REVIEW

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STUDY ON DRUG RELEASING BEHAVIOUR OF DIFFERENT BIOPOLYMERS

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ABSTRACT

Biopolymers play an important role in controlling drug release from various drug delivery systems. This work is done to identify their drug releasing pattern based on previously published articles since 1990.Both research and review articles are selected which discuss about various drug delivery systems which shows extended drug release behaviour of different biopolymer. Guar gum is a hydrophilic polymer, which on exposure to aqueous fluid, gets hydrated and form viscous gel layer which further retards drug release. Xanthan gum being an anionicpolymer, following exposure to an acidic media will impede gel formation and shows initial slow release of drug. Chitosan shows pH dependant solubility. The solubility is increased in acidic solutions, hence Chitosan is more commonly used for gastric delivery of drugs. The hydration property of Sodium alginate is responsible for modifying drug release at different pH values. Mucoadhesive property of Hyaluronic acid(HA) is very well utilised in various drug delivery systems. Carrageenan being an anionic polymer, undergo ionic interactions, which resulted in favorable increases in the water uptake capacity and gel viscosity, leading to a better control over the drug release. The drug release from Polycaprolactone (PCL) based drug delivery system can be accelerated by reducing crystalline nature of sample. Poly Lactide co glycolide(PLGA) microspheres shows tri phasic drug release; that is initial diffusion, matrix hydration and degradation. The self crosslinked Gelatine as hydrogel is utilised for controlled drug delivery. The side chain functional group of pectin derivatives interacts with nasal mucosal tissues enabling its utility in nasal drug delivery. Biodegradable polymers have proven their potential for the development of new, advanced, safe and efficient drug delivery system. Over the various biopolymers evaluated for biodegradation and extended drug release, PCL is identified as the best.

KEYWORDS: Biopolymers, Drug delivery system, extended drug release, in vitro drug release study.

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INTRODUCTION

The term 'Biopolymers' refers to the naturally occurring materials formed in nature during the life cycles of green plants, animals, bacteria , fungi or synthesized using naturally occurring monomers (e.g., lactic acid and glycolic acid) [1] . They have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. They are nontoxic, biocompatible,biodegradable and capable of chemical modificatio[2]. The specific application of biopolymers in pharmaceutical formulations include their use in the manufacture of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations[3]. Within these dosage forms, biopolymeric materials have fulfilled different roles such as binders, matrix formers or drug release modifiers, film coating formers, thickeners or viscosity enhancers, stabilisers, disintegrants, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives[4] . Polymers are often utilised in the design of colon specific drug delivery systems because matrices manufactured from these polysaccharides remain intact in the stomach and the small intestine, but once they reach the colon they are degraded by the bacterial polysaccharidases. This can be done via different mechanisms including coating of tablets with polymers having pH dependent solubilities or incorporating non-digestible polymers that are degraded by bacterial enzymes in the colon[5] .

This review discusses the use of different biopolymers and their utility in drug delivery system. Specific reference is made to the use of natural and synthetic biopolymers in the design of novel dosage forms such as modified release matrix type tablets and other new drug delivery systems under investigation.

METHODOLOGY

Both research and review articles are selected which discuss about various drug delivery systems which shows extended drug release behaviour of different biopolymers. The drug release behaviour of ten different biopolymers are compared and discussed. The sources include Google scholar, Elsevier, Science direct . The articles published since 1990 are taken and reviewed and a table is created for each polymer.

DISCUSSION

GUAR GUM:

Guar gum is a non-ionic, hydrophilic polysaccharide consisting of galactose and mannose residues. It is derived from the seeds of *Cyamopsistetragonolobus*, belonging to Family *Leguminosae*. In pharmaceutical formulations, guar gum is used as a thickener, binder , disintegrant, suspending agent, thickening agent and stabilizing agent with added advantage of abundant availability, naturally occurring,highviscocity and inexpensive. Guar gum is mainly utilised in drug delivery system as a matrix forming material for prolonging the drug release[6] .

Guar gum based Diltiazem Tablet is being formulated for its sustained drug release. The in vitrodrug release study shows that 41% guar gum was used to sustain the drug release for 24 hours. The dissolution was independent of stirring speed under normal conditions[7] . It was found that, on exposure to dissolution fluids ,it gets hydrated and forms a viscous gel layer that slows down further penetration of dissolution fluids towards the core of the matrix tablet. The strength of the viscous gel layer around the core of the matrix tablets generally depends on several factors such as drug particle size, force of compression, presence of other excipients, viscosity of the polymer, solubility of the drug, etc[6].The drug release from the matrix depends on the releasing area produced. Increasing the drug concentration in the gel and keeping the amount of gum constant in the formulation increases the amount of drug released as the diffusional path length of the drug remains constant. Swelling of the gum attains a steady state after initial hydration, and the drug is released in a sustained fashion over a long period of time[8] .Refer Table 1 for detailed study of in vitro drug release pattern of Guar gum.

It is also demonstrated that alkali-treated guar gum can be used as a hydrophilic matrixing agent. The in vitro study shows sustained drug release for 12 hours. Hydrophilic matrix tablets swell upon ingestion and a gel layer forms on the tablet surface. This gel layer fills interstices within the tablets, which retards further ingress of fluid and subsequent drug release. The dissolution rate

for soluble drugs is controlled by both diffusion through the gel layer and by matrix erosion, whereas the dissolution rate for insoluble drugs is dependent on matrix erosion[9]. The drug release rate can also be lowered by reducing the matrix area exposed to dissolution fluid helps in lowering matrix hydration rate and swelling rate ,also the surface through drug is released is reduced. During dissolution, barrier layers are progressively eroded and surface available for drug release increases, the drug release decrease due to increase in diffusion path length. The hydration is independant on pH of dissolution medium. The drug release in colon is due to microbial degradation of guar gum matrix tablet in presence of rat caecalconten[10] . The *in vivo* performance depends upon the biodegradability of the polymer in GI tract. It is determined that guar gum compression coated tablet released only less than 2% of drug in simulated gastric and intestinal fluids; 93%drug release occurs in colonic fluid. The major portion of drug release occurs in colon because of the susceptibility of compression coating to enzymatic action of colonic bactera[11]. Guar gum cannot be degraded by the human small intestinal enzymes and thus reaches the colon unaltered[12] .

