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An Overview On Role Of Precise Polymers As Functional Components In Formulation Of Chronotherapeutic Pulsatile Drug Delivery Systems For Disease Management

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ABSTRACT

Polymers play a significant role in the formulation of several dosage forms and they are considered as backbone of pharmaceutical dosage form development because they assist in controlling/modifying the release of drug from the dosage form. Polymers utilized for developing pulsatile drug delivery systems (PDDS), release the drug in a synchronized approach which benefits the patient, where the release of drug is matched with circadian rhythm and biological rhythm of disease. These pulsatile systems are designed according to circadian rhythm of disease and they release the drug rapidly after a predetermined off - release period termed as lag time. The drug should be released completely and rapidly after off release period. It can be simply described as immediately after administration of dosage form there should not be any drug release and drug should be released completely and rapidly after the lag time. They are advantageous for disease conditions exhibiting chronopharmacological behavior, examples include asthma, cardiovascular diseases, peptic ulcer, Rheumatoid arthritis, Osteoarthritis, attention deficit syndrome in children, hypercholesterolemia, etc. The review article centers on discussion about specific polymers of various categories utilized in the formulation of Chronotherapeutic pulsatile systems and the article also includes examples of some major research work done in the field of development of pulsatile formulations using those polymers.

***Keywords*:** Pulsatile, Lag time, Polymers, Natural, Drug release.

INTRODUCTION

Chronotherapeutic dosage forms are principally the drug delivery systems which releases the therapeutic agent based on time (Chrono) and circadian rhythms of the disease. They are specifically designed to accomplish location specific and time specific delivery of active ingredients in accordance with circadian rhythm of disease in the body. Pulsatile drug delivery systems (PDDS) represents a form of regulated drug delivery system. Conventional dosage forms with continuous drug release are not perfect in treatment of some situations which follows a circadian rhythm in their disease pattern, they require the drug release in a pulsed approach, instead of

immediate release or sustained release and in such situations these Chronotherapeutic dosage forms are useful. This approach holds positive benefits for the diseases exhibiting chronopharmacological performance.

The rationality for usage of these dosages depends on nature of drug release and they are suitable for diseases and drugs which doesn't mandate a constant release of drug. The disease which displays circadian rhythms necessitates the drug to be discharged at precise location, at precise time completely after an initial lag time generally designated as off release period[1]. It indicates that the therapeutic ingredient should not be discharged immediately after administration of medication but the drug release should be observed after the lag time (time where no drug is released). The basic principle here is the drug discharge from the dosage form is harmonized with circadian rhythm of disease, so that it provides greatest therapeutic gain to the patient with slightest side effects. They are also beneficial for steering the drugs which irritate stomach mucosa and also for drugs displaying broad pre-systemic metabolism. The situations which demand such pulsatile drug release, induce the design and development of this dosage forms, in such a way that the therapeutic agent is released completely after the off release period. Maximum numbers of PDDS are depository devices which are coated by polymeric layers which act as barriers. The barrier coating releases the drug from core after the polymeric layer is completely dissolved, eroded, or ruptured after definite lag time, such that drug is released quickly from inner layers.

People exhibit different circadian rhythms which are regulated by the suprachiasmatic core. Many conditions like bronchial asthma, angina pectoris, rheumatoid arthritis, peptic ulcer, hypercholesterolemia that express circadian rhythms in their disease and illnesses pattern need pulsatile drug delivery, so that by which medicine is delivered rapidly and perfectly as a heartbeat after an inactive time[2]. Other circumstances which exhibit biological rhythm includes, production of substances like follicle-stimulating hormone, luteinizing hormone, estrogen, progesterone, other process like gastric emptying, blood flow to GIT. Circadian rhythms are defined as endogenous alternations which happen with period of 24 Hours day and light cycles and the principle mechanism which regulates circadian rhythm is biological clock. This in turn regulated by a master clock, which co-ordinates all the biological clocks and maintains them in sync with body. Chronotherapy is well-defined as the co-ordination of biological rhythms of the body and medical treatment provided[2]. Depending on the route of administration pulsatile drug delivery systems are categorized into different types like oral, transdermal and implants which are represented in figure 1 and specifically orally administered time controlled pulsatile formulations are classified into various types depending on the method of their preparation and it is displayed in figure 2.

Benefits of Chronotherapeutic Pulsatile formulations

- They produce improved therapeutic activity, increased bioavailability.
- They maintain the constant drug levels at site of activity without fluctuations.
- Protect the drugs from stomach pH which are unstable and degrade in that pH[2].
- Reduced first pass metabolism, reduced gastric irritation and no dose dumping problems.
- Targeting to distal part of intestine and colon targeting is possible.
- The Dose size and dosing frequency can be reduced without reducing the activity by improving patient compliance.
- They synchronize the drug release with circadian rhythms of disease and helps in treatment.

Limitations of Chronotherapeutic Pulsatile formulations

- Drug loading capacity is very less with an incomplete release of drug.
- Dose manipulations are not possible for pediatrics and geriatrics.
- The termination of therapy is not possible immediately[3].
- Numerous Process variables are involved in the production of these dosage forms.
- Greater expense of production.
- Trained/skilled person is required.
- Advanced technology is required.

