A REVIEW ON PULSATILE SYSTEM CONSIDERING ANTIHYPERTENSIVE DRUGS

Shilpi Kashyap¹* and Aman Thakur²

*¹Assistant Professor Pharmaceutics Himachal Institute of Pharmacy, Paonta Sahib.
²Himachal Institute of Pharmacy, Paonta Sahib.

ABSTRACT
Pulsatile drug delivery system is gaining increasing attention as it offers a more efficient approach to the traditional sustained drug delivery i.e. a constant amount of drug released per unit time or constant blood levels. An intelligent drug delivery system has a capability for the adjustment of release rates of drug with a response to physiological need. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release i.e. a zero-order release is not desired. Pulsatile drug delivery system (PDDS) is characterized by a time period of no release (lag time) followed by a rapid (burst) and complete drug release. 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, such as the pH or enzymes present in the intestinal tract and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, recent update and PDDS product currently available in market.

KEYWORDS:

INTRODUCTION
PULSATILE DRUG DELIVERY SYSTEM (PDDS):- are time control drug delivery system. These systems are design to achieve time specific delivery of drugs according to the circadian rhythm of the body. Pulsatile release pattern has gained most popular form of control drug delivery system. Pulsatile systems are beneficial for the drugs having chronopharmacological behaviour. The principle rationale for the use of pulsatile release is
for the drugs where a constant drug release i.e., a zero-order release is not desired. A pulsatile drug delivery system that can be administered at night before sleep but that releases drug early morning would be a promising chronopharmaceutics system. The combinations of floating- pulsatile principle are very suitable for above mentioned diseases. Floating pulsatile drug delivery system concept was applied to increase the gastric residence of the dosage form, thereby targeting site specific drug release.

Upper gastrointestinal tract Pulsatile drug delivery system (PDDS) is characterized by a time period of no release (lag time) followed by a rapid (burst) and complete drug release. A pharmaceutical dosage form capable of delivering therapeutic agents into the body in a time-controlled or position-controlled pulsatile release fashion, is composed of a single unit system (tablet, capsule) or multiple unit system having multitude of multicoated particulates.

![Image of drug release profile]

FIG.1- DRUG RELEASE PROFILE OF PULSATILE DRUG DELIVERY SYSTEM
A: IDEAL SIGMOIDAL RELEASE, B & C: DELAYED RELEASE AFTER INITIAL LAG TIME

CLASSIFICATION
I. TIME CONTROLLED PULSATILE RELEASE
A. Single unit system
B. Multi-particulate system

II. STIMULI INDUCED
A. Inflammation-induced Pulsatile Release
B. Temperature induced systems
C. pH Sensitive Drug Delivery System
III. CHEMICAL STIMULI INDUCED PULSATILE SYSTEMS
A. Glucose-responsive Insulin Release Devices
B. Drug release from intelligent gels responding to antibody concentration

IV. EXTERNAL STIMULI PULSATILE RELEASE
A. Micro Electro Mechanical Systems (MEMS)
B. Electro responsive pulsatile release
C. Magnetically induced pulsatile release

I: TIME CONTROLLED PULSATILE RELEASE SYSTEM
These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A. Single unit system capsular systems: Different single unit capsular PDDS have been developed. A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution.

![Diagram of Single Unit System Capsular System](image)

**FIG. 2 - SINGLE UNIT SYSTEM CAPSULAR SYSTEM**

The Pulsincap system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug. The time lag can be controlled by manipulating the dimension and the position of the plug. The plug material consists of insoluble but permeable
and swellable polymers e.g.: polymethacrylates, erodible compressed polymers (e.g.: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g.: saturated polyglycolated glycerides, glycercylmonoole and enzymatically controlled erodible polymer e.g.: pectin. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

![FIG.3 - DESIGN OF PULSINCAP SYSTEM](image)

PULSATILE SYSTEM BASED ON OSMOSIS

**PORT SYSTEMS:** This system consists of a gelatin capsule coated with a semi permeable membrane (e.g.: cellulose acetate) housing an insoluble plug (e.g.: lipidic) and an osmotically active agent along with the drug formulation. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after lag time. The time lag is controlled by the thickness of semi permeable membrane. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.
DELIVERY BY A SERIES OF STOPS
This system is described for implantable capsules. The osmotically driven delivery capsule contains therapeutically active agent and water-absorptive osmotic engine separated by a slider partition to deliver the drug in a pulsatile manner through the orifice. The lag time needed for pulsatile delivery is achieved by a Series of stops placed along the inner wall of capsule which obstruct its movement. As the hydrostatic pressure rises above the threshold level the partition is forced to deliver the next batch of drug. The pulse intensity is controlled by the number of stops and their position along the longitudinal axis.