Table 1: In vitro drug release pattern of Guar gum

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Tablet	41%	Sustained release of Diltiazem	Sustained drug release for 24 hours	Altaf SA et al 1998
2	Coated tablet	80%	colon targeted drug delivery of 5-Flurouracil	2.38% drug release in upper GIT 41%drug is released in colon	Krishnaiah YS et al 2002
3	Matrix tablet	20%	Colon targeted drug delivery of Mebendazole	8-15% drug release in upper GIT 83% drug release in colon	Krishnaiah YS et al 2001
4	Coated tablet	55%-70%	colon targeted drug delivery of Metronidazole	Less than 1%drug release occur in upper GIT 62%drug release in colon from 20-24 hours	Krishnaiah YS et al 2002
5	Matrix tablet	50%	colon targeted drug delivery of Sennosides	5-8% drug released in upper GIT 96% drug released in colon	Momin M et al 2004
6	Matrix Tablet	85%	Oral controlled delivery of TrimetazidineDihydrochloride	60% drug release by 12 hours	Krishnaiah YS et al 2002
7	Matrix tablet	64%	Sustained release of Furosemide	80.74% drug release for 14 hours	S Jain et al 2008
8	Matrix tablet	50%	Oral controlled delivery of Metoprolol tartarate	55% drug release in 12 hours	Al-Saidan SM et al 2004
9	Matrix tablet	20%	Colon targeted delivery of Celecoxib	2-4% drug release in upper GIT 37% drug release in colon	Krishnaiah YS et al 2002
10	Coated tablets	52%	colon targeted delivery of 5 - Aminosalicylic acid	2% drug release in upper GIT 93% drug release in colon	Krrishnaiah YS et al 1999

Table 2: In vitro drug release pattern of Xanthan gum

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Matrix Tablet	33.30%	Sustained release of Isosorbide-5-mononitrate	92.12% drug released within12 hours.	RajatKar et al 2010
2	Matrix Tablet	5-25%	Oral sustained release of Flourbiprofen	70% drug release in 8 hours at intestinal pH.	Syed Nisar Hussain Shah et al 2009
3	Matrix Tablet	29.30%	Controlled release of Pentoxifylline tablets	85% drug release wihin 24 hours.	Omaima N et al 2003
4	Matrix Tablet	6%	Sustined release of Diclofenac	89.67% drug release in 12 hours.	PG Yeole et al 2006
5	Coated Tablet	4.30%	Colon specific delivery of Aceclofenac	80.12% drug release at the 8th hour in colonic medium.	Ramaswamy T et al 2011
6	Hydrogel microspheres	90.00%	Sustained release of Ciprofloxacin	90% drug release within 8hours.	Bhattacharya S et al 2013
7	Matrix Tablet	10-20%	Controlled release of Indomethacin Sodium	90% drug release in 15 hours.	M MTalukdar et al 1998
8	Matrix Tablet	8%	Oral controlled delivery of Theophylline	90 % drug release in 8 hours.	Vendruscolo et al 2005
9	Matrix Tablet	5%	Sustained release of Theophylline	40% drug release in 5 hours.	Praveen Khullar et al 1998
10	Matrix Tablet	5%	Sustained release of Acetaminophen	70% drug release in 12 hours.	Dhopeshwarkar, V et al 1993

XANTHAN GUM

Xanthan gum is an anionic, extracellular polysaccharide, produced from the fermentation of gram negative bacterium *Xanthomanas campestries*. It is a hydrophilic polymer, which is utilised for its thickening, suspending and emulsifying property in water based systems. The moleculeconsists of a backbone identical to that of cellulose, withside chains attached to alternate glucose residues. Xanthan gum not only retards drug release, but can also provide time independent release kinetics It can be used in both acidic and alkaline media[13].

The Xanthan gum matrix tablet composed of 38% xanthan gum released 83.77% of drug in 12 hours. The slower drug release is due to formation of thick gel layer that delayed release from tablet matrix, where hydration of individual xanthan gum particles results in extensive swelling. As a result of the rheological nature of the hydrated matrix, the swollen particles would coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet and retarding further penetration of dissolution medium. The dissolved drug would then diffuse out of the matrix and enter the dissolution medium. It is also proposed that for highly water soluble drugs,

the rate of drug release is determined by diffusion of the drug from the gel, which in turn is dependent on gel thickness and poorly soluble drugs dependent on erosion of the matrix[13]. The higher ionic strength, higher will be drug release rate, because of increased diffusion of the dissolved drug out of the matrix. Also drug release was faster in gastric fluid because, the dissolution medium penetrates more rapidly, solubilizing a greater quantity of the drug which is then diffused out of the tablet[14]. Refer Table 2 for detailed study of in vitro drug release pattern of Xanthan gum.