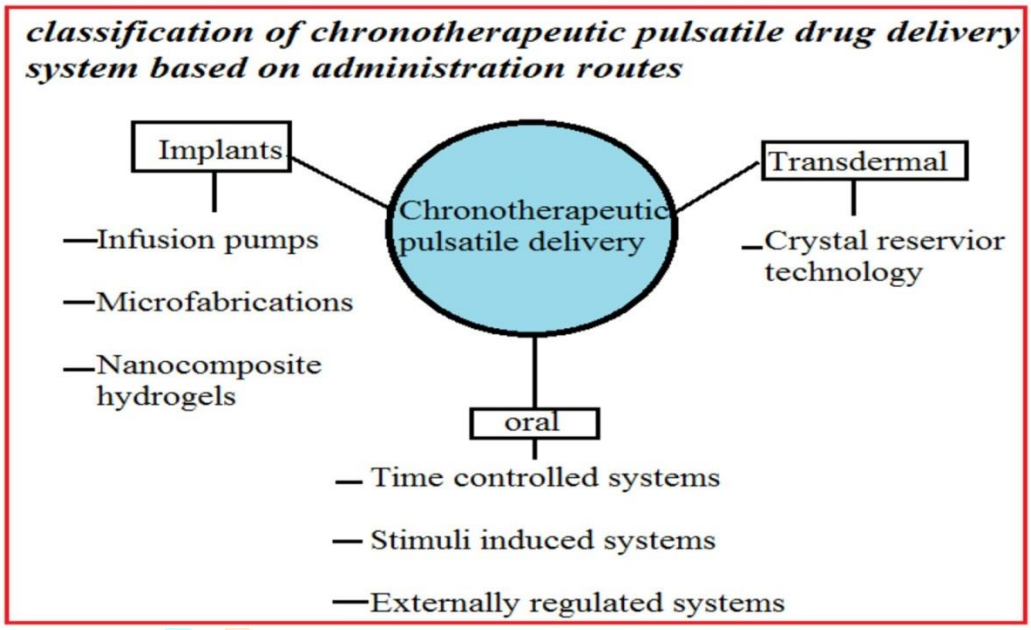

Figure 1: Classification of Chronotherapeutic pulsatile drug delivery systems

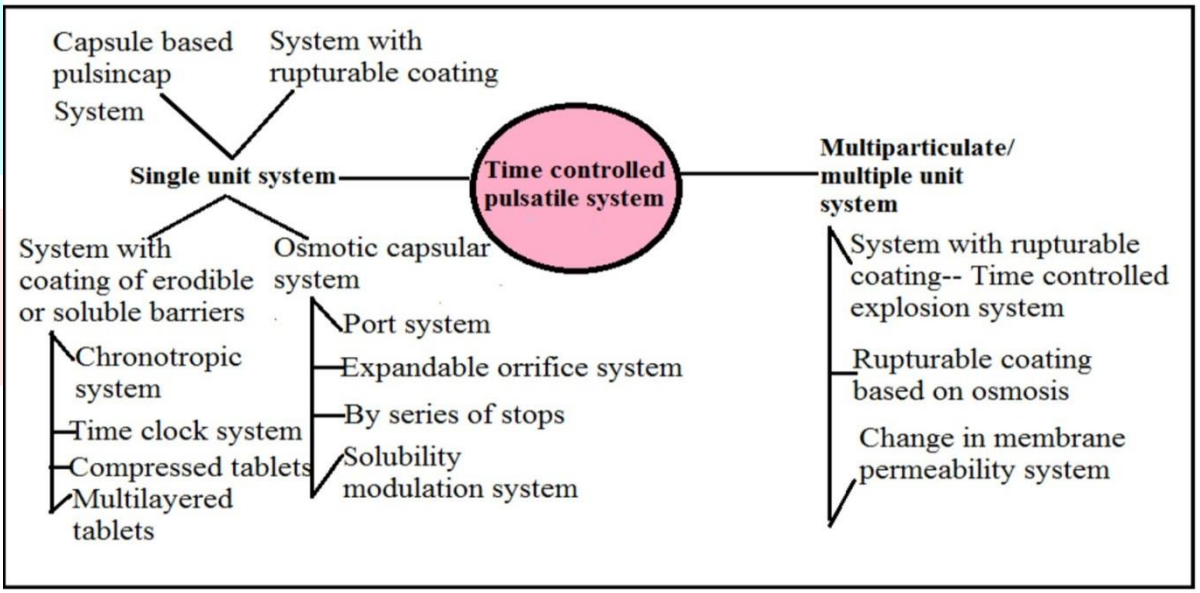

Figure 2: Classification of time controlled pulsatile systems

POLYMERS IN PDDS

Improvement in the modern drug delivery formulations starts with the usage of polymer as carriers to customize the drug release of the therapeutic agents from the dosage forms. Even though conventional formulations have a major contribution in the management and treatment of diseases, the advent of influential and specific therapeutics has accelerated the motivation for development of novel intelligent delivery systems[7]. Polymers have a functional role in the formulation development of dosage forms because they modify drug release configuration of dosage form, for example- by providing controlled release of the drugs in controlled release formulations, by producing an initial lag time where the drug is released in a regulated fashion as in the preparation of pulsatile formulations, by releasing the drug in intestine in enteric dosage form etc[4]. Polymers are defined as substances of high molecular weights that are formed from units of monomers[5]. They are useful in drug delivery systems formulation, In the pharmaceutical applications polymers exhibit various functionalities

like binders, disintegrants, flow regulators, drug release controlling agent, targeted delivery of drug to particular organ, film coating agent, enteric coating agent, etc. Table 1 represents basic classification of polymers.

