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An Overview of Stimuli-Induced Pulsatile Drug Delivery Systems

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Abstract: Any therapeutic agents are efficacious when made available at constant rates or near the absorption sites. The absorption of therapeutic agents yielded results in desired plasma concentrations leading to maximum efficacy and minimum toxic side effects. In the field of modified/controlled release, matching of drug release to the body's circadian rhythms have been fundamental strategies involves for selecting a new drug delivery system which increase the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. Especially, the latest literature studies on a number of chronotherapeutic drug delivery systems, which have been recognized as potentially beneficial to the chronotherapy of widespread chronic diseases that display time-dependent symptoms such as ulcers, asthma and cardiovascular disease. The pulsed or triggered delivery systems are developed to alter their rate of drug delivery in response to stimuli such as changes in a specific molecule, a magnetic or electric field, temperature, light or mechanical forces. Such chronotherapeutic drug delivery system controls drug release according to circadian rhythms and the timing of symptoms. The aim of this review is to describe, several types of drug delivery systems which cause the pulsed release due to certain external stimuli, mostly focuses on thermally-, chemically-, electrically- and magnetically- induced pulsatile release in detail.
Keywords: Pulsatile release, triggered release, thermo-responsive, electro-responsive.

INTRODUCTION

As newer and more powerful drugs keep on to be developing, more attention is being given to the methods by which these active substances are administered [1]. A lot of effort has been given to develop advanced drug delivery systems such as osmotic devices for oral application. However, in some cases where maintaining a constant blood level of a drug is not desirable. For example, the main aim of chronotherapy for cardiovascular diseases is drug delivery in higher concentrations during the time of greatest need- the early morning hours- and in lesser concentrations when the need is less- during the late evening and early

sleep hours. In chronotherapeutic delivery systems not only a properly designed drug delivery system but also the time of administration is equally important. Pulsatile release is usually found in the body, for example during hormone release, in which a baseline release is combined with pulsed, one-shot type release, was observed within a short time range [2, 3]. A good example of a hormone which experiences pulsatile release in the body is insulin. Based on available knowledge of the molecule and its pH-dependent solubility profile, pharmacokinetic parameters, absorption along the gastrointestinal tract and elimination half-life, the unique pharmacokinetic profile needed for the target product can be calculated using computer simulation and modelling techniques. The use of such methods results in reduced feasibility development time and enhances probability of success of the program.

Pulsatile devices may have many applications in areas of other medicine where a constant rate of drug release does not match the physiological requirements of the body. This is often the case when treatments involve hormone-based drugs. Secretion of many hormones exhibits pulsatile patterns comprising frequent pulses over periods from hours to weeks [4], so it is more effective to mimic this with a synthetic delivery system. Current research in the field of drug delivery devices, by which triggered and/or pulsatile release is achieved, has been intensified. Pulsatile drug delivery system is capable of providing one or more rapid release pulses at predetermined lag times which results in better absorption of the active solute, and thereby provides more effective plasma concentration-time profile [Figure 1]. However, only a few such orally applicable pulsatile release systems are available due to potential limitations of the dosage form size, and/or polymeric materials and their compositions used for producing such dosage forms[5]. Such a novel drug delivery has been attempted for the following diseases listed in [Table 1][6]. Two different methodologies have been broadly investigated as possible solutions to these requirements. One is the designing of a drug delivery system that releases its payload at a predetermined time or in pulses of a predetermined sequence. The other is to develop a system that can respond to changes in the local environment. These systems have been shown to alter their rate of drug delivery in response to stimuli including the presence or absence of a specific molecule, magnetic fields, ultrasound, electric fields, temperature, light, and mechanical forces [7]. This review article focuses on recent developments on several types of responsive delivery systems due to external stimuli, using various formulations such as microparticles, coarse particulates, large solid implants, hydrogels that showed triggered and/or pulsatile drug delivery characteristics.

Disease	**Chronological behaviour**	**Drugs used**
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Asthama	Precipitation of attacks during night or at early morning hour	β_2 agonist, Antihistaminics
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors etc.
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Hypercholesterolemia		
Neoplastic	It has been demonstrated that "susceptibility rhythms" to drugs may differ between healthy tissue and cancerous tissue.	Alkylating agents, Antimetabolites, Vinca alkaloids, antibiotics etc.
Peptic ulcer	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