The in vivo release of drug in extreme acidic medium will be negligible and thereby bioavailability of the drugs from these dosage forms will be largely dependent on the gastric emptying time. The reason is Xanthan gum being an anionicpolymer, following exposure to an acidic media will impede gel formation and shows initial slow release of drug[15]. The rate of drug release was slowed by decreasing the particle size of gum or by increasing gum concentration[16]. The tablets prepared with high concentrations of xanthan gum showed a lower rate of erosion and a faster rate of swelling, as compared with the tablets containing lower concentrations of xanthan gum. This effect may be attributed to an increase of water uptake in the presence of a larger amount of the polymer and viscoelastic mass formation in dissolution media and swelling[17].Xanthan gum is a highly stable polysaccharide not easily degraded by most microorganisms[18] .

CHITOSAN

Chitosan is a semi synthetic, cationic polysaccharide built from glucosamine and N90 acetyl glucosamine, derived from chitin, the main component of the exoskeleton of crustaceans such as shrimps and crabs [19] . It is the most suitable biopolymer to develop formulations for prolonged ocular delivery of drugs [20] . It is having mucoadhesive property, which facilitates oral and pulmonary drug delivery. Chitosan is a weak base and is insoluble in water and however, it is soluble in dilute aqueous acidic solution[21] . Refer Table 3 for detailed study of *in vitro* drug release pattern of Chitosan.

The drug release from Chitosan nanoparticles depends on the extent of matrix crosslinking as well as molecular weight of Chitosan. Higher release rates were observed for nanoparticles with lower crosslinking extent and low molecular weight of Chitosan. A slow release of Timolol Maleate during 24 hour period was observed, which ensures its utility in prolonged ocular drug delivery [22].Chitosan increases ofloxacintranscorneal penetration rate, via an enhancement of corneal permeability. This effect is attributed to the poly cationic nature of Chitosan, allowing it to strong interaction with negatively charged corneal surface[23] .

A composite hydrogel consist of polymeric network of chitosan and droplets of micro emulsion was being formulated for suataining the release of hydrophobic drugs. They exhibited a prolonged release of up to 48 hours because of formation of intermolecular interactions between the micro emulsion droplets and the polymeric network[24] . The Ionic cross linked chitosan beads were able to extend the drug release of Ciprofloxacin. . The drug release was reduced with decrease in drug concentration and increase in chitosan concentration. The diffusion of drug from the surface creates a pore in the matrix which causes a channelling effect. Incorporation of higher concentration of drug causes more pore formation leading to faster and higher drug release[25] . Also, Chitosan shows pH dependant solubility. The amine groups undergo protonation in acidic environment that increases its solubility in acidic solutions,hence Chitosan is more commonly used for gastric delivery of drugs. At the end of 4hours, 98% of drug was released in simulated gastric fluid, whereas only 70 %of drug release in simulated intestinal fluid. The degradation rate of the beads depended on the pH of test medium. In acidic medium the degradation was faster, whereas the degradation was found to be negligible at pH 7.4. The release of ciprofloxacin depends on its concentration in the bead and chitosan, thus beads exhibit burst release. An initial burst release of drug was observed, that can be due to either leaching of drug on the bead outer surface or Faster access of dissolution medium and subsequent diffusion of drug[26].

The release of ciprofloxacin from the beads decreased with increased cross-linking agent concentration. The reason is by increasing cross linking density reduces swelling of beads and thus hinders drug release. Fast and complete drug

release was observed from the batch of formulation containing equal ratio of ciprofloxacin and chitosan[26]. The degradation of Chitosan is by the action of colonic microflora and hence it is utilised for colon targeted drug delivery[27].

Table 3: In vitro drug release pattern of Chitosan

CHITOSAN					
SL. No	**Type of formulation**	**Percentage of polymer**	**Purpose of Drug delivery system**	**In vitro Drug Release**	**Reference**
1	Beads	2%	Extended release of Ciprofloxacin	93.2% drug release in acidic media 70%drug release in intestinal fluid	Srinatha A et al 2008
2	Hydrogel	1%	Extended release of hydrophobic drug Genipin	Prolonged drug release upto 48 hours	Delmar et al2015
3	Micro particle	25%	Controlled release of Clozapine	Drug release extended upto 12 hours at pH 7.4	Agnihotri SA et al 2004
4	Nanoparticle	0.20%	Delivery system for Doxorubicin	Prolonged drug release upto 5 days	Kevin A Janes et al 2000
5	In situ gel	0.50%	Controlled ocular delivery of Timolol maleate	Controlled drug release for 24 hours	Gupta S et al
6	Mucoadhesive film	2%	Ophthalmic delivery of Timolol maleate	Controlled drug release for a period of 4 weeks	Fulgencio GD et al 2012
7	Nanoparticle	66%	Controlled drug release of Timolol maleate	60 %drug release within 24 hours	Agnihotri SA et al 2007
8	Hydrogel	2%	Topical ocular delivery of Latanoprost	50% drug release in 7 days	Cheng YH et al 2016
9	Microgel	66%	Targeted pH-Mediated Intracellular Release of Methotrexate disodium	At pH 5.0 , 93% drug release in 5 days	Zhang et al 2006
10	Matrix tablet	14.60%	Prolonged drug release of Pentoxifylline	100% drug release after 12 hours	ZS Teksin et al 2009