Ideal properties of polymers for PDDS

- Polymers should be inert with required compatibility with the formulation.
- They have to be free from toxicity, they must be inert physiologically[5], they must be easy to manufacture, it should be cost effective.
- Polymers should possess excellent mechanical strength[5].
- It must hold compatible behavior with other excipients and drugs.
- They should not badly affect the release rate of the drug from formulation[6]

Table 1: Basic classification of Polymers

Classification	***Types and Examples***		
Depending on source	Natural polymers like Protein-Albumin, Collagen, gelatin, Polysaccharides like Agarose, alginate, carrageenan, chitosan, cyclodextrins, dextran,	Semi-synthetic polymers like cellulose derivatives, polyethylene, PGA, Polyacrylamide, Polypropylene	Synthetic polymer like Nylon, Teflon, Polysterylin
Depending on solubility and interaction with water	Water-soluble polymers like Cellulose derivatives, Xanthan gum, Chitosan, Hydroxy-propyl cellulsoe, Hydroxy-propyl methyl cellulose,	Water-insoluble polymer like Ethyl cellulose, polydimethylsiloxane	Hydro gels like Polyvinyl pyrrolidone
Depending on thermo response	Thermoplastics like polyacrylonitrile, polypropylene	Thermosetting like Bakelite	----
Depending on degradability	Biodegradable polymers like Polylactic acid, Polyglycolic acid, Nylon polycaprolac	Non-biodegradable polymers like ethyl cellulose, poly dimethylsiloxane.	----
Depending on Polymerization	Additional polymerization polymers like Polyethylene, polypropylene, polyvinyl, chloride	Condensation polymerization polymers like Polyester, polyamide, polystyrene.	----
Depending on stimuli response	pH responsive polymers like Chitosan, albumi, gelatin, poly(acrylic acid) /chitosan	Enzyme Responsive Polymers like Pectin, chitosan, cyclodextrin	Electro-Responsive Polymers like Polythiophene
Depending on Charge	Cationic : Aminodextran, chitosan, (DEAE)- dextran, TMC	Anionic: Chitosan-EDTA, , CMC, pectin, sodium alginate,	Non-ionic : Hydroxy ethyl starch, HPC, PVA

POLYMERS UTILIZED IN FORMULATION DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEMS

Polymers play a major role in formulation of pulsatile systems because they maintain the required lag time before the release of the drug completely. The lag time produced varies from 2-10 hours depending on the type of polymer used along with its concentration in the formulation[7]. Varying the concentration of the polymers and using various combinations of natural, synthetic, semi-synthetic, pH dependent, pH independent and time dependent polymers assists in handling the required off-release period. Depending on the preparation method of pulsatile drug delivery dosages various polymers will be used as listed below either singly or in combination, list of various polymers used in PDDS are represented in Table 2.

- Natural polymers
- Synthetic polymers
- Semi-synthetic polymers
- pH dependent polymer
- pH independent polymers
- Time dependent polymers

Table 2: Polymers used in PDDS formulations

Polymer type	***Examples***	***Uses in PDDS formulation***
Natural polymers	Karaya gum, Guar gum, Kondagogu gum, Tragacanth, locust bean gum, okra gum, Xanthan gum, etc	Used In Pulsincap hydrogel plugs Also utilized in formulation of the press coated tablets, etc
Synthetic polymers	Carbopol Polyvinyl alcohol (PVA), Polyethylene oxide(PEO), etc	Utilized in preparing hydrogel plugs in Pulsincap system, carbopol also used in formulating press coated tablets and preparing hydrogel plug. PVA and PEO are used in thermoresponsive (temperature as stimuli) pulsatile drug delivery systems
Semi-synthetic polymers	Hydroxypropyl methyl cellulose, Ethyl cellulose, Methyl cellulose, Sodium carboxymethyl cellulose, etc	Used In Pulsincap systems to prepare hydrogel plug, in reservoir systems cellulose derivatives like HPMC are used , ethyl cellulose is used in barrier coating, rupturable coating, in preparing hydrogel plug, etc
pH dependent polymer	Eudragit L 100, Eudragit S 100, Eudragit Fs grade Cellulose acetate phthalate, HPMC phthalate, etc	Used In pulsatile preparations like reservoir systems, press coated tablets, etc
pH independent polymers	Eudragit RS 100, Eudragit RL 100, Eudragit RS PO Eudragit RL PO, Eudragits NE grade, etc	RS 100, RL 100 used in preparing press coated tablets, Eudragit RS PO used in preparing reservoir based Multiparticulate formulations as coating agent to drug loaded pellets, etc
Time dependent polymers	Eudragit of RS, RL grades like RS 100, Eudragit RL 100, etc	In pulsatile tablets, in preparing press coated tablets and other pulsatile preparations, etc

NATURAL POLYMERS

They include Plant mucilages and gums are used in drug delivery system for various functionalities like tablet binder, disintegrant, emulsifier, suspending agent, gelling agent, stabilizing agent, thickening agent and film forming agent[7]. Plant Mucilage is considered as usual product which is formed by metabolism within the cell i.e., intracellular formation. Mucilage dissolves in water and leads to formation of slimy masses. Mucilage is chemically polysaccharide and obtained from certain plants which can be used as in many formulations. Gums are the products, formed due to pathological conditions produced either by injury or by adverse conditions of growth and frequently formed by changes in existing cell wall. Gums are substances formed due to pathological conditions and mucilage is a physiologically formed substance.

Xanthan gum

It is formed as a result of culture fermentation containing carbohydrate with Xanthomonas campestris. The other name is Corn sugar gum. It is considered as sodium, potassium and calcium salts of polysaccharide with high molecular weight holding D-glucose, D-mannose, D-glucuronic acid. The physical appearance of the gum is a cream coloured powder which is soluble in hot/cold water with neutrality to litmus. 1% solution of Xanthan gum has viscosity nearby 1000 centipoises[7]. The solutions of gum established extreme stability at pH value in the range 4 to 10. In comparison to other gums like tragacanth, Xanthan gum was found to be at ease to use and proficient in preparing various formulations with better quality.