Table 1. Diseases requiring pulsatile Drug delivery

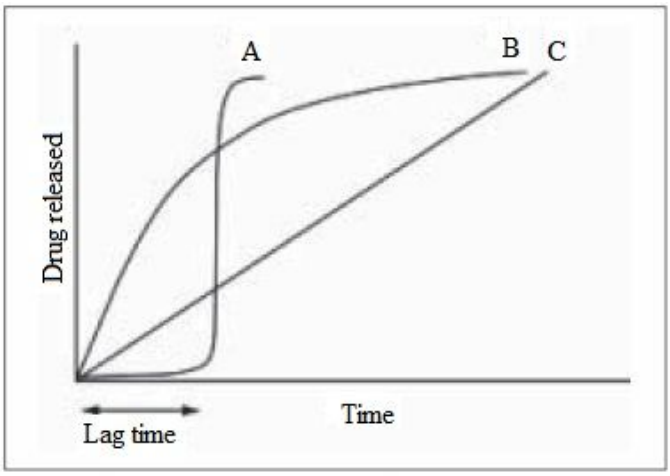

Figure 1: Drug release profiles: (A) pulsatile, (B) and (C) conventional extended release

STIMULI INDUCED PULSATILE/ TRIGGERED RELEASE SYSTEM

In these systems the release of the drug takes place after stimulation by any biological factor like temperature, or any other chemical stimuli [Figure 2] [8]. Many of the polymeric delivery systems experience phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition ionic strength, temperature, electric fields, and light [9]. Pulsatile drug delivery systems (PDDS) can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation [6]. Stimuli induced pulsatile/triggered drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanisms of drug release include drug diffusion along a concentration gradient, ejection of the drug from the gel as the fluid phase synerses out, liberation of the entrapped drug as the gel or micelle complex erodes and electrophoresis of charged drugs towards an oppositely charged electrode.

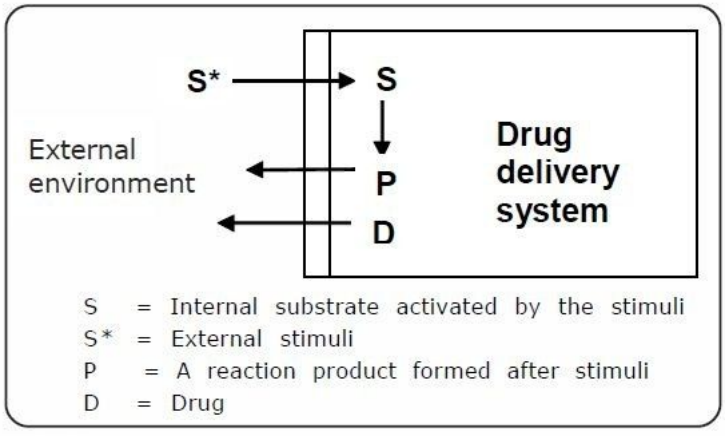

Figure 2. General scheme for stimuli sensitive pulsatile drug delivery system

1. Temperature-induced pulsatile release

Temperature is the most widely applied triggering signal for a variety of triggered or pulsatile drug delivery systems. The importance of temperature as a signal has been justified by the fact that the body temperature often deviates from the physiological temperature (37^0 C) in the presence of pathogens or pyrogens. This deviation sometimes can act as a stimulus that triggers the release of therapeutic agents from several temperature-responsive drug delivery systems for diseases accompanying fever. The temperature-induced pulsatile/triggered drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting [10-12.]

1.1. Thermoresponsive hydrogel systems

Thermo-responsive hydrogel systems employ hydrogels which undergo reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature that is referred to the lower critical solution temperature (LCST) of the linear polymer from which the gel is made. Thermo-sensitive hydro-sensitive hydrogels have a certain chemical attraction for water, and therefore they absorb water and swell at temperatures below the transition temperature whereas they shrink or deswell at temperatures above the transition temperature by expelling water. Thermally-responsive hydrogels and membranes have been extensively exploited as platforms for the pulsatile drug delivery [13].

Temperature-sensitive hydrogels can also be positioned within a rigid capsule comprising holes or apertures. The on-off release is accomplished by the reversible volume change of temperature-sensitive hydrogels [14, 15]. This device is called as a squeezing hydrogel device since the drug release rate was influenced by the hydrogel dimension and was also found to be proportional to the rate of squeezing of the drug-loaded polymer.

For stimuli-responsive drug delivery systems thermoresponsive hydrogels have been referred as potential drug delivery carriers [16, 17]. Kaneko and co-workers [18] presented a method to stimulate gel swelling/deswelling kinetics relied on the molecular structure of the gel, by implanting the free mobile linear PNIPPA chains inside the cross-linked PNIPPA hydrogels as shown in [Figure 3]. PIPAAm cross-linked gels showed thermoresponsive, off-and-on swelling/deswelling phases: for example, swelling below 32^0 C temperature, on the other side shrinking above this temperature. A sharp temperature increase above the transition temperature of these gels led in the formation of a thick, shrunken layer upon the gel surface ('skin layer'), which obstructed water diffusion from inside the gel into the environment. At temperatures below 32^0 C drug release from the PIPAAm hydrogels was regulated by diffusion, while above this temperature drug release was ceased entirely, owing to the formation of 'skin layer' on the gel surface (on–off drug release regulation) [11,12,19]. Swelling-deswelling kinetics of conventional cross-linked hydrogels are usually inverse of the square of gel dimension [20]. The mobility of the cross-linked chains in the gel is influenced by the encompassing chains and the swelling/deswelling phases of the gel are controlled by the collective diffusion of the network chains. Thus, to hasten structural changes of the gel in reply to external stimuli, various methods have been developed which form porous structure within the gel and rather decrease gel size [21-25].