Table 4: In vitro drug release pattern of Sodium Alginate

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Matrix tablet	50%	Controlled release of Simvastatin	100% drug release In 6 hours	B.Brahmaiah et al 2013
2	Matrix tablet	25%	Sustained release of Theophylline	40% dryg release in8 hours	Manuel E et al 2002
3	Microsphere	1%	Controlled release of Diclofenac sodium	70% drug release in 7.5 hours	Gohel M et al 1998
4	Beads	2%	Controlled drug delivery of Ibuprofen	90% drug release in 8 hours	Hwang S J et al 1995
5	Matrix tablet	50%	Sustained drug release of Chlorpheniramine Maleate	Sustain drug release upto 8 hours	Liew CV et al 2006
6	Matrix tablet	46-50%	Sustained release of Metronidazole	Sustain drug release from 8-10hours	Sriamornsak P et al 2007
7	Microspheres	2-8%	Extended drug release of Theophylline	70% drug release within 8 hours	Soni ML et al 2010
8	Microgel	2%	Controlled release of Ibuprofen	90% drug release in 11 hours	Ramesh Babu V et al 2006
9	Hydrogel	10%	Colon targeted drug release of Embelin	released only 9% of drug in upper GIT, majority of release in large intestine	MuniraMomin et al 2013
10	Beads	4%	Controlled release of Cefadroxil	low burst release rates followed by 80 % drug release in 6 hours	Anandrao R. Kulkarni et al 2000

SODIUM ALGINATE

Sodium alginate (NaAlg), a natural, anionic polysaccharide, composed of d-mannuronic acid and d-guluronic acid is derived from brown seaweeds. The naturally occurring alginate is used as binder, disintegrant, thickening agent, gelling agent and colloidal-stabilising agent. The pH sensitivity and ability to form a gel barrier in both acidic and near-neutral environment is a unique feature of sodium alginate which is very efficiently utilised in the development of controlled drug delivery system[28]. Refer Table 4 for detailed study of in vitro drug release pattern of Sodium Alginate.

The hydration property of sodium alginate is responsible for modifying drug release at different pH values[28] . The gel formed around alginate matrices in acidic conditions is of a different structure to that formed at near neutral pH

At neutral pH, sodium alginate is soluble and hydrates to form a viscous gel , and this gel critically influence the drug release. However, at pH below 3, sodium alginate is converted to alginic acid rapidly, which has the ability to swell on hydration, but is virtually insoluble and therefore drug release depends on diffusion through polymer matrices. These factors not only control the drug release but also influence the release mechanisms. The viscosity of the polymer is also having a great influence on the extent of drug release. The drug release can vary from 100% in 3 hours to 50% in 8 hours in case of low viscosity and high viscosity alginate respectively. The results show that erosion/ dissolution rate of the tablet varied according to the viscosity of the alginate[29].

The drug release decrease with increase in polymer concentration. Reduction in particle size results in slower drug release and diminished initial burst effect[30]. At low alginate concentration, drug release is sensitive to particle size effect because at this concentration, the porosity of the gel barrier is highly dependent on the relative abundance of particles available on the tablet surface. At higher alginate concentration, there are adequate particles to form a stable gel barrier. Hence, drug release from these matrices is modulated by factors include differences in liquid uptake, swelling and matrix deformation during dissolution[31] .

Close examination of the alginate matrix tablets shows the presence of surface cracks, grooves and lamination, which indicates that the integrity of the matrices was adversely affected during the dissolution study. The extent of deformation was greater at higher alginate concentrations. As alginate content increased, the extent of matrix swelling increased due to greater liquid imbibition. This caused pressure built-up within the matrix which could be released by matrix deformation. These effects will cause explosion of greater surface area to the dissolution medium and hence improved drug release [31].

HYALURONIC ACID (HA)

Hyaluronic acid is a linear ,naturally occurring high molecular weight anionic polymer, consisting of repeating units ofD-glucuronic acid and N-acetyl-D-glucosamine units. It is biodegradable, biocompatible, non-toxic, and non-immunogenic. I t is found in synovial fluid, extracellular matrices, connective tissues and organs of all higher animals [32] . It is the only non-sulfated glycosaminoglycan that is abundant in the synovial fluid and extracellular matrix [33]. It is hydrophilic in nature, which plays a critical role in the retention of proteoglycans in the cartilaginous matrix, has been recently developed as a cell carrier[34] .Natural HA is sensitive to strong acid, alkali, heat, free radicals and hyaluronidase, and it is easy to be degraded, which limits its application in prolonged release formulations, so chemically modified HA has been widely accepted as an alternative[35] . Refer Table 5 for detailed study of in vitro drug releasing pattern of Hyaluronic acid.

The ability of HA-Taxol bioconjugate to target cancer cells depends on cellular uptake of bioconjugate followed by hydrolytic cleavage of labile ester linkage, exhibits 40%drug release in 24 hours[36]. HA based microparticles for sustained release of recombinant human growth hormone was being formulated to enable once a week injection. It was found out that the drug release followed first order kinetics which ensures complete and sustained drug release for 72 hours. It was degraded by the action of hyaluronidase[37]. In the case of sustained drug delivery of protein drugs, particle size plays a very important role. The particle size of protein drugs in the range of 3 nm to 15 nm, the pore size of HA hydrogels should be approximately 5–25 nm for sustained release of protein drugs by single pass diffusion. It was shown that crosslinked hydrogel prolong the drug release for 3 weeks, taking the advantage of pKa difference between hydrazide groups of HA–ADH and amine groups of protein drugs[38.] The mucoadhesion of drug in the nasal cavity is influenced by the polymeric structure. During the process of mucoadhesion hydrogen bond is formed between hydrophilic functional group of HA and mucus glycoprotein. The ability of polymer to absorb water is dependent on the opening of polymer network and the percentage of charged group in the molecule[39]