Guar gum

Guar gum is produced from the seed endosperm of plant Cyamopsis tetragonolobus, which belongs to the family Leguminosae. It is also known as cluster bean, Guaran, Cyamopsis, Guarina. It is produced by drying the plant pods in direct sunlight followed by manually detaching from seeds. In commercial process it is mechanically done by using various processes like roasting, differential attrition, sieving, and polishing. From every seeds on splitting two separate halves of endosperm is obtained which is termed as Guar splits[7]. The husk is removed from the guar splits and treated with various techniques like flaking, hot air grinding to produce final product of guar gum which can be used in drug delivery formulations. It is used for delivering the drug to colon because it retards drug release and susceptible to microbial degradation in large intestine[8]. The gum holds the gelling property which assists in retarding the drug release from dosage form and useful for modified drug release systems. It is also used as a controlled drug release ingredient in formulations because of its great hydration rate.

Locust bean gum

It is produced from endosperm of seeds after complete refining from the carob tree Ceratonia siliqua belonging to family Leguminosae. It has several applications in the biopharmaceutical field specifically in oral delivery of drugs. It has been employed as matrix forming substance in tablets, profiting from the fact polysaccharides are commonly reflected to show significant role in the drug release mechanisms from the matrixes. The polymeric constituents are marginally soluble in the cold water and require warmness to accomplish complete hydration, solubilisation, producing maximum viscosity[9]. The locust bean gum has been inspected for controlled delivery property and also observed for compression coat property so that when applied over the core tablets it acts as proper carrier for the colonic delivery of drugs.

Kondagogu gum

It is a polysaccharide produced from the tree Cochlospermum religiosum belonging to the family Bixaceae. The Gum contains various constituents like glucuronic acid, rhamnose, galacturonic acid, glucose, mannose, galactose, arabinose and fructose. The literature Studies indicated that the gum retards the drug release from the dosage form and used in formulating extended and modified release dosage forms. The studies also indicated that increase in gum concentration decreases the drug release[9].

Grewia Gum.

It is a polysaccharide obtained from the inner bark of plant Grewia mollis which belongs to the family Tiliaceae. The constituents include rhamnose and glucose along with galacturonic acid. The studies from the literature indicates that the gum possess exceptional binding properties, compressional properties[9]. Various studies indicated that it can be used to retard the drug release as a controlled release agent in formulations

Okra gum

It is produced from the fresh fruits of plant Abelmoschus esculentus belonging to the family Malvaceae. They contain polysaccharide which is majorly constituted by various molar ratios of galactose, galacturonic acid, rhamnose, small fractions of glucose, mannose, arabinose, and xylose It was used in various formulations for controlling and sustaining the release of the drug from dosage form. It is advantageous when compared to synthetic polymers because of its safety, chemically inert, non-irritant[9], biodegradable, biocompatible. Due to

the high viscous nature of Okra mucilage it is used as drug release retarding polymer in formulation of sustained release and modified release dosage forms.

Karaya gum

It is dried, gummy exudates acquired from the tree Sterculia urens and other species of Sterculia, which belongs to family Sterculiaceae. The gum when dispersed in water, the particles do not dissolve but they absorb water as a result they swell significantly to more than 60 times of its original volume and produce a viscous colloidal sol. The gum swells due to the presence of acetyl groups in structure[10].The gum is used to control the release of drugs because of the above properties[11].

Examples of pulsatile formulations developed using natural gums - from collected literature

- Pulsatile drug delivery system of zafirlukast was prepared using Karaya gum and carbopol along with other polymers as the coating ingredient on the core tablets, to prepare press coated tablets. It produced a lag time up to 5 hours[12].

- Pulsatile Drug Delivery system of Lovastatin was prepared and the hydrogel Plug for sealing capsule body was formulated by compressing equal quantities of karaya gum, kondagogu gum, xanthan gum, guar gum along with lactose using 7 mm punches on tablet press. It produces a Pulsincap system[13].

- Pulsatile Drug Delivery System of Atenolol was formulated using saaj gum and ethyl cellulose in different ratios to produce press coated tablets and lag time of 5-7 hours was observed[10].

- Theophylline pulsatile formulations were developed in which the hydrogel plug for closing the body of capsule was prepared from endosperm of seeds of Delonix regia which is swellable in nature, it produced required lag time[15].

- Colon specific formulations for chronotherapeutic delivery of Eterocoxib was developed using HPMC and okra gum as coating ingredient on the core tablets, to prepare press coated tablets. It produced a lag time up to 4-5 hours[16].

- Pulsatile drug delivery system of theophylline was developed by producing press coated tablets using grewia mollis gum, which produced a lag time of 6 hours[17].

- Tolterodine pulsatile drug delivery systems were prepared using locust bean gum, Ethyl cellulose, HPMC K15M and other polymers to prepare core in cup tablets and lag time of 4 hours was produced with changing the HPMC concentrations[18].

SYNTHETIC POLYMERS

They include polymers like carbopol of various grades 971, 71G, 934, 941, etc which are used in formulating hydrogel plugs and also utilized in preparation of press coated tablets. Compressible erodible polymers like polyethylene oxide, polyvinyl alcohol are also utilized in preparing hydrogel plugs in Pulsincap system.