SINGLE UNIT SYSTEMS DELIVERY BY SOLUBILITY MODULATION
These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was developed for delivery of salbutamol sulphate. The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

A SYSTEM BASED ON EXPANDABLE ORIFICE
This device is in the form of capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. There is an orifice consisting of elastic material on the capsule's wall. It is so small that under relaxed condition flow of the drug through the orifice is nearly zero. When the pressure is developed inside the shell elastic wall is stretched.
Consequently the orifice expands sufficiently from time to time to allow the release of drug in pulsatile manner.

**DELIVERY BY RESERVOIR SYSTEMS WITH ERODIBLE OR SOLUBLE BARRIER COATINGS**

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer.

![Diagram of delivery system with soluble or erodible membranes](image)

**FIG.5 - DELIVERY SYSTEM WITH SOLUBLE OR ERODIBLE MEMBRANES**

**B) MULTIPARTICULATE SYSTEMS**

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients.

Pulsatile Delivery by Change in Membrane Permeability: These systems are designed when a sigmoidal release pattern is desired, therapeutically beneficial for timed release and colonic drug delivery. Drug release is achieved by change in permeability of polymeric coating layer in presence of certain counter ions of surrounding media, based on this Narisawa et al, developed a device capable of pulse-release depending on the change in diffusion properties of Eudragit RS. The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane.
Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific form but cannot be generally applied to all drugs.

![Diagram of Delivery System with Repturable Coating](image)

**FIG.6 - DELIVERY SYSTEM WITH REPTURABLE COATING**

II. STIMULI INDUCED PULSATILE RELEASE SYSTEM

A. *Inflammation-induced pulsatile release*

Inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when H is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.

B. *Temperature induced systems*

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide.
C. pH sensitive drug delivery system
Such type of pulsatile drug delivery system contains 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 selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose, Eudragit E-100.

III. Chemical stimuli induced pulsatile systems
This system was divided into three subparts and is discussed below.

A. Glucose-responsive insulin release devices
Systems as well as in other applications such as actuators, regulators, and separation systems with glyco-sensitivity. The fabrication of insulin delivery systems for the treatment of diabetic patients. Delivering insulin is different from delivering other drugs, since insulin has to be delivered in an exacts. There has been much interest in the development of stimuli-sensitive delivery system that releases therapeutic agents in presence of specific enzyme or protein. In these systems there is release of the drug after stimulation by any biological factor like enzyme, pH or any other chemical stimuli. This novel type of glyco-sensitive gel may have potential utilities in self-regulated drug-releasing t amount at the exact time of need. Many devices have been developed for this purpose and all of them have a glucose sensor built into the system. This enzyme is probably the most widely used in glucose sensing, and makes possible to apply different types of pH-sensitive hydrogels for modulated insulin delivery. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release.

B. Drug release from intelligent gels responding to antibody concentration
There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very specific. The difference in association constants between polymerized antibodies and
naturally derived antibodies towards specific antigens reversible gel swelling/deswelling and drug permeation changes occurs.

IV. EXTERNAL STIMULI PULSATILE RELEASE
This system was divided into three subparts and is discussed below.

A. Micro electro mechanical systems
A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs; each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

B. Magnetically induced pulsatile release.
Use of an oscillating magnetic to regulate the drug delivery from a polymer matrix was one of the first methodologies investigated to develop an externally controlled drug delivery system. Magnetic carriers receive a response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic. Basically the mechanistic approach behind the strategy is based on the slowing down the movement of oral drugs in the gastrointestinal system through magnetic attraction. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption into stomach or intestine.
C. Electro responsive pulsatile release
The combination of developments in several technologies, such as microelectronics and micromaching, as well as the potential need for chronotherapy, have currently assisted the development of electronically assisted drug delivery technologies. These technologies include iontophoresis, infusion pumps, and sonophoresis. They utilized a chemomechanical system, which contained a drug model within the polyelectrolyte gel structure. These gels exhibited reversible swelling/shrinking behaviour in response to on-off switching of an electric stimulus. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.