Table 5: In vitro drug release pattern of Hyaluronic acid

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Hydrogel film	5%	Controlled and sustained release of Prednisolone	Sustained drug release for 24 hours	Luo Y et al 2000
2	Nanoparticle	0.10%	Ocular drug delivery of Dexamethasone	70% drug release for 12 hours	Kalam MA et al 2016
3	Matrix Tablet	83%	Controlled release of protein drug Ovalbumin	72% drug release in 12 hours at PH 6.8	Jinping Du et al 2015
4	Tablet	0.50%	Mucoadhesive drug delivery of fluorescein isothiocyanate-dextran	Slower release rate with a complete drug release in 12-24 hours	Krum Kafedjiiski et al 2007
5	Insitu Hydrogel	1%	Mucoadhesive sustained drug delivery of Acyclovir	10% drug release in 5 hours	Mayol L et al 2008
6	Hydrogel	13.99%	Mucoadhesive and Ophthalmic drug delivery of Ciprofloxacin	90% drug release in 20 hours	KY Cho et al 2003
7	Nanoparticle	86%	Targeted delivery of Doxorubicin	30 % drug release in 4 days	Cho HJ et al 2012
8	NanohybridLiposomes	80%	Drug delivery of Doxorubicin for cancer treatment	sustained drug release for 7 days	Park JH et al 2014
9	Nanocomposite hydrogel	1.50%	Ocular drug elivery of Latanoprost	Sustained drug release for 22 days	Widjaja LK et al 2013
10	InsituMicrogel	2%	Sustained topical ocular delivery of Cyclosporin A	80% drug release in 48 hours	Yao J et al 2013

CARRAGEENAN

Carrageenans are naturally occurring high molecular weight,anionic, sulfated polysaccharides which are hydrophilic in nature and are found in certain marine plants of the class *Rhodophyceae.*Carrageenans are classified into 3 types based on the degree of sulfation: kappa , lambda, iota . Kappa and iota -carrageenans form gels with water, lambda-Carrageenan forms viscous aqueous solutions but does not gel[40] . Carrageenan based matrix tablet exhibited prolonged drug release for 8-12 hours. The factors influencing drug release were found to be tablet diameter, drug-polymer ratio, ionic strength of dissolution media. It was found that the drug release was insensitive to moisture content. Polymers that swell in an aqueous medium have been widely used to formulate controlled-release tablets. Swellable polymers can be divided into two categories: water-insoluble polymers called hydrogels; and water-soluble hydrophilic polymers[40] .

The release of drugs from swellable controlled release systems is usually dependent on one or more of the following processes: wetting of the polymer matrix by the solvent, swelling of polymer, diffusion of drug through the hydrated polymer, dissolution of drug in the solvent and erosion/dissolution of polymer. A disadvantage of the use of hydrophilic polymers for controlled-release of very water soluble drugs is the rapid dissolution of the surface drug and quick diffusion of drug through the outer hydrated gel layer. This often causes initial rapid release followed by a period of slow release because of the increase in path length of diffusion of the drug through the polymer as the hydration and swelling of polymer matrix progresses It has also been shown that anionic polymers can control the early release of

soluble basic drugs, probably through ionic interactions[40] . The oral controlled release tablet based on Diltiazem –Carrageenan complex, were able to sustain the drug release for a period of 20 hours. The slower drug release rate was due to low porosity of tablet and slow medium penetration. The polymer reacts with drug and causes decrease in hydrophilicity and loses its ability to gellify[41] . Refer Table 6 for in vitro drug releasing pattern of Carrageenan.

The cross linking of beads exhibited less swelling which retards the drug release. The drug release is proportional to swelling ability of beads, which results in slower drug release. Also cross linking of beads results in enhanced stability and structure[42] .

The matrix tablets that contained a blend of carrageenans and cellulose ethers successfully sustained the release for a period of 10–12 h. The drug release was controlled by the amount of the gelling polymers,. The presence of viscosity enhancers in the polymer blend retarded matrix hydration. Anionic polymers undergo ionic interactions with the non-ionic polymers, which resulted in favorable increases in the water uptake capacity and gel viscosity, leading to a better control over the drug release .Cross-sectional SEM images on hydrated tablets showed a highly porous network formed by hydration of the polymers . The drug release occurs by diffusion through the porous network and polymer relaxation[43] .

Table 6: In vitro drug release pattern of Carrageenan

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Tablet	38%	Oral controlled release of Diltiazem	Complete drug release in 20 hours	M. C. Bonferoni et al 2004
2	Gel	1.50%	Oral sustained delivery of Acetaminophen	80% drug release in 5 hours	Miyazaki S et al 2011
3	Pellets	10%	Sustained release of Theophylline	100% drug release in 8 hours	Siepmann F et al 2007
4	Matrix Tablet	10%	Sustained release of TripellenamineHCl	100% drug release in 12 hours	Hariharan M et al 1997
5	Tablet	13.50%	Controlled release of Theophylline	sustained drug release for 8-12 hours	Vishal K. Gupta et al 2001
6	Matrix Tablet	30%	Controlled release of Theophylline monohydrate	100% drug release in 3 hours	Picker KM et al 1999
7	Matrix Tablet	0.06%	Controlled release of Ibuprofen	Sustained release over 12-16 hours	Jayanti Nerurkar et al 2005
8	Hydrogel Beads	3.50%	Controlled release of Betamethasone	60% drug release for 4 hours	Mohamadnia Z et al 2007
9	Gel	0.50%	Controlled drug release of Miconazole	90% drug release in 1.6 hours	Lefnaoui S et al 2011
10	Suppository	3%	Controlled release of Tenofovir	40% drug release in 2 hours	Zaveri T et al 2014

Table 7: In vitro drug release pattern of Poly Caprolactone (PCL)