Carbopol

They are widely recognized ingredients in preparing pharmaceutical dosage forms from controlled release preparations up to oral suspensions and also in other novel Delivery Systems. Carbopols are acrylic acid derivatives crosslinked with allyl sucrose or allyl pentaerythritol. They absorb water readily as a result they get hydrated in turn leads to swelling of polymer. They are white-colored, fluffy, acidic, hygroscopic powders with a characteristic odor. It is also available in granular form it is Carbopol 71G.The mechanism can be explained as they are in dry form the structure is tightly coiled so the polymer is not capable of thickening[15]. When it is dispersed in water, the molecules of polymer get hydrated and uncoil their structure which increases the viscosity. Maximum viscosity is produced when it is completely uncoiled, that is produced by neutralizing carbopol with

base[16]. The resins of carbopol are hydrophilic materials which are not soluble in water, but when dispersed in water they form mucilaginous substances. They can swell in water up to 1000 times when compared to their original volume. Carbopols are being utilized in formulation of controlled release solid dosages, because they swell quickly in water and absorb them. They are useful in formulating controlled, extended release dosage forms to regulate the drug release. It is used in the preparation of formulations as a Bioadhesive material, controlled-release agent, emulsifying agent, emulsion stabilizer, rheology modifier, stabilizing agent, suspending agent, tablet binder[17]. Various grades of carbopol used in formulations are represented in Table 3

Polyvinyl alcohol (PVA)

PVA is generally synthesized from polyvinyl acetate using a continuous process, even though numerous methods are available for synthesis this is widely used for commercial purpose. The physical properties of PVA depend on the degree of polymerization and also on degree of the hydrolysis[18]. PVA is odorless, tasteless, translucent and white to cream-colored powder in granular form. It has solubility in water with slight solubility in ethanol and insoluble in other organic solvents. It is biodegradable polymer, and the degradability is generally enhanced by hydrolysis due to presence of hydroxyl groups on carbon atoms. The basic properties of PVA and PVA based systems depend on properties of poly (vinyl acetate), the polymerization conditions, the degree of hydrolysis[18].

Polyethylene oxide (PEO)

PEO resins are commercially prepared by polymerization of ethylene oxide in presence of a metallic catalyst. They are very hydrophilic and nonionic in nature. They are white/off-white, free-flowing powders with Minor ammoniacal odor. Polyethylene oxides have solubility in water and number of regular organic solvents like acetonitrile, chloroform, methylene chloride, but insoluble in aliphatic hydrocarbons, ethylene glycol, etc. They are used as thickening, sustained-release agent, for lubrication, in various formulations[19]. Studies conducted indicate that PEO is used to formulate PDDS, liposomes, nanoparticles, microparticles etc. The PEO of high molecular weight grades deliver delayed release of drug through the hydrophilic matrix approach.

Table 3: Various grades of carbopol for developing formulations

Carbopol grades	Physical Properties	Applications/uses
Carbopol 934	White powder, rheology modifier	Used in lotions and creams
Carbopol 940	Rheology Modifier	Used of preparing clear gels, hydro-alcoholic gels, and creams
Carbopol 971P	White powder, with mild sour/acidic odour	Used for oral and mucosal applications, including Extended and controlled release tablets
Carbopol 974P	White, fluffy powder, slightly acetic odour	oral care formulations, and extended release tablets
Carbopol 980	White powder	clear gels, hydro-alcoholic gels, and creams
Carbopol 5984	White powder	Produces very low viscosity at lower than 0.2% and very high viscosity at greater than 0.5%

Examples of pulsatile formulations developed using synthetic polymers like carbopols, PVA, PEO - from collected literature

- Pulsatile drug delivery system of amlodipine besylate was designed as Pulsincap system using various polymers like HPMC, Sodium CMC, methocel, carbopol etc. The carbopol 971 was used at concentration of 50, 75, 100 mg to prepare hydrogel plug. It was found that by increasing the amount of polymer, release rate was decreased[20].

- Pulsatile Drug Delivery System of Enalapril Maleate was developed as Pulsincap system and the capsule body is closed with plug formulated through various polymers like HPMC K4M, HPMC K15M, HPMC K100M, carbopol. The grade of carbopol used is 971 at concentration of 100 and 120 mg in each plug formulation. A change in release of drug was observed with change in polymer concentration[21].

- Gastroretentive Pulsatile release tablet of propranolol hydrochloride were prepared using press coated technology and the polymers for coating the core tablet to produce required lag time were hydroxypropyl methyl cellulose K100 M and carbopol 934 P. The prepared tablets provided drug release for 24 h with lag time of 5-6 h before drug release [22].

- Thermoresponsive pulsatile drug delivery system of Acetaminophen was developed which is sensitive to temperature. A mixture of poly (ethylene oxide) - poly (propylene oxide)-poly (ethylene oxide) triblock copolymer and poly vinyl alcohol forms a polymeric gel due to inter and intra molecular bonding of hydrogen, based on this temperature sensitivity of hydrogen bonding pulsatile drug delivery was formulated. The drug was released from the pulsatile system due to change in temperature between 35°C and 40°C[23].

- Pulsatile drug delivery system of Bosentan was developed as press coated tablets using polymers like Ethyl cellulose, HPMC K 15, Carbopol. The carbopol 974 P was used at concentration of 20, 40 and 60 mg. The lag time was optimized by changing the polymer concentrations[24].

- Olmesartan medoxomil Chronotherapeutic pulsatile formulations were produced as compression coated tablets. Initially core tablets were designed followed by compression coating with polyethylene oxide (peo) 1105 and polyethylene oxide (peo) WSR as coating polymers. Optimized formulation produced lag time of 6 hours[25].