TARGETS OF PULSATILE DRUG DELIVERY[^3]

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CHRONOLOGICAL BEHAVIOUR</th>
<th>DRUGS USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning</td>
<td>Antihistamines, B2 agonist</td>
</tr>
<tr>
<td>Attention deficit syndrome</td>
<td>Increase in DOPA level in afternoon.</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain increases in early morning caused by the marked release of inflammatory cytokines, including interleukin-6 in the early hours of the morning.</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Cancer</td>
<td>Blood flow to tumour is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase</td>
<td>Vinca alkaloids, Taxans</td>
</tr>
<tr>
<td>Duodenal ulcers</td>
<td>Gastric acid secretion is highest at night, bowel motility &amp; gastric emptying are slower at night</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>Acid secretion is high in afternoon &amp; at night</td>
<td>H2 Blockers</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day time</td>
<td>HMG CoA reductase inhibitor</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in blood sugar level after meal</td>
<td>Sulfonylurea, Insulin</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>Central pathophysiology of epilepsy and behavioural classification of convulsive events</td>
<td>MAO-B inhibitor</td>
</tr>
</tbody>
</table>
Cardiovascular disease | BP is at its lowest during sleep cycle | Nitro-glycerine, CCBs, ACE inhibitors

**ADVANTAGE OF PULSATILE DRUG DELIVERY SYSTEM[^4]**

1. Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
2. Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules)
3. Reduces dose of drug without decrease in therapeutic effects.
4. Decreases side effects.
5. Decreases drug interaction due to lower cytochrome P450 isoenzymes.
6. Decreases food effect (change occurring in bioavailability of drug when given with food).
7. Improved compliance.
10. Allows site specific release for local treatment of diseases. Drug release is not affected by change in pH of the gastrointestinal tract, viscosity of lumen contents and agitation rate of GI tract.
11. The system can be utilized for many solid dosage forms like granules, microspheres, micro particles, tablets, capsules and pellets.
12. Limit risk of mucosal irritation.
13. Loss of drug by extensive first pass metabolism is prevented.
15. No risk of dose dumping.
16. Flexibility in design.

**DISADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM**

1. Low drug loading capacity and incomplete release of drug.
2. Higher cost of production.
3. Large number of process variables.
4. Lack of manufacturing reproducibility and efficacy.
5. Batch manufacturing process.
6. Unpredictable IVIVC.
7. Need of advanced technology.
PULSATILE DRUG DELIVERY SYSTEM

In traditional days, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. A second generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ‘‘zero-order’’ in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects. The oral route of drug delivery is most favoured and the most users friendly Means of drug administration having the highest degree of patient compliance, as a result of which much effort are aimed to identify orally active candidates that would provide reproducible and effective plasma concentrations in vivo. The drug delivery system on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a "pulse" after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoideal release systems.

FIG.7-Schematic Representation of different drug delivery systems where (A)=Sigmoidal release after lag time, (B)=

8. Multiple manufacturing steps.[5]
DELAYED RELEASE AFTER LAG TIME, (C) = SUSTAINED RELEASE AFTER
LAG TIME, (D) = EXTENDED RELEASE WITHOUT LAG TIME.

CHRONOPHARMACOTHERAPY

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. “Chronopharmaceutics” consist of two words chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:-

Circadian, Ultradian, Infradian

1.1.1 Circadian: “Circa” means about and “dies” means day.

1.1.2 Ultradian: Oscillation of shorter duration is termed as ultradian (more than one cycle Per 24 h).

1.1.3 Infradian: Oscillations that is longer than 24 h (less than one cycle per day).

Chronopharmacotherapy of diseases (bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension) that show circadian rhythms in their pathophysiology and treatment of such diseases require pulsatile drug delivery systems, by which drug is released rapidly and completely as a pulse after a lag time.

Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

Control drug delivery dosage forms offer many advantages over the conventional drug delivery systems are as follow,

- Constant drug level at the site of action
- Prevention of peak-valley fluctuations
- Reduction in dose of drug
- Reduced dosage frequency
- Avoidance of side effects
Improved patient compliance.\cite{11}

**Chronopharmaceutics:** “Chronopharmaceutics” consist of two words chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms (circadian, ultradian and infradian) and their mechanisms.