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Microsphere	80%	Sustained drug delivery of Pentoxifylline	90.34% drug release at 15 hours.	Tamizharasi S et al 2008
2	Micpcapsule	50%	Controlled release of Vancomycin	40% drug release in 2 hours	Petitti M et al 2009
3	Nanoparticle	48%	Tumour Targeted delivery of Tamoxifen	40% drug in first hours followed by complete and sustained drug release in 50 hours	Chawla JS et al 2002
4	Microparticle	80%	Oral controlled delivery of Nifidipine and Propranolol HCl	60 % Nifidipine release in 8 hours and 30% release of Propranolol HCl in 8 hours	MH Perez et al 2000
5	Extrudates(Matrices	70%	Controlled release of model drug (Methylene blue)	80% drug release for 7 days	C Zhang 2016
6	Microsphere	96%	Controlled delivery of Nicardipine	Initial rapid release in first 8 hours followed by slow and sustained (30%) drug release	Barbato F et al 2001
7	Implant	75%	Controlled release of Praziquantel	64.3% drug release in 150 days	Li C et al 2010
8	Intra vitreal implant	25%	Controlled and prolonged delivery of Dexamethasone	20% drug release in 150 days	Fialho S et al 2008
9	Nanoparticle	90%	Sustained drug delivery of Docetaxel for cancer treatment	30% drug release for 28 days	Mei L et al 2011
10	Microsphere	80.00%	Sustained drug release of Papaverine	80% drug release in 6 days	Jeong JC et al 2003

POLY CAPROLACTONE (PCL)

PCL is a hydrophobic, crystalline, synthetic biodegradable polyester that is widely used in drug delivery applications. High permeability to many drugs and a lack of toxicity has made PCL and its derivatives well suited for colloidal drug delivery. It is much more resistant to chemical hydrolysis and is achiral, so the possibility of property modulation through the configurational structure of polymer chains is limited. The in vitro degradation can be enhanced in the presence of the enzyme Lipase[44] .

The release of papaverine from PCL micro particles is controlled by drug diffusion through the amorphous region of the polymer matrix, not by polymer erosion. The mechanism of drug release involves diffusion through the polymer matrix, diffusion through pores in the matrix, and drug liberation by polymer erosion. The sample prepared with a higher PCL solution concentration showed a lower drug release rate. In the case of a high

molecular weight polymer resulted in a rapid release[45] . The drug release from PCL Matrix occurs by a combination of both diffusion and dissolution process. Here PCL is hydrophobic in nature, various other hydrophilic components are added to improve the drug release rate. The drug is distributed in both PCL matrix and hydrophilic components. So the release of drug follows first order kinetics in the initial stage , then in later stage drug release occurs by diffusion of drug through porous PCL matrix[46] . Larger the diameter of the implant, slower will be drug release. Drug release increase with increase in drug loading. But the effect of drug loading on drug release weekens with increase in diameter of the implant[47]. Refer Table 7 for in vitro drug releasing pattern of PCL.

The PCL microparticles possessed a low degradation rate due to higher crystallinity. In the presence of lipase, the PCL microparticles appeared to be slightly porous on the surface only after 3 weeks of degradation . After 9 weeks, channels and pores could be observed on the surface of the microparticles. The degree of degradation was estimated from the reduction of molecular weight and the change in molecular weight distribution. After 5 weeks of degradation the reduction rate of molecular weight of PCL microparticles in the case of with lipase was 24%, which is much faster than that without lipase (only 11%). The degradation of PCL first occurs in the amorphous area of microparticle, so that the degradation rate can be accelerates by reducing the crystallinity of polymer[48].

POLY LACTIDE CO-GLYCOLIC ACID (PLGA)

PLGA is a synthetic, biodegradable polymer , which is a copolymer of poly lactic acid (PLA) and poly glycolic acid (PGA) which is relatively hydrophobic in nature. PLGA protects the encapsulated drug from enzymatic degradation, provides a wide range of degradation rates, from months to years, depending upon its composition and molecular weight. The biodegradation rate of PLGA polymers is dependent on the lactide/glycolide, molecular weight, degree of crystallinity and the transition glass temperature of the polymer.

PLGA polymeric nanoparticles have got certain advantages like being biocompatible and bioerodible and further its monomers i.e., lactic acid and glycolic acid are also biodegradable and are substrates of Kreb's cycle, hence produce least toxicity[49] .

The release profile of PLGA nanoparticles can be divided into 4 different phases: initial burst, induction period, slow release period and final release period. Various lactide to glycolide ratio of the copolymer shows different release profile of the drug which can significantly covers extended and rapid drug release in one formulation[50]. Refer Table 8 for in vitro drug releasing pattern of PLGA.

The release of Ganciclovir from PLGA microspheres shows tri phasic drug release; that is initial diffusion, matrix hydration and degradation. During initial diffusion, the drug release depends on the space in the microsphere matrix through which drug diffuses. Degradation studies with PLGA shows that as the lactide content increases, molecular weight increases, lipophilicity increases, resulting in requirement of longer hydration period for onset of bulk degradation. The dispersion of microsphere inside gel can slows down initial burst effect and result in controlled drug release[51] . The targeting efficiency of PLGA microspheres for intraarticular administration of Lornoxicam is being utilised for prolonded drug delivery. Drug targeting in joint cavity is due to prolonged stagnation time of drug in joint. PLGA microspheres are effective in preventing the drug leakage induced by clearance of small drug molecule and prolong retention time in joint cavity[50] . The controlled delivery of Aspirin from PLGA based phase sensitive system. exhibited drug release for 7 days. The drug release was affected not only by polymer's self catalysed degradation but also by drug specific polymer degradation[52] . The burst effect was due to diffusion of dissolved drug deposited inside the pores of particle near to surface[53] . Drug release was due to matrix diffusion with simultaneous erosion of the controlled system. Takahashi et al 2004 developed an Implantable tablet for a week long sustained drug release.The release rate is dependanton rate of absorbtion of dissolution medium[54] .