SEMI-SYNTHETIC POLYMERS

Chemically modified cellulose derivatives are used in advanced drug delivery systems and are considered as semi- synthetic polymeric derivatives. Cellulose is naturally occurring substance in plants, many natural fibers like cotton and higher plants contain cellulose as one of their chief componen[26]. The characteristic modifications of the cellulose are esterifications, etherifications at hydroxyl group positions of cellulose. Cellulose ether derivatives are methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose. Cellulose ether derivatives up on contact with water, they swell and a hydrogel layer is formed around the dry core dosage of tablet, which acts as barrier layer and helps in formulating various dosage forms. Cellulose is insoluble in water and most common solvents. Cellulose derivatives like hydroxypropyl methylcellulose, ethyl cellulose are used in pulsatile formulations HPMC is used in preparing hydrogel plug in Pulsincap systems, Ethyl cellulose is used in barrier coated formulation and in Multiparticulate pulsatile formulations.

Ethyl cellulose (EC)

It is produced by reaction of ethyl chloride with the alkali cellulose. It is non-ionic and non pH sensitive cellulose ether derivative which is insoluble in water but produce solubility in many of polar organic solvents. It is a compatible, nonirritant, colorless, odorless hydrophobic polymeric material. It is insoluble in solvents like propylene glycol, glycerin and water and soluble in some organic solvents based on their ethoxy content. The grade of ethyl cellulose that comprises of not less than 46.5% of ethoxyl groups is easily and freely soluble in solvents like chloroform, ethyl acetate, ethanol, methanol, etc.it is used as water insoluble constituent in preparing matrix systems, coating systems in pulsatile formulations etc[27]. It has a Glass transition temperature of 1200 degrees centigrade. The viscosity of ethyl cellulose depends on degree of substitution of ethoxy groups. It is a tasteless, odourless inert stable substance at a pH in the range 3 to 11. It is compatible with many drugs because of its non-ionic behavior. It has numerous applications in drug delivery formulations like matrix systems, in coating solid dosages, as a film forming agent etc[27]. It could be used in dry form or as solution in hydro-alcoholic form for wet granulation process. It is one of the worthy non-aqueous binder for preparations which

are sensitive to water. Various commercial grades of ethyl cellulose along with their trade names are listed in the Table 4

Hydroxypropyl methyl cellulose (HPMC)

HPMC is generally considered as water soluble derivative of cellulose ether and could be used as hydrophilic polymer for formulating controlled release dosages. It is odourless, white/ creamy white fibrous/granular powder. When water penetrates the matrix and hydrating through polymer chains they ultimately untangle from matrix. It is normally familiar that drug release from HPMC follows two types of mechanisms, the drug diffusion through swelling layer of gel and drug release by erosion of matrix of swollen layer. Various grades of HPMC polymers are available based on the difference in the substitution of methoxy and hydroxyl groups and the difference in these substitution produces various viscosity grades of HPMC like HPMC K15M, HPMC K100M, HPMC K4M, HPMC E5, etc[28]. HPMC physicochemical properties depend on parameters like methoxy content, hydroxypropyl content and molecular weight. The behavior of solubility and swelling of the polymer depends on the molecular weight, amount of substitution along with crosslinking and grafting. It is utilized in film coating of formulations. , it was also observed that HPMC exhibits excellent gastric protection and it is used in colon targeted formulations[28].

HPMC is available in the form of Methocel Products (A trademark of Dow Chemical Company for cellulose ether products), which are considered as water-soluble polymers. Methocel products are obtainable in two types which include methylcellulose and hydroxypropyl methylcellulose, both types Both of Methocel hold a polymeric backbone of cellulose. These products are generally used as thickeners, binders, film formers, and water-retention agents. They are available in many viscosity grades, alternating from 3 to 200,000 mPa ·s. They are obtainable in three diverse forms which include powder, surface-treated powder, and granular form. In the nomenclature the letters E, F, J, K indicates different hydroxypropyl methylcellulose products. The number indicated after the letter indicate the viscosity in milli pascal-seconds (mPa·s) of that material. Further in designating the products the letter C indicates 100 and letter "M" indicates 1000. Further the suffixes utilized in designation of the methocel include LV which indicates low viscosity, G indicates granular materials, S indicates surface-treated and CR represents a controlled-release grades. HPMC is also available in other trade names like Benecel, it is obtainable as XR and XRF HPMC grades which are used for preparing matrix controlled-release formulations[28].

Table 4: Commercial ethyl cellulose grades used in formulations

Ethyl cellulose Trade name	***Grades/ Types***	***Properties/ Applications/uses***
Ethocel	4 Premium, 7 Premium 10 Premium, 20 Premium, 45 Premium, 100 Premium	It is a white to light-tan powder (granular). They dissolve in solvents like aliphatic alcohols, chlorinated solvents, natural oils and insoluble practically in propylene glycol, water, glycerin.
Aqualon	Based on ethoxy substitution; N (low substitution) T (mid substitution) X (high substitution/n)	It is soluble in organic solvents. It is used as non-swellable, insoluble constituent in matrix system or coating system and could be used to coat one or additional active ingredients of a tablet dosage form and prevent them from reacting with the other materials
Surelease	E-7-19029, E-7-19030,	They contain aqueous dispersions of EC holding 25% (w/w) of solid content which is available in four types as mentioned in

(Aqueous dispersion of ethylcellulose)	E7-19040, E-7-19050.	grades column. Applications comprise of coating beads and particles, granulation of matrix, for taste-masking coating, nutritional enteric coating, etc.
Aquacoat ECD	It comprises principally EC along with surfactant and stabilizer.	Used as aqueous film coating for solid dosage forms to produce extended drug release, for taste masking, protection against moisture. Surfactant is sodium lauryl sulfate (SLS), cetyl alcohol (CA) as stabilizer.