**DISEASE TARGETED FOR PULSATILE TECHNOLOGY**

**Cardiovascular Disease** - Several functions such as blood pressures (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile.\cite{7}

**METHODOLOGY**

**MATERIAL USED IN PREPARATION OF MICROSPHERES**\cite{33}

**TABLE 2 - MATERIAL USED IN MICROSPHERES**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Apparatus Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Beaker</td>
</tr>
<tr>
<td>2.</td>
<td>Glass rod</td>
</tr>
<tr>
<td>3.</td>
<td>Magnetic stirrer</td>
</tr>
<tr>
<td>4.</td>
<td>Hot air oven</td>
</tr>
<tr>
<td>5.</td>
<td>Ice bath</td>
</tr>
<tr>
<td>6.</td>
<td>Propeller</td>
</tr>
<tr>
<td>7.</td>
<td>Centrifugation</td>
</tr>
<tr>
<td>8.</td>
<td>pH meter</td>
</tr>
<tr>
<td>9.</td>
<td>Conical flask</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Poly Methyl Methacrylate</td>
</tr>
<tr>
<td>2.</td>
<td>Acrolein</td>
</tr>
<tr>
<td>3.</td>
<td>Glycidyl Methacrylate</td>
</tr>
<tr>
<td>4.</td>
<td>Epoxy polymers lactides</td>
</tr>
<tr>
<td>5.</td>
<td>Glycolides &amp; their co polymers</td>
</tr>
<tr>
<td>6.</td>
<td>Poly alkyl cyano acrylates</td>
</tr>
<tr>
<td>7.</td>
<td>poly anhydrides</td>
</tr>
<tr>
<td>8.</td>
<td>Albumin</td>
</tr>
</tbody>
</table>
METHODS OF PREPARATION OF MICROSHERES

SELECTION OF DRUGS

In the selection of a drug for formulation of magnetic microspheres, following points are taken into consideration:

The drug is so dangerous or labile that we cannot allow it to circulate freely in the bloodstream. The agent is so expensive, that we cannot afford to waste 99.9% of it. Requires a selective, regional effect to meet localized therapeutic objective. Requires an alternative formulation essential to continue treatment in patient whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selective organs.

METHODS

CONTINUOUS SOLVENT EVAPORATION METHOD

In this method the drug and polymer (Carrier) are dissolved in appropriate volatile organic solvent and then magnetite (if magnetic microspheres) is added to this solution along with stirring in order to form a homogeneous suspension. This suspension is added to an immiscible auxiliary solution along with vigorous stirring. Now the volatile organic solvent is evaporated slowly at 22-30°C to form microspheres. Microspheres are centrifuged then freeze dried and stored at 4°C.

PHASE SEPARATION EMULSION POLYMERIZATION METHOD

Homogenous aqueous suspension is prepared by adding albumin water-soluble drug and agent with magnetite in quantity of water (if magnetic microspheres). This aqueous suspension is then emulsified in the presence of suitable emulsifying agent to form spheres in emulsion. This aqueous proteinaceous sphere thus formed in the emulsion are stabilized either by heating at 100- 150°C or by adding hydrophobic cross linking agents like formaldehyde, glutaraldehyde or 2-3 butadiene, microspheres thus produced are centrifuged out and washed.
either in ether or some other appropriate organic solvent to remove excess of oil. Microspheres are freeze dried and stored at 4°C.

MULTIPLE EMULSION METHOD
Water dispersible magnetite with a PEG/PAA coating was added to the BSA containing inner water phase. 0.2 mL of a 1 mg/mL BSA solution added to a 4 mL mixture of DCM and EA at a ratio of 3 to 1 containing 200 mg of PLGA (first w/o emulsion was prepared using a homogenizer (Polytron PT10-35; Kinematica, Luzern, Switzerland) in an ice bath at 26 000r/min for 2.5 min). Fifteen mL of a 1% PVA solution poured directly into the primary emulsion using the same homogenizer under the same conditions for another 2.5 min. W/o/w emulsion immediately poured into a beaker containing 85 mL of 1% PVA solution and stirred in a hood under an overhead Propeller for 2 h, allowing the solvent to evaporate. Solidified microspheres harvested by centrifugation at 2500 r/min for 10 min and washed with distilled water three times.