Table 8: In vitro drug release pattern of ;PolyLactide co glycolide (PLGA)

SL.No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Microspheres	50%	Sustained delivery of Ganciclovir	90% drug release for 56 days	Duvvuri S et al 2005
2	Microspheres	4%	Targeted drug delivery of Lornoxicam	80% drug release for 29 days	Zhang Z et al 2011
3	Nanoparticle	83%	Delivery of Capecitabine for Prostate cancer	80% drug release for 4 days	Sun SB et al 2015
4	Nanoparticle	30%	Oral drug delivery system of Acyclovir	60% drug release in 32 hours	UV Bhosale et al 2013
5	Insitu gel	30.00%	controllled delivery of Aspirin	Constant rate drug release for 7 days	Tang Y et al 2008
6	Implant tablet	83%	Sustained release of Ketoprofen	75% drug release for 5 days	H Onishi et al 2005
7	Nano particle	76%	Dual drug delivery of Clozapine and Risperidone	80% drug release in 10 days	Panda A et al 2016
8	Micro particle	90%	Ramizolmicroparticl e	sustained release over 72 hours	Wright L et al 2018
9	Implant	10%	Controlled release of Thymosin alpha 1	slow and controlled release upto 28 days	Liu Q et al 2010
10	Micro particle	20%	Controlled release of 5-Flurouracil	Initial burst release followed by75% drug release within 21 days	Faisant N et al 2002

GELATIN

Gelatin is a natural polymer that is derived from collagen, and is commonly used in pharmaceutical industry because of its excellent biocompatibility, controllable biodegradability and non-immunogenicity. Commercially, gelatin is available as both cationic (gelatin type A, isoelectric point 7–9, prepared by an acid hydrolysis of pig skin type I collagen) or anionic (gelatin type B, isoelectric point 4.8–5, prepared by an alkaline hydrolysis of bovine collagen). The two different types of gelatinare electrically different in nature because the alkaline processed gelatin possesses a greater proportion of carboxyl groups, rendering it negatively charged and lowering its isoelectric point (IEP) compared to acidic-processed gelatin which possesses an IEP similar to collagen[55] . The drug release from Gelatin nanoparticles may be due to three predominant mechanisms including desorption, diffusion and biodegradation [56] .

The self crosslinkedGelatin as a hydrogel is utilised for controlled drug delivery. It was found that coss linking is essential to prevent gelatin dissolution and immediate drug release at body temperature. Electrostatic drug-matrix interaction is responsible for the difference in drug releasing behaviour at acidic and basic pH. At pH 4, electrostatic repulsion enhanced drug release , while at pH 6.4 electrostatic attraction reduced drug release[57] . The smaller the molecular weight of drug, faster will be the drug release because the entrapment of drug within gelatin nanoparticle was based on weeker interaction as compared to high molecular weight drug[58] .Refer Table 9 for in vitro drug releasing pattern of Gelatin.

The paclitaxel loaded gelatin nanoparticles shows 93% drug release after 2 hours. The entrapped drug is present in amorphous state which represent higher water solubility than crystalline state. It shows rapid degradation of nanaoparticles with half life of 23.8 minutes in presesnce of 0.01 mg/ml Pronase[59] . The in vitro release of anticancer drug from swellablegelatin nanoparticles. increasewitn increase in gelatin content upto 8g,but after that drug release decreases. The reason for enhanced swelling is that by increasing the amount of gelatin, the nanoparticles of large size and wide pores are produced, which allow greater number of water molecules to enter into the nanoparticles. This consequently results in larger release of drug into the release medium. However, beyond 8.0 g of gelatin content, the volume fraction of gelatin increases in the nanoparticles, and as a result, both the water and drug molecules will have to travel a longer path through the nanoparticle to penetrate into the release medium. This results in fall of both the swelling ratio as well as the amount of drug released[60].

Table 9: In vitro drug release pattern of Gelatin

SL. No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Nanoparticle	98%	Targeted delivery of Zidovudine	80%drug release in 24 hours	Namdeo R Jadhav et al 2013
2	Nanosphere	10%	Sustained delivery of osteogenic proteins	90% drug release in 4 weeks	Wang H et al 2012
3	Nanoparticle	10%	Delivery of protein and peptide drugs	Burst release of 48% in first 30 minutes, followed by 80% drug release in 3hours and then sustain drug release for 6 days	K Ofokansi et al 2010
4	Nanoparticle	99%	Intravesical therapy of Paclitaxel for bladder cancer	92% drug release in 3 hours	Ze Lu et al 2004
5	Nanoparticle	95%	Controlled release of Reservatrol for lung cancer	80% drug release for 54hours	S Karthikeyan et al 2013
6	Nanoparticle	64%	Sustained oral delivery of Amphotericin B	rapid release up to 12 hours followed by sustained release until 72 hours	S Jain et al 2012
7	Nanoparticle	75%	Controlled drug delivery of Amphotericin B	80% drug release for 8 days	Nahar M et al 2008
8	Nanoparticle	50%	Site specific delivery of Didanosine	60% drug release for 5 days	Jain SK et al 2008
9	Microsphere	4%	Controlled release of Ceftiofur-Na	90% drug release for 50 hours	Hao Z et al 2013
10	Ocular insert	20%	Sustained release of Aceclofenac	80% drug release for 24 hours	Mathurm M et al 2010

The use of gelatinnanospheres instead of microspheres resulted in reduced burst release due to the higher specific surface area of nanospheres, thus facilitating stronger binding by poly ion complexation. The stronger interparticle forces between nanosphere will improves cohesion and confinement to the target site of application Gelatinnanospheres showed much faster degradation, with more than 70% of gelatin degradation after 4 weeks when the study is conducted in presence of collagenase-containing phosphate buffer solution to induce enzymatic degradationofgelatin. The faster degradation is due to the large specific surface atrea available for enzymatic degradation[61]. The main advantage of gelatin is its ability to control drug release by fine tuning of its biodegradabilitty[62]

