary Aspergillosis
#Penicillium [68,70,71]	fatal systemic mycosis, pulmonary penicillosis
#Malassezia [66]	Tinea versicolor, seborrheic dermatitis, dandruff
#Candida (*C. albicans, C. parapsilosis etc.*) [66]	Cutaneous candidiasis, oral thrush etc. *C. albicans* infects about 50% of the population.

Owing to the fact that lipases are very essential factors contributing to fungal and bacterial infections, they can be utilised as a signal to design a lipase triggered drug delivery system to impede bacterial or fungal infections. A lipase responsive triple layered nanogel is prepared which will get activated during bacterial infection. Polyphosphoester was used to entrap an antibacterial drug which is again coated by poly (ε-caprolactone) (PCL) which has lipophilic nature and PEG having hydrophilic nature, to form a controlled release coat. When bacteria capable of producing lipase invaded, the PCL undergoes degradation and the coating is eroded to release the antibiotic drug. When the bacteria are inhibited as a result of the drug's action, the lipase level drops down which acts as a feedback signal to stop the release of antibiotic from the formulation.

This formulation has potential to inhibit intracellular as well as extracellular bacterial infections [24]. Such a formulation was also developed for fungal infections wherein phytantriol nanoparticles were stabilised using polysorbate 80, a lipase sensitive polymer. When fungal lipase causes degradation of polysorbate 80, this caused destabilization of nanoparticles to release the drug from the formulation [24].

Opioid Poisoning

Opioids are the class of psychedelic drugs that are legally available only under prescription, generally used in relieving severe and intolerable pain. They are also used for inducing anaesthesia, supressing chronic cough and diarrhoea, executions (only in United States) [72-73]. These drugs (Morphine, Codeine, Pethidine, Fentanyl etc.) bind to opioid receptors of central nervous system which are of three types namely mu (μ), delta (δ) and kappa (κ), of which morphine has the highest affinity to interact with mu receptors [74].

However, these medications are used illegally for non- medical purpose for its euphoric action [75]. Opium is abused by nearly 32.4 million people worldwide according to 2014 statistics [76]. In 2017, America witnessed death of nearly 47,000 citizens who abused opioids [77].

Today, approximately 130 residents of United States abuse opioids and die each day [78]. These cases also include prescription opioids overdose demises. Prompt administration of naloxone, an opioid antagonist can save the person afflicted by opioid overdose. Naloxone has highest affinity to inhibit mu receptors, yet it can also block other opioid receptors [74].

On demand delivery of naloxone can be solely achieved by closed loop systems which will deliver the antidote in response to changed microenvironment during opioid toxicity. One of the most important symptoms of morphine toxicity is shallow breathing which gradually leads to collapsed respiration. During this emergency situation, the oxygen level in the blood falls down and blood gets saturated with carbon dioxide, causing blood acidosis.

This is considered as the indicator of morphine toxicity and accordingly closed loop naloxone delivering device can be designed that will deliver the antidote as soon as morphine reaches its toxic levels. Thayumanavan *et al.* developed a carbon dioxide responsive naloxone delivering vehicle. The acidosis caused during morphine toxicity drops the blood pH just below 7.35.

A polymeric system was developed which would swell when exposed to altered blood CO_2 percentages. Hydrogel was prepared by crosslinking poly (N, N-dimethylaminoethyl methacrylate) (DMAEMA) with trimethylolpropane trimethacrylate (TMPTMA). Human blood is having pH of about 7.4 and normal carbon dioxide concentration of 5%. During morphine induced acidosis the CO_2 percentage in blood rises up to 7%. When tested in 7% CO_2, the polymeric hydrogel ionised and experienced electrostatic repulsive forces leading to swelling of hydrogel.

Naloxone was diffused out through swollen pores of the gel. The released naloxone would reverse the effects of morphine toxicity and bring back the CO_2 level to normal, which will be utilised as feedback signal to cease the naloxone delivery from the device. The system was capable enough to control the complications of opioid toxicity [1].