Yuk and co-workers developed temperature-sensitive drug delivery systems utilizing admixture of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer (F-68) and poly vinyl alcohol (PVA). Alteration in the proportion of F-68/PVA can be practised to regulate the swelling transition of polymer complex gel. The pulsatile release of acetaminophen in reply to pulsatile change in temperature between 35^0 C and 40^0 C was demonstrated by the authors [26].

US Patents 6733788 [27] and 20020015712 [28] key out a medical device comprising thermosensitive cellulose gel structure, which delivers the active solute compounds to a specific location in the body. At a particular temperature the gel structure deswells and releases the biologically active solute as the temperature is increased, under the influence of increased temperature of the body entire loaded solute was released in a comparatively short period of time.

Figure No: 03

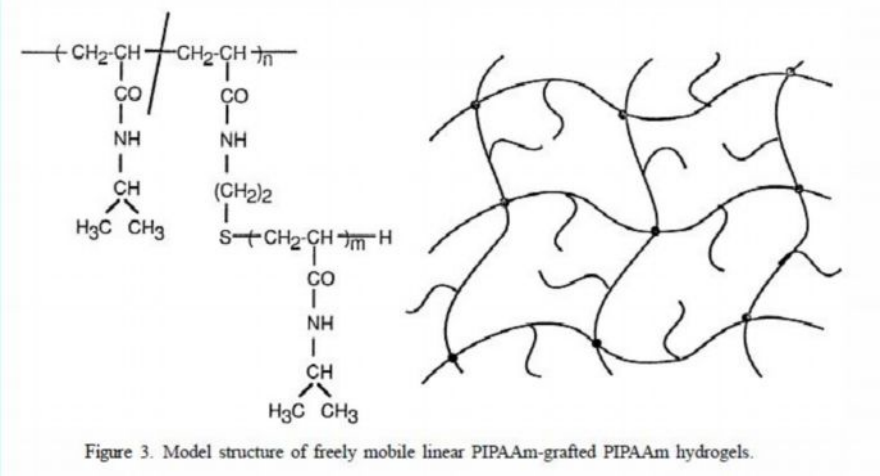

Figure 3. Model structure of freely mobile linear PIPAAm-grafted PIPAAm hydrogels.

1.2. Thermoresponsive polymeric micelle systems

These represent polymeric micelles whose properties and biological interests make them a most noteworthy candidate as drug carrier for the treatment of cancer [29]. Kataoka and co-workers [29] reported that the polymeric micelle is built up of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona, on account of this unique structural characteristic, polymer micelles exhibit stealth characteristics and are not recognised by the body defence system (reticuloendothelial system; RES). Thus, passive targeting could be accomplished through an enhanced permeation retention (EPR) effect [30] of the tumour sites.

J.E. Chung and co-workers [31, 32] have been working on the development of an end-functionalized PIPAAm to prepare block copolymers with hydrophobic polymers, such as poly(butyl methacrylate) (PBMA), polystyrene (PSt) or poly(lactic acid) (PLA) [33, 34]. Below PIPAAm's transition temperature block copolymers formed micellar structure (with core-shell structure) in aqueous solution [Figure. 4]. The shell was constructed from thermoresponsive PIPAAm, while the core comprised of hydrophobic polymer aggregates. The PIPAAm corona exhibited a change in its hydration/dehydration properties with changing temperature. Towards all the biological entities the hydrated corona acted as an inert material, such as proteins and cells below the PIPAAm's LCST. However, upon temperature increase above 32^0 C hydrated PIPAAm chains became hydrophobic, due to the dehydration of polymer chains, thus resulting in aggregation and precipitation.