FIG. 8 - PREPARATION OF MICROSPHERES BY MULTIPLE EMULSION METHOD

2. CROSS LINKING METHOD
Acetate buffer—used as solvent for the chitosan polymer; Glutraldehyde—used as the cross-linker; Sodium solution—used as medium. Synthesis of magnetic fluid: A 35% (w/v) ferrous sulfate solution, 54% (w/v) ferric chloride solution and 36% (w/v) sodium hydroxide solution were prepared using distilled water. Then the ferric salt and ferrous salt were mixed, stirred and heated. When the temperature reached 55°C, the alkaline solution was added. The
mixture was stirred for 30 min and then 5 of polyethylene glycol-10000 (PEG-10000) was added. The temperature was raised to 80°C and maintained for 30 min. The mixture was then neutralized while cooling and the magnetic fluid was prepared. 1% (w/w) chitosan was dissolved in acetate buffer at pH 4.5. The dissolved chitosan was added drop wise on the magnetic fluid. Formed chitosan magnetic microspheres were washed with deionized water and soaked in 1, 3 and 5 mol% glutaraldehyde solution for 2 h and then washed with deionized water.

**ALKALINE CO-PRECIPITATION METHOD**

Treat poly (acrylic acid–divinylbenzene) microspheres with dilute aqueous NaOH solution (0.5 M) for hours at suitable temperature to transform the carboxylic acid groups to sodium carboxylates and then washed thoroughly with water to remove the excess NaOH till neutral pH. Purged the microsphere suspension with nitrogen for 30 min. To this suspension add an aqueous solution of FeCl3 and FeCl2 that had been purged with nitrogen. Stirred the mixture overnight under nitrogen atmosphere for ion exchange. The resulting microspheres were washed repeatedly with water under nitrogen atmosphere to remove excess iron salts. Added drop wise aqeu NaOH solution (3M) to a suspention of the microsphere taken up with iron ions under nitrogen atmosphere to adjust the pH value to be > 12. The mixture was then heated to 60°C and kept for another 2 h. The resulting magnetic microsphere were suspended in an aqueous HCL solution (0.1M) to transform the –COONa to COOH and then washed thoroughly with water to netral pH, dried under vaccum at 50°C overnight giving magnetic microsphere.

**INVERSE PHASE SUSPENSION POLYMERIZATION METHOD**

A 250 mL three-neck flask fitted with a mechanical stirrer used for performing the reaction. Continuous phase includes: 100 mL of castor oil and 10 mL of span 80. Determined (DVB) and N, N-Methylene-bisacrylamide (BIS) dissolved completely in DMSO and the organic phase was added drop wisely into the flask, with 70°C heating using an oil bath. Ammonium persulfate (INITIATOR) added drop wise using a syringe. The reaction proceeded for 8 h with continuous stirring. The resulting microspheres were separated by centrifugation. Further washed with diethyl ether and then by deionized water.

**SONO CHEMICAL METHOD**

The microspheres composed of iron oxide-filled and coated globular bovine serum albumin (BSA). The magnetic microspheres were prepared from BSA and iron penta carbonyl, or
from BSA and iron acetate. Protein microspheres have a wide range of biomedical application, i.e. use as echo contrast agents for sonography. The microsphere were formed by either heat naturation at various temperatures, or by cross linking with carbonyl compounds in the ether phase. Cross linking was done as: the microspheres are formed by chemically cross-linking cysteine residues of the protein with HO2 radical formed around a non-aqueous droplet. The chemical cross-linking is responsible for the formation chemical ejects of the ultrasound radiation on an aqueous medium. Two sonochemical methods for the fabrication of iron oxide nanoparticles were (i) Water as the solvent and (ii) Decalin as solvent. Decane and iron pentacarbonyl Fe (CO)5 (7.43U1034 M) were layered over a 5% w/v protein.

Solution. The bottom of the high-intensity ultrasonic horn was positioned at the aqueous organic interface. The mixture was irradiated for 3 min, employing a power of W150 W/32cm with the initial temperature of 23°C in the reaction cell. The pH was adjusted to 7.0 by adding hcl. This procedure was performed again with an aqueous solution of iron acetate, Fe (CH3CO2)2 95% (Sigma) (7.66U1033 M). After the synthesis, the products were separated from the unreacted protein and from the residues of iron acetate or iron pentacarbonyl by centrifugation (1000 r/min for 5 min). The magnetic microspheres were washed a few times with sufficient volumes of water to remove the residues of the precursors.