Examples of pulsatile formulations developed using Semi-synthetic polymers like HPMC, EC - from collected literature

- Pulsatile Drug Delivery formulations of Rabeprazole Sodium were developed as compression coated tablets. Polymers like HPMC K100M and EC were used as coating layer on core tablets in various concentrations. The required lag time was produced by varying the concentrations of polymers in coat layer[29].

- Indomethacin pulsatile formulation was developed as Pulsincap system. The hydrogel plug was prepared using HPMC K100M and lactose followed by compression into a plug, which is used for sealing the capsule body to produce the required lag time[30].

- Pulsatile press coated tablets of Candesartan cilexetil were developed. HPMC K100 and HPMC K4 were used as coating layer on core tablets to produce press coated tablets, which produced the required lag time by altering the concentration of polymer[31].

- Naproxen pulsatile formulations were developed as Press coated tablets. Polymers like methocel LV premium E5, methocel LV premium E15, methocel LV premium E50 were used as coating materials on the core tablets, which produced lag time of 5 to 6 hours[32].

- Telmisartan pulsatile formulation was developed as Pulsincap system. The hydrogel plug was formulated using equal quantities of HPMC K4M and lactose and granules to be filled in capsule were prepared with various polymers. The required lag time was produced by altering polymer concentrations[33].

- Dapagliflozin propanediol monohydrate pulsatile formulation was developed as press coated tablet. The polymers like HPMC K4M and ethyl cellulose were used as coating layer on core tablet. The lag time of 4 to 5 hours was produced [34].

PH DEPENDENT POLYMERS

The pH dependent polymers are also termed as pH sensitive polymers which produce response based on changes in pH of the environment around it by altering their structural dimensions. The polymeric material may swell or absorb water, fluids, collapse, uncoil, etc with relation to the pH of surrounding environment. The above said behavior is observed because of presence of required functional groups in the polymeric structure. The materials could be acidic or basic which responds to either acidic/ basic pH values[35]. They are utilized for formulating controlled drug delivery systems, targeted delivery systems, etc.

Eudragits

They are copolymers obtained from esters of acrylic and methacrylic acid and termed as polymethacrylates. Eudragits are obtainable in wide range of physical forms like powders, granules, aqueous dispersion and organic solution. They are 2 types based on solubility -- soluble and insoluble, examples for soluble polymethacrylates include Eudragits S, L, FS and insoluble Polymethacrylates includes Eudragit RL and Eudragit RS derivatives[36]. Eudragit polymers could be used individually or as a combination with other polymers to harmonize practically with any target drug release profile which includes immediate, delayed, sustained, pulsatile, accelerated and zero order release. Eudragit polymers can be easily combined into single or a multiple layer coating which creates interesting opportunities to propose and design tailored profiles for sustained drug release that could help to progress patient compliance. Eudragit RL and RS coatings have been effectively used to produce Chronotherapeutic formulations which are based on pulsatile drug release[37]. Different types of pH dependent polymers are represented in Table 5

Examples of pulsatile formulations developed using pH dependent polymers like Eudragit L 100, Eudragit S 100- from collected literature

- Rosuvastatin press coated tablets were formulated using Eudragit-L100, Eudragit-S100 and other ingredients as coating polymers for core tablets through process of direct compression. The required lag time was produced by using various concentrations of polymers[38].

- Pulsatile formulations of Montelukast sodium were developed by formulating core tablets later they are coated using Eudragit S 100, ethyl cellulose and other materials through dipcoating method to produce coated pulsatile tablets. The required lag time was achieved by altering the concentrations of coating materials[39].

- Doxofylline pulsatile tablets were prepared, initially core tablets were prepared followed by they were press coated using HPMC K4M, then final pulsatile coating was given using Eudragit L 100 and other ingredients by dip coating process[40].

- Pulsatile tablets of Nifedipine were developed as press coated tablets. Initially core tablets were formulated followed by press coated with Eudragit L 100 and Eudragit S 100 in various concentrations to produce the required lag time[41].

- Chronomodulated delivery system of Nimodipine was developed. The core tablets were prepared followed by coating was done using standard coating pan by spraying the coating solution containing Eudragit L 100 which is prepared using suitable solvent. Optimized formulation produced mandatory lag time[42].

- Candesartan cilexetil was formulated as pulsatile formulation, primarily core tablets were prepared and subsequently coated with polymers HPMC K15M, Eudragit L100, Eudragit S100 to produce compression coated tablets and lag time of 6 hours was produced in the study[43].

Table 5: Different pH dependent Polymers

Name of Polymer	***Formulation uses***	***Physical form***	***Polymer Solubility pH***
Eudragit L 100	Modified release formulations, enteric coated tablets, pulsatile dosage forms, colon targeted drug delivery, etc	Powder	6 and above
Eudragit S 100	Modified release formulations, enteric coated tablets, pulsatile dosage forms, colon targeted drug delivery, etc	Powder	7 and above
Eudragit FS 30D	Enteric formulations, colonic delivery	Aqueous dispersion	7 and above

Eudragit FS 100	Colonic delivery	Powder	7 and above
Eudragit L 100-55	Enteric coated formulations, resistant to gastric fluids	Powder	5.5 and above
Eudragit L 30 D-55	Enteric film coated formulations, resistant to gastric fluids	Aqueous dispersion	5.5 and above
Cellulose acetate phthalate	Enteric film coated formulations, binder for matrix tablets	Free flowing powder, granule	5.5 and above
Hydroxypropyl methylcellulose Phthalate	Enteric coating material	Granular powder/ flakes	5 (HPMC-P50) 5.5(HPMC p55)

PH INDEPENDENT POLYMERS

Insoluble polymethacrylates exhibit pH independent swelling and time controlled drug release, examples includes: Eudragit RL, RS polymers which are alkaline and Eudragit NE which holds neutral groups examples includes Eudragits RS 30 D, Eudragit RS 100, Eudragit RL 100, Eudragit NE 40 D etc. They exhibit permeability in gastrointestinal fluids but are insoluble in performance. The other examples for pH independent polymers include Carbopols like carbopol 934P, Cellulose derivatives like ethyl cellulose[44].