Jun Akimoto and co-workers [35] prepared a well-defined diblock copolymers consisting thermoresponsive segments of poly(N-isopropylacrylamide-co-N, N-dimethylacryl amide) (P(IPAAm-co-DMAAm)) and hydrophobic segments of poly(d,l-lactide) were synthesized by combination of RAFT and ring-opening polymerization methods. Terminal conversion of thermoresponsive segments was accomplished through reactions of maleimide or its Oregon Green 488 (OG) derivative with thiol groups exposed by cleavage of polymer terminal dithiobenzoate groups. Thermoresponsive micelles formed from these polymers were about 25 nm when below the lower critical solution temperature (LCST) of 40°C, and their sizes increased to an average of approximately 600 nm above the LCST due to aggregation of the micelles. Interestingly, the OG-labeled thermoresponsive micelles exhibited thermally regulated internalization to cultured endothelial cells, unlike linear thermoresponsive P(IPAAm-co-DMAAm) chains. Even though intracellular

uptake of P(IPAAm-co-DMAAm) was extremely low at temperatures both below and above the micellar LCST, the thermoresponsive micelles displayed time-dependent intracellular uptake above the LCST without exhibiting cytotoxicity. These results suggest that the new thermoresponsive micelle system may be a greatly promising intracellular drug delivery tool.

Figure No: 04

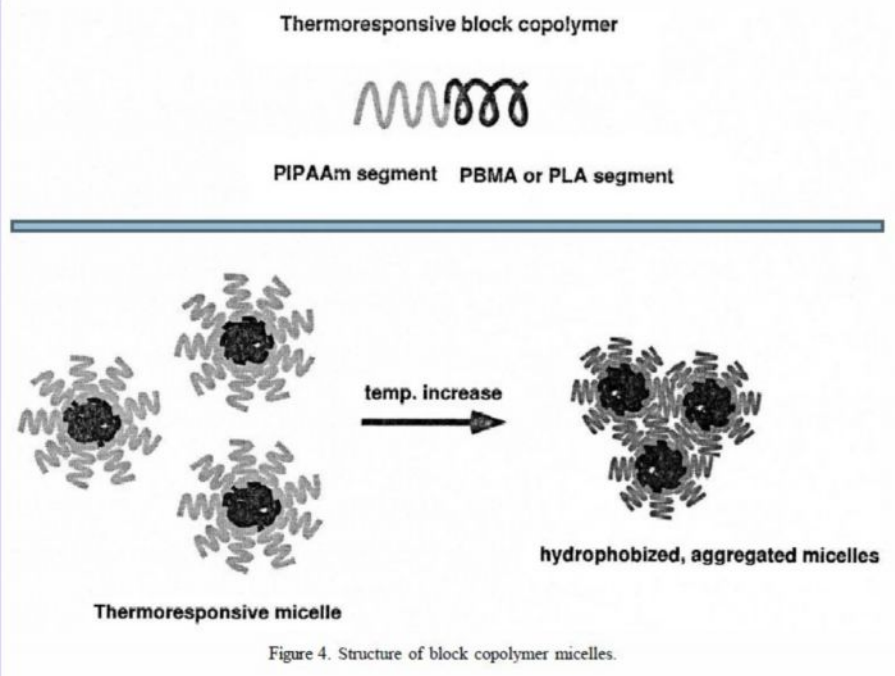

Figure 4. Structure of block copolymer micelles.

Although there are still various parameters to be clarified, such as the targeting efficiency and drug release behaviour at specific sites in vivo, the above results apparently indicate that thermoresponsive polymer micelles can be utilized for the thermoresponsive drug delivery to tumour sites in conjunction with an induced hyperthermia.

2. Chemical stimuli-induced pulsatile release

2.1. Glucose-responsive insulin release devices

Ishihara and co-workers [36] prepared two types of gel membrane systems to regulate insulin permeability by utilizing the reaction glucose oxidase (GOD) catalyzes glucose oxidation. GOD and nicotinamide-immobilized gel membranes were made separately. While glucose was oxidized by the immobilized GOD, the resulting hydrogen peroxide oxidized the nicotinamide units inducing positive charges. The gel membranes turned hydrophilic and permeability increased. Horbett' *et al*.[37,38] prepared GOD-immobilized hydrogels from 2-hydroxy-ethyl methacrylate and N,N-dimethylaminoethyl methacrylate. Glucose in the medium was converted to gluconic acid via a reaction mediated by hydrogel-immobilized GOD. Therefore, the protonation of hydrogel amino groups took place resulting in swelling of hydrogel membrane. Practising this type of membrane, insulin permeability through the hydrogel was 2.4-5.5 times higher at 400 mg/dl glucose than that at 0 mg/dl.

An alternative method to acheive glucose-sensitive delivery system is based on the competitive binding of concanavalin (con A), which is a glucose binding lectin. Obaidat *et al.* developed a copolymer of acrylamide and allyl glucose. The side chain glucose units in the copolymer were attached to concanavalin A. These hydrogel exhibited a glucose-responsive, sol-gel phase transition, depending on the external glucose concentration owing to the competition between free glucose and con A. Con A acts as cross linker for the polymer chains because of the presence of four glucose-binding sites on the molecule, but competitive binding with glucose interrupts these cross links, causing the material

more permeable and thus increasing the rate of drug delivery [Figure. 5]. Membranes and hydrogels comprising of these copolymers can act as gates or depots for glucose dependent insulin delivery [39, 40].