![Synthesis of microspheres](image)

**FIG. 9 - SYNTHESIS OF MICROSPHERES**

**SWELLING AND PENETRATION METHOD**

For swelling of polymer micro particles, 0.25 g of PS (Micron-size polystyrene) p 2 articles was mixed with 35mL of a NMP/water solution in a specific v/v NMP (N-methyl-2-pyrrolidone)-to-water ratio. In later preparations of magnetic microspheres, SDS (Sodium
dodecyl sulfate) was added to the NMP/water solution. Whenever SDS was used, 0.025 g of SDS were added to each NMP/water solution. The NMP/water mixture with PS spheres was left soaking for 24h at room temperature while stirring. 2.5mL of the super paramagnetic nanoparticle dispersion (24mg/mL or other specified concentration) was added to the mixture of PS sphere and NMP/water solution at 30°C while shaking (at 140r/min) for 1-5 days to allow the magnetic nanoparticles to penetrate into the interior of the PS particles.

Afterwards, the polymer particles were separated from the solution by centrifugation. Finally, particles were sequentially washed with methanol, deionized water and vacuum dried at room temperature for 1-2 days to yield the magnetic polymer microspheres.

LOW-TEMPERATURE HYDROTHERMAL METHOD

0.1g FeO was dispersed in the aqueous glucose solution without additives, the hydrothermal reaction catalyzed only by Fe3O4was kept at 180°C for 5 h.

EVALUATION PARAMETER

DRUG CONTENT

Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 20 mg of Rosuvastatin calcium and transferred to a 100ml volumetric flask containing few ml of methanol and mixed well, made up the volume up to 100ml with methanol. Pipette out 1.0 ml from the stock solution into another 10 ml volumetric flask and made up the volume with methanol. From the above solution withdraw the aliquots of 1.0 ml, 2.0 ml and 3.0 ml (as per Beer’s range 10 to 30 μg/ml) and the volume was made up to 10 ml with methanol. The absorbance was measured at 245 nm using methanol as blank.

IN-VITRO RELEASE STUDIES

The in-vitro dissolution profile of the designed formulations was carried out using USP type I apparatus under conditions specified (Temp 37± 0.5oC, at 100 rpm). As artificial gastric fluid, 0.1N HCl (pH 1.2) was used. The artificial intestinal fluid was prepared phosphate buffer (pH 6.8).

WATER UPTAKE STUDIES

The water uptake studies were carried out on the coated tablet, i.e. tablets with the inner hydrophobic layer and the outer drug release-triggering layer. The coated tablets were accurately weighed and immersed in the artificial colonic medium (pH 5.4) in USP apparatus
I, with the stirring speed at 100 rpm. The conditions for the water uptake studies were kept the same as for the dissolution study. At predetermined time intervals, the tablets were removed from the release medium, washed twice with distilled water in order to remove the buffer solution from the surface of the tablets and then blotted with lint free tissue paper. The weight of the tablets was recorded before and after drying to constant weight in an oven at 50°C.

The water uptake was calculated as follows:

\[
\text{Water uptake} = \frac{W(t) - W(d)}{W(d)}
\]

Where \( W(t) \) is the weight of the wet tablets removed at time \( t \) and \( W(d) \) is the weight of the tablets after drying at time \( t \). The water uptake data are represented tablet.

**RUPTURE TEST**

The Rupture test on Coated tablets was Carried out using USP paddle apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The Time at which the outer coating layer starts to rupture is called a slag time. This was determined by Rupture test.