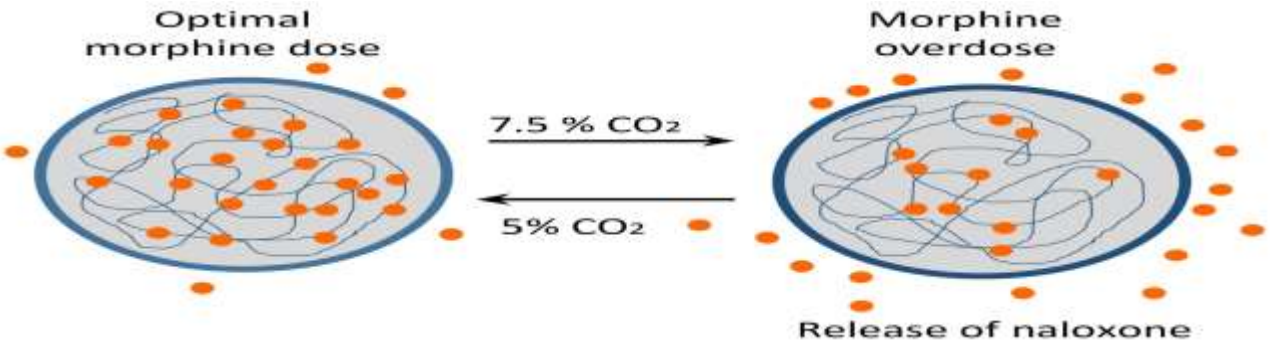

Figure 5: Working of Feedback Regulated Naloxone Delivery System

Conclusion

Diverse closed loop drug delivery mechanisms have been developed for varied medical conditions by employing different stimuli responsive polymers. The drug release from the devices is controlled by unique physiochemical reversible transformations in the polymeric structure. Though these newly transpired approaches are confronting many challenges, even so they are able to perform effectively considering research, preclinical and clinical aspects. They are competent to deliver

superior therapy. However, minute change in the process or product parameters can intensely affect the properties of final formulation especially its sensitivity towards the triggering agent.

The principle mechanism of disease progression, the mediators involved therein, the mechanism of generation of numerous biomolecules and the course of change in the microenvironment of affected tissue must be extensively studied to identify the specific molecules which can be used as triggering agents to design the desired system. The system might also get activated undesirably due to false signals which might come from change in microenvironment as a consequence of many causes, generation of similar microenvironment in coexisting medical conditions or due to interaction of similar derivatives of triggering agent. The other perturbing part regarding these devices is that they can generate immune reaction in some sensitive individuals and result in bioincompatibility. Considering the complexity in the design and working of these devices, development of advanced and sophisticated techniques is needed to monitor and evaluate their working efficiency.

List of Symbols:

α – Alpha

μ – Mu

δ – Delta

κ – Kappa

ε – Epsilon

LIST OF ABBREVIATIONS:

DNA	Deoxyribonucleic acid
siRNA	Small interfering RNA
IDDM	Insulin-dependent diabetes mellitus
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
CGM	Continuous glucose monitoring
GOx	Glucose oxidase
GOD	Glucose oxidase
GBPs	Glucose Binding Proteins
PBA	Phenyl boronic acid
NI	Nitroimidazole
HA	Hyaluronic acid
PBE	Phenyl boronic ester
PEG	Polyethylene glycol
Con A	Concanavalin A
PHEMA	Poly(hydroxyethyl methacrylate)
DMAEMA	N-(2-(dimethylamino) ethyl)-methacrylamide
GEMA	Glucosyloxyethyl methacrylate
RBCs	Red blood cells
Glu-insulin	Glucosamine modified insulin
GLUT	Glucose transporter
PBA-MSNs	Phenyl boronic acid conjugated mesoporous silica
c-AMP	Cyclic adenosine monophosphate
PBOx	

WHO	Poly(styreneboroxole)
EPR	World Health Organization
ATP	Enhanced permeation and retention
HEMA	Adenosine triphosphate
PCL	2-hydroxyethyl methacrylate
TMPTMA	poly(ε-caprolactone)
	trimethylolpropane trimethacrylate

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