Figure No: 05

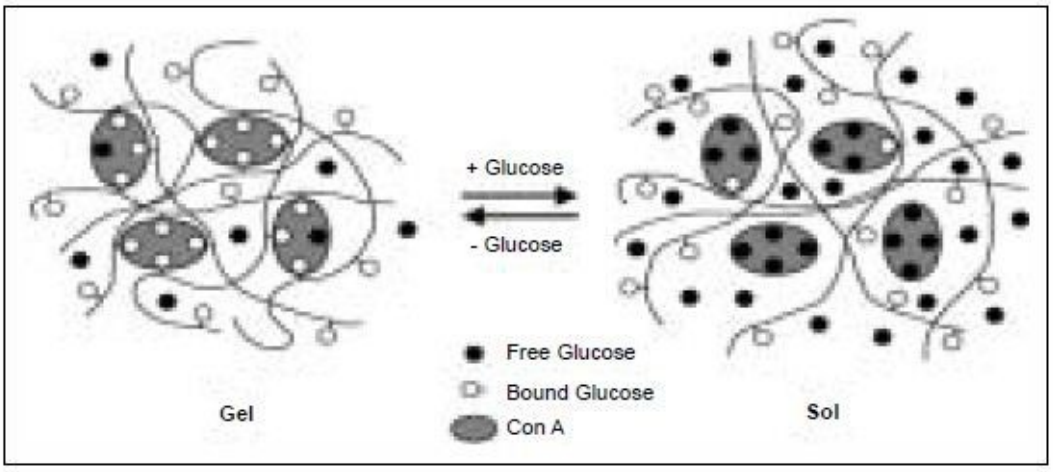

Figure 5. Sol-gel phase transition in polymers cross linked with Con A.
Con A (●) = Concanavalin A, (●) = Free glucose, (◇) = Glucose bound to the polymer

Kim *et al* [41, 42] developed a self-regulating insulin delivery system utilizing microcapsules consisting the glucose-binding lectin, concanavalin A (Con A) and Con A-bound glucosylated insulin. Glucosylated insulin attached to Con A was released through exchange with external glucose, because of the difference in their binding constants. Even though this system is a promising approach for the treatment of diabetes mellitus patients, direct injection of microcapsules into the peritoneal cavity might cause unwanted side-effects originating from the immune response toward Con A, if the microcapsules were to break and the Con A was to be exposed to the immune system.

Moreover, it is essential to refill the glucosylated insulin after exhausting initially bound insulin molecules. Therefore, incorporation of these microcapsules within biocompatible pouch membranes was considered.

2.2. pH sensitive drug delivery system

This type of pulsatile drug delivery system consists two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By choosing the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include polyacrylates, sodium carboxymethylcellulose, and cellulose acetate phthalate. These polymers are used as enteric coating materials so as to render release of drug in the small intestine. Yang and co-workers designed pH-dependent delivery system of nitrendipine in which they have mixed three kinds of pH dependent microspheres made up of acrylic resins Eudragit E-100, Hydroxypropyl methylcellulose acetate succinate and Hydroxypropylmethylcellulose phthalate as pH dependent polymers. In one of the study carried out by Mastiholimath and co-workers, an effort was made to deliver theophylline into colon by considering the advantage of the fact that colon has a lower pH value (6.8) than that of the small intestine (7.0–7.8). Therefore, by using the mixture of the polymers, i.e. Eudragit S and Eudragit L in proper proportion, pH dependent release in the colon was achieved [43].

2.3. Inflammation-induced pulsatile release

Physical or chemical stress, such as injury, broken bones, etc., initiates inflammation reactions at the injured sites, there the inflammation-responsive phagocytic cells, such as macrophages and polymorph nuclear cells, play a role in the healing process of the injury. During inflammation, hydroxylradicals ('OH) are produced from these inflammation-responsive cells. Yui *et al*. [44, 45] designed drug delivery systems based on the inflammatory-induced hydroxyl radicals, which responded to the hydroxyl radicals and degraded in a limited manner. Yui and co-workers used hyaluronic acid (HA), a linear mucopolysaccharide composed of repeating disaccharide subunits of N-acetyl-D-glucosamine and D-guluronic acid. In the body, HA is mainly degraded either by hydroxyl radicals or a specific enzyme, hyaluronidase. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation through hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, they designed cross-linked HA with ethylene glycol diglycidylether or polyglycerol polyglycidylether. These HA gels degraded only when the hydroxyl radicals were generated through the Fenton reaction between Fe^{2+} ions and hydrogen peroxide in vitro. Thus, a surface erosion type of degradation was achieved. When microspheres were incorporated in the HA hydrogels as a model drug, these microspheres were released only when hydroxyl radicals induced HA gel degradation. The microsphere release was governed by the surface erosion type of degradation. Furthermore, in vivo tests of HA hydrogel degradation evidenced that HA gels were degraded only when inflammation at the implanted sited was induced by surgical incision. Control HA gels implanted in the animals were comparatively stable over a period of 100 days. Thus, patients with inflammatory diseases, such as rheumatoid arthritis, can be treated using anti-inflammatory drug-incorporated HA gels as new implantable drug delivery systems.