**HYPERTENSION**

Hypertension is defined conventionally as blood pressure - 140/90. Elevated arterial pressure causes pathological changes in vasculature and hypertrophy of left ventricles; as a consequence hypertension is the principle cause of stroke, leads to disease of coronary arteries with myocardial infarction and is a major contributor to cardiac failure. Hypertension in adults is defined by World Health Organization (WHO) as a systolic pressure equal to or greater than 160mmHg (21.3kPa) and a diastolic pressure (fifth phase) equal to or greater than 95 mmHg (12.7kPa).Hypertension results from increased peripheral resistance and reduced capacitance of the venous system. Although many of these individuals have no symptoms, chronic hypertension—either systolic or diastolic—can lead to CHF, MI, renal damage and cerebrovascular accidents.\(^{[16,17]}\) Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). The blood pressure declines form mid afternoon and is minimum at midnight. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or “a.m.” Systolic blood pressure rises approximately 3mm Hg/hour for the first 4-6 hours postawakening, while the rate of rise of diastolic blood pressure is approximately 2mm Hg/hour. Hypertension has been classified as "primary or essential hypertension" where definite cause for risk in blood pressure is not
known and "secondary hypertension" which is secondary to renal, endocrine and vascular lesions. Hypertension, particularly essential or primary hypertension is wide spread and a major risk factor for stroke and to some extent ischemic heart diseases.\textsuperscript{12}

\textbf{Ambulatory BP measurements}: criteria for the diagnosis of hypertension and assessment of antihypertensive therapy have thus been established on the basis of mean values determined from data gathered over a single 24-hour span.

\textbf{Clinic BP measurements}: The diagnosis of hypertension relies on clinic BP, as universally performed using the same static reference thresholds, i.e. 140 and 90 mm Hg for systolic (SBP) and diastolic (DBP) BP.\textsuperscript{13}
ANTI-HYPERTENSIVE DRUGS

Drugs used in treatment of hypertension called Anti-hypertensive drugs. Major drugs used in the treatment of hypertension are described as follows:

**TABLE 3 - ANTI- HYPERTENSIVE DRUGS**[12]

<table>
<thead>
<tr>
<th>Direct Vasodilators</th>
<th>Centrally Acting Sympatholytics</th>
<th>α -Blockers</th>
<th>Angiotensin II Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine,</td>
<td>Clonidine,</td>
<td>Doxazosin</td>
<td>Losartan potassium,</td>
</tr>
<tr>
<td>Minoxidil Sodium-</td>
<td>Guanabenz,</td>
<td>Prazosin</td>
<td>Olmesartan,</td>
</tr>
<tr>
<td>nitroprusside</td>
<td>Methyldopa,</td>
<td>Terazosin</td>
<td>Candesartan</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Guanfacine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>ACE Inhibitors</th>
<th>β-Blockers</th>
<th>Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Captopril Benazepril Enalapril</td>
<td>Atenolol</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>Spirolonolactone</td>
<td>Fosinopril,</td>
<td>Labetalol</td>
<td>Diltiazem Felodipine</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Quinalpril,</td>
<td>Metoprolol</td>
<td>Nicardipine,</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Ramipril</td>
<td>Propranolol</td>
<td>Nisoldipine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Timolol</td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION**

Although sustained and controlled drug delivery systems have acquired a lot of success and application in field of Pharmacy. These systems are not able to deliver drug according to circadian behaviour of diseases but pulsatile systems have importance in this regard. Due to their high efficiency and lack of undesirable adverse effects to the whole body, the stimuli-responsive feature of these systems is useful for treatment of patients. But major drawbacks arise from the biological variations among individuals. The basic parameters in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used. It can be concluded that Pulsatile drug delivery system provide a unique way of delivering drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. Pulsatile drug delivery system shall be promising in future. In chronobiology has demonstrated the importance of biological rhythms in drug delivery. Since it seems that timing of drug delivery has significant effect on treatment success. So this can be concluded that pulsatile drug delivery system provides a solution for delivery of drugs for those disease conditions regulated by circadian rhythm.

**REFERENCE**

6. Patil. d. Nayana,. bari m.m.. barhate s.d “a review on novel approach pulsatile drug delivery system”p-34.
9. Sai rekha g, sowjanya battu and uma maheshwar rao. “a review on various polymers and approaches used to design pulsatile drug delivery system” 4(08): 1767-1783.
16. Patri´cia severinoa, georgeg.g.deoliveirab, humbertog.ferrazb, eliana b.soutoc,d,n, mariah.a.santana “preparation of gastro-resistant pellets containing chitosan microspheres


32. Salunkhe k. Anuradha, Dias j. remeth, Mali k. kailas, Mahajan s. niranjan and Ghorpade s. vishwajeet “formulation and evaluation of floating pulsatile drug delivery system of metoprolol tartrate” 2011; 147.