Eudragit RL grades

Eudragit grades RL100, RLPO, RL 12.5, Eudragit RL 30D are considered as copolymers of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. RL100 is solid available in the form of clear to cloudy granules with faint odour similar to amine, physical properties of RLPO includes it is a solid substance obtainable as white powder with faint amine odour. Eudrgait RL 12.5 is available as organic solution which is light yellow coloured liquid with characteristic odour[45]. RL 30D is available as aqueous dispersion.

Eudragit RS grades

Eudragit grades RS100, RSPO, RS 12.5, Eudragit RS 30D are considered as copolymers of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. RS100 is available as granule with faint odour similar to amine, physical properties of RSPO include it is a solid substance available as white powder with faint amine odour. Eudragit RS 12.5 is available as organic solution which is light yellow coloured liquid with characteristic odour[46]. RS 30D is available as aqueous dispersion with faint characteristic odour. All these grades of Eudragit are insoluble. They display low permeability and pH independent swelling. These polymers are used for controlled release formulations[47].

Examples of pulsatile formulations developed using pH dependent polymers like Eudragit RL, Eudragit RS grades- from collected literature

- Flurbiprofen press coated tablets were formulated, the core tablets were prepared later compression coated with Eudragit RL 100 and other materials to prepare press coated tablets, it produced a lag time of 6 hours[48].

- Chronomodulated delivery system of Terbutaline sulphate was prepared, primarily core tablets were prepared followed by swellable layer with HPMC followed by coating of outer layer with Eudragit RS/RL. The lag time up to 6 hours was observed[49].

- Nicorandil Chronotherapeutic system was formulated firstly as core tablet by direct compression method, followed by subsequent coating with HPMC E5 which acts as swellable inner layer, followed by outer coating with Eudragit RL/RS (1: 1). A lag time of 6 hours was observed with the study[50].

- Captopril Chronomodulated delivery dosage form was formulated using the principle of rupturable coating, core tablets prepared by direct compression, later coated with inner swellable layer using HPMC E5, followed by outer rupturable coating layer of Eudragit RL/RS (1 : 1) in various percentages in different formulations, lag time of 6 hours was achieved[51].

- Multiparticulate pulsatile drug delivery system of Montelukast sodium was prepared, firstly drug loaded pellets were formulated using spray drying technique, further they are coated with coating solution containing Eudragit RL100 and Eudragit S100 in a fluidized bed coater, it produced a lag time of 4 to 8 hours[52].

TIME DEPENDENT POLYMERS

Time dependent polymers indicate any polymeric material which may include synthetic or natural polymer whose properties changes with time such that improving their functionality and applicability in formulations. The mechanical properties of the solid polymeric materials generally depend on time, which indicates whether they are deformed rapidly or slowly. The folding, unfolding, swelling of polymers changes with time. Examples include, Eudragits of RS, RL grades like Eudragit RS 100, cellulose derivatives, etc.

Examples of pulsatile formulations developed using Time dependent polymers like Eudragit RL, Eudragit RS grades- from collected literature

- Pulsatile tablets in the form of capsule device were formulated using Amlodipine and Olmesartan, primarily immediate release tablets of Amlodipine were prepared and Olmesartan pulsatile tablets were formulated, it includes the steps-initially core tablets were prepared followed by coating with polymers like Eudragit RL100 and Eudragit RS100, then immediate release tablets along with pulsatile tablets were filled into capsule. The required dissolution profiles and lag time were produced using various polymeric concentrations[53-55].
- Nifedipine pulsatile dosage was prepared as Multiparticulate pellets, firstly solid dispersion (SD) of the drug was prepared, later the SD was loaded on non-pareil sugar spheres in various formulations to achieve immediate and controlled release pellets, followed by coating of Eudragit L100 and RS100 on controlled released pellets to produce pulsatile pellets with required lag time and dissolution profiles[56-59].

CONCLUSION

Pulsatile drug delivery systems are beneficial for treatment of diseases and ailments which follow a circadian - biological rhythm in their disease pathological pattern. To design these dosage forms and to obtain satisfactory off release period (lag time), polymers play a functional operative task by modifying and altering the release of drug from dosage form according to the requirements of formulation. Polymers possess exceptional potency for application in the direction of drug delivery systems of different types, which helps in development of advanced novel delivery systems like PDDS which progresses the therapy along with patient compliance. Polymers should be selected with utmost care to meet the requirements and also to produce safe dosage form. Natural, synthetic, semi-synthetic and other pH dependent, independent polymers including, other types which are potential in altering and amending the drug release patterns can be selected for PDDS. The multi-functionalizing performance of polymers suggests that these polymers must be characterized for biopharmaceutical activities, practical functional activities along with other properties. Numerous research works were operated on usage of several types of polymers including natural novel plant derivatives as functional agents in preparing Pulsatile Chronotherapeutic dosages and it is continued for further improvements in the field of novel delivery technologies.

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