2.4 EnzymaticaIIy-activated Liposomes

Liposomes have structural resemblance to cell membranes, thus they have been used as drug delivery carriers. Major drawbacks are uptake by the reticuloendothelial system or a destabilization due to the absorption of plasma proteins on the lipid bilayer and have thus limited the application of these formulations. Drug loaded liposomes was incorporated into microcapsules of alginate hydrogels by Langer *et al*. [46, 47]. The hydrogel matrix was formulated in such a way that it protects the liposomes from degradation and/or dispersion in vivo, as well as possibly controls the release rate of incorporated drug molecules. The liposomes inside the microcapsules were coated with phospholipase A_2 to achieve a pulsatile release of drug molecules. Phospholipase A_2 was shown to accumulate at the water/liposome interfaces and remove an acyl group from the phospholipids in the liposome. Destabilised liposomes release their drug molecules from the inside, thus allowing drug release to be regulated by the rate determining microcapsule membrane [Figure 6].

Figure No: 06

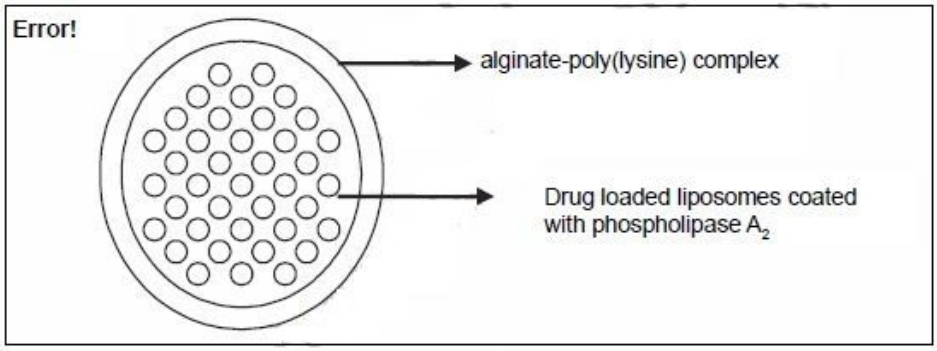

Figure 6. Schematic representation of liposome-loaded alginate-poly(l- lysine) microcapsules.

2.5. Drug release from intelligent gels responding to antibody concentration

Miyata and co-workers developed novel gels which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Miyata *et al*. [48, 49] focused on the development of stimuli-responsive cross-linking structures into hydrogels. Special care was given to antigen-antibody complex formation as the cross-linking units in the gel, since specific antigen recognition of an antibody can provide the foundation for a new device fabrication. Using the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurred. Thus, biological stimuli-responsive hydrogels were created.

3. Electric stimuli-responsive pulsatile release

The advantages of an electric field as an external stimulus are accessibility of equipment, which provides precise control with respect to the magnitude of the current, duration of electric pulses, interval between pulses etc. Electrically responsive delivery systems are devised from polyelectrolytes (polymers which contain comparatively high concentration of ionisable groups along the backbone chain) and are thus pH-responsive as well as electro responsive. The exploitations in several technologies, such as microelectronics and micromachining, as well as the potential need for chronotherapy, have currently aided the evolution of electronically assisted drug delivery technologies. These technologies include iontophoresis, sonophoresis and infusion pumps [50]. Various approaches have also been demonstrated in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels.

Kishi and co-workers [51] devised an electric stimuli-induced drug delivery system using the electrically-stimulated swelling/deswelling characteristics of polyelectrolyte hydrogels. Kishi *et al*. used a chemomechanical system, which comprised a drug model within the polyelectrolyte gel structure. These gels displayed reversible swelling/shrinking behaviour in response to on-off switching of an electric stimulus. Thus, drug molecules within the polyelectrolyte gels might be extruded out from the electric stimuli-induced gel contraction along with the solvent flow. To actualise this mechanism, poly(sodium acrylate) microparticulate gels containing pilocarpine as a model drug were formulated. By the application a direct current pilocarpine release from microparticulate gel beads was investigated. On application of electric stimuli, pilocarpine release increased proportionally with applied current-dependent manner. However, since the matrix itself exhibited higher swelling in the medium, pilocarpine release was not terminated after removal of the electric current. Thus, on-off release regulation of drugs could not be realized with this system.

Kwon *et al*. [52-54] exploited cross-linked poly(2-acrylamide-2-methylpropanesulfonic acid-co-butyl methacrylate) (P(AMPS-co-BMA)) hydrogels for electric stimuli-induced drug delivery systems. The mechanisms of drug release include expulsion of drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, and electrophoresis of charged drug towards an oppositely charged electrode and release of the entrapped drug as the gel complex erodes [55]. Synthetic as well as naturally occurring polymers, individually or in combinations, have been used for this purpose. Examples of naturally occurring polymers include chondrotin sulphate, calcium alginate, carbomer, hyaluronic acid, xanthan gum and agarose. The synthetic polymers are usually acrylate and methacrylate derivatives such as partially hydrolysed polyacrylamide, polydimethylamino propyl acrylamide. Within the negatively charged P(AMPS-co-BMA) hydrogels positively charged edrophonium chloride was incorporated as drug molecule. On applying an electric held, ion exchange between edrophonium ions and protons commenced at cathode, resulting in rapid drug release from hydrogels. This rapid drug release was attributed due to the electrostatic force, squeezing effect, and electro-osmosis of the gel. Complete on-off drug release was achieved, as no drug release was evident without the application of electric current.

Complex multi-component gels or interpenetrating networks have been developed in

order to increase the gel's electroresponsiveness [56]. Lee *et al*. developed calcium alginate/ poly (acrylic acid) composites, where the polyacrylic acid (PAA) chains were expected to be entangled through the calcium alginate matrix. PAA consists a large number of free carboxylic groups and thus included to enhance the gel's sensitivity to pH and electrical stimuli. The enhanced proportion of PAA in the composites resulted to a greater pH and electro-response[57].

4. Magnetic stimuli-induced pulsatile release

Use of an oscillating magnetic held to regulate the rates of drug delivery from a polymer matrix was one of the first methodologies investigated to achieve an externally controlled drug delivery system [58]. Magnetic carriers can experience their magnetic response to a magnetic field from incorporated materials such as iron, magnetite, cobalt, nickel and steel.

Magnetic steel beads were engrafted in an ethylene and vinyl acetate (EVAc) copolymer matrix that was loaded with bovine serum albumin as a model drug. Edelman and co-workers proved increased rates of drug release in the presence of an oscillating magnetic field [59]. The beads oscillate within the matrix on exposure to the magnetic field, alternatively creating compressive and tensile forces. This in turn acts as a pump to push more amount of the active solute out of the matrix. Co-polymers having higher Young's modulus were more resistant to the induced motion of steel beads, and accordingly the magnetic held has less effect on the rate of drug release from these materials [60].

Saslawski and co-workers [61] prepared various formulations for in vitro magnetically induced pulsatile delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1 μm) and insulin powder were dispersed in sodium alginate aqueous solution. This ferrite-insulin alginate suspension was later added to aqueous calcium chloride solution in dropwise manner which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(L-lysine) or poly(ethylene imine). Authors reported that the magnetic field characteristics due to the ferrite microparticles and the mechanical properties of the polymer matrices could play role in governing the release rates of insulin from the system.

US Patent 20066997863B2 [62] offers a treatment method that involves the administration of a magnetic material composition, which contains single-domain magnetic particles attached to a target-specific ligand, to a patient and the application of an alternating magnetic field to inductively heat the magnetic material composition, which induce the triggered/pulsed release of therapeutic agents at the target tumour or cancer cells.

5. Ultra sound induced pulsatile release

Ultrasound is predominately used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. There are various reports describing the effect of ultrasound on controlled drug delivery [63-69]. Kost and co-workers depicted an ultrasound-enhanced polymer degradation system. Incorporated drug molecules were released during polymer degradation, by repeated ultrasonic exposure. As degradation of biodegradable matrix was increased by ultrasonic exposure, the rate of drug release also increased. Thus, pulsed drug delivery was achieved by the on-off application of ultrasound [70]. Supersaxo and co-workers [71] also described macromolecular drug release from biodegradable poly(lactic acid) microspheres. Drug release from porous poly(lactic acid) microspheres exhibited an initial burst accompanied by a sustained release for over several months. Pulsatile and reversible drug release was observed when ultrasound was applied to this release system. Supersaxo *et al.* assumed that ultrasonic exposure resulted in the enhancement of water permeation within microspheres of the polymer matrix, inducing drug dissolution into the releasing media.

Miyazaki and co-workers [72] employed ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. Enhancing the strength of the ultrasound resulted in a relative increase in the amount of 5- fluorouracil released.

Enhancement in the rate of p-nitroaniline delivery from a polyanhydride matrix during ultrasonic irradiation is reported [73]. The authors noticed that the increase in drug delivery was greater than the increase in matrix erosion when the ultrasound triggering was active. Thus it was

speculated that acoustic cavitation by ultrasonic irradiation was responsible for the modulated/controlled delivery of p-nitroaniline[74].

6. Light induced pulsatile release

The interaction between light and material can be used to regulate drug delivery. This can be achieved by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to regulate drug delivery. A new class of optically active nanoparticles are Gold nanoshells which comprise of a thin layer of gold surrounding a core. The optical properties of the nanoshells can be adjusted over the visible and near IR spectrum. Implanting the nanoshells in a NIPAAm-co-AAM hydrogel resulted in the formation of required composite material. On exposure to near-infrared light, nanoshells absorbs the light and converts it to heat, raising the temperature of composite hydrogel above its lower critical solution temperature (LCST). The hydrogel collapses and this results in an enhanced rate of release of soluble drug held within the matrix [75, 76], [Figure 7].

7. Mechanical force induced pulsatile release

Drug delivery can also be achieved by mechanical stimulation of an implant. To achieve mechanical force induced pulsatile/triggered release alginate hydrogels which release vascular endothelial growth factor in response to compressive forces of varying strain amplitudes were prepared. Free drug that is held with in the polymer matrix is expelled during compression, once the strain is removed hydrogel returns to its original volume. This concept is basically similar to squeezing the drug out of a sponge [77].

8. Conclusion

A substantial amount of progress has been made towards achieving pulsatile drug delivery systems that can effectively treat diseases with non-constant dosing therapies, such as diabetes. In the present review, we described the recent approaches for stimuli-induced pulsatile release. The stimuli-responsive feature of these systems is useful for treatment of patients, due to their resulting high efficiency and lack of undesirable adverse effects to the whole body. Consequently, pulsatile release systems using stimuli-responsive materials should be promising in the future but major drawbacks arise from the biological variations among individuals. The fundamental considerations in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used, response to the external stimuli, the ability to maintain the desired levels of drugs in serum, the shelf life and reproducibility. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this area would stretch well into future and ensure in the betterment of quality of life.

9. Current and Future Developments

In the field of drug delivery, increased attention has lately been focused on the potential of systems that are able to release drugs after a programmable lag phase commencing at administration time, i.e. in a pulsatile mode. Among these systems, multi-particulate systems (e.g. pellets) offer several advantages over single unit which include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time [78].

The commercial products based on novel drug delivery systems have significantly increased in the past few years, and this development is required to continue in the future. Biomicroelectronic and microfabricated systems are currently targeted by many researchers and even by companies. A commercially available microchip, ChipRx, which integrates silicon and electroactive polymer technologies for controlled delivery and micromachined particles for a variety of drug delivery applications. Products that are presently under development for commercialization are external and implantable microchips for the delivery of hormones, proteins, pain medications, and other pharmaceutical compounds, for example Three-dimensional printing® an externally regulated system for the delivery of diclofenac sodium.

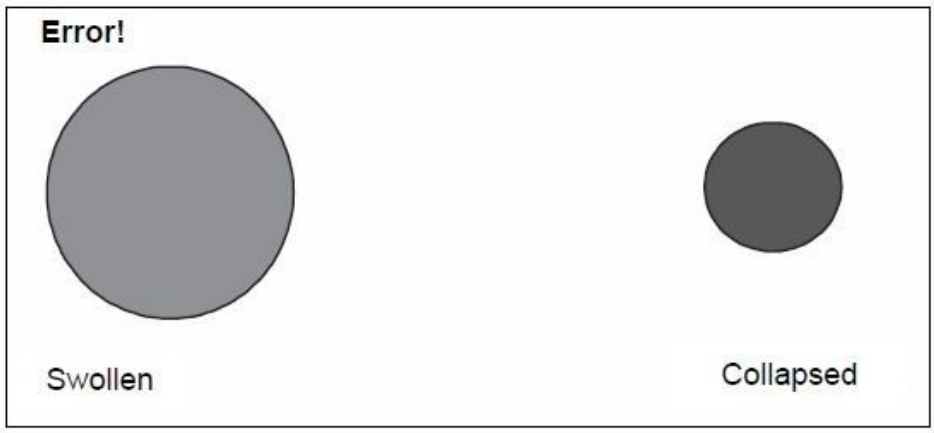

Figure 7. A representative nanoshell-composite hydrogel in the fully swollen and collapsed states

.

Microchips can be formulated as a "medicine on a chip" since various drugs can be placed in different reservoirs of the same microchip, and the release could be accomplished by applying the electrical potential to a specific reservoir. Some of the present programmable drug delivery systems that utilise polymer-based are Verelan PM, Innopran XL, Covera- HS, Cardizem LA, Uniphyl, and naproxen sodium from Andrx Pharmaceuticals [79]. The medical and pharmaceutical scientists should now focus profoundly over the importance of triggered/pulsedrelease of drugs.

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