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Table 10: In vitro drug release pattern of Pectin

SL.No	Type of formulation	Percentage of polymer	Purpose of Drug delivery system	In vitro Drug Release	Reference
1	Coated pellets	2%	colon specific delivery of 5-flurouracil	85% drug released in simulated colonic media	He W et al 2008
2	Matrix Tablet	20%	Colonic delivery of Theophylline	At pH 7.4, 80% drug is released in 8 hours	Mura P et al 2003
3	Beads	6%	Sustained release of Piroxicam	80% drug release in 2 hours	Aydin Z et al 1996
4	Gel beads	5%	Controlled drug delivery of Indomethacin	90 % drug release in 6 hours	Sriamornsak P et al 1998
5	Gel beads	5%	Oral delivery of BSA(Bovine serum albumin)	80% drug release in 12hours	Sriamornsak P et al 1998
6	Matrix Tablet	30%	Colonic delivery of Naproxen	92% drug release in 4 hours	KP Rao et al 2003
7	Pellets	10%	Colonic delivery of Theophylline	Complete and sustained drug release for 14 hours at pH 6	Semde R et al 2000
8	Nanospheres	80%	Sustained drug delivery of 5-FU	80 % drug release for 125 hours at PH 7.4	Cui-Yun Yu et al 2009
9	Insitu gel	1.50%	Oral sustained delivery of Paracetamol	15% drug release for 6 hours	Kubo W et al 2004
10	Micropheres	3%	Sustained release of Sulphathiazole	86% drug release in 22.5 hours	TW Wong et al 2002

PECTIN

Pectin is an anionic, polysaccharide widely utilised by the pharmaceutical industry, for the development of controlled-release oral dosage forms. The basic chemical structure of pectin is a linear polymer of D-galacturonic acid units and their methyl esters connected with a-(1,4)-glycosidic bonds It has high potential as a hydrophilic polymeric material for controlled release matrix drug delivery systems, but its aqueous solubility contributes to premature and fast release of the drug from these matrices[63] . One of the options to reduce the high solubility of pectin in aqueous medium is through chemical modification without affecting favourable biodegradability properties[64,65] . The pectin based matrix tablet swell in contact with aqueous medium and formed a continous gel layer. The mechanism of drug release may be diffusion or erosion controlled or their combination. The drug release was faster in acidic medium, because pectin showed lower swelling ability in acidic medium. In neutral medium, the hydration of pectin results in extensive swelling. Initially when separated particles comes into contact and thus swollen particles coalesced, this results in viscoelastic matrix, which retard further penetration of dissolution medium[66] .

Drug release also depends on the degree of methyl esterification. The lower degree of esterification, faster will be drug release because of higher hydrophilicity and solubility . Pectin is resistant to protease and amylase, which are active in theupper gastrointestinal tract, whereas it can be digested by pectinase in the colon. This makes pectin an ideal drug carrier for colon-specific drug delivery, which is known to have the advantage to achieve higher bioavailability because the pH in the colon is neutral and peptidase activity is relatively lower[66].

The side chain functional groups of pectin derivatives interacts with nasal mucosal tissues enabling its utility in nasal drug delivery .Pectin derivatives reacted with mucin to form gel complexes, which can diffuse into nasal mucosal tissues and pectin gel formulations can regulate the adsorption of incorporated drugs. Pectin adsorption in nasal tissues was dependant on gel concentration and the side chain functional groups of the pectin [67]

The drug- pectin interaction could markedly retard drug release in HCl/KCl and NaOH/ KH2PO4 buffers,thus enabling its utlity in formation of colonic delivery systems of potent drugs[68] . Pectin based microparticles have a high pH sensitivity, The drug release rates at both pH 6.0 and pH 6.8 in the presence of pectinase are faster than that in the absence of pectinase. These data imply that the microparticle drug delivery systems allow the rapid drug release in the colon[63] .Refer Table 10 for invitro drug releasing pattern of Pectin.

CONCLUSION

Biodegradable polymers have proven their potential for the development of new, advanced, safe and efficient drug delivery system. Both natural and synthetic polymers are well explored and used in pharmaceutical formulation development in recent years. They are increasingly included in dosage forms to fulfil specialised functions for improved drug delivery because many new drugs have unfavourable physicochemical and pharmacokinetic properties. Some polysaccharides obtained from plants such as carrageenan,
alginate, guar gum have shown excellent potential as carrier materials in matrix type controlled release dosage forms such as microparticles, beads, tablets and cross-linked hydrogels. Synthetic polysaccharides like polycaprolactone, poly lactide co glycolide have been investigated for their sustained delivery in implants. The drug is released from the polymeric matrix by changes in the chemical or physical properties including biodegradation of the polymer (surface erosion), progressive swelling with subsequent drug diffusion from the swollen region, and hydrolysis of drug-polymer bonds. The diffusion of drug from the surface creates a pore which causes channelling effect. Biodegradability depends not only on the origin of the polymer but also on its chemical structure and the environmental degrading conditions. In the area of drug targeting, there needs to be continuing emphasis on understanding the interaction between polymeric particles and biological systems such as blood components, cell types (e. g., phagocytes), and cell receptors. To enhance the properties of biodegradable polymers, considerable measures of techniques have been created, for example, copolymerization, gelation, crosslinking or joining. These strategies enhance both the biodegradation rate and the mechanical properties of the polymer. In general, these polymers are biocompatible, non-toxic and biodegradable. Provided the drug is continuously

delivered at a constant rate by a controlled-release device and its removal follows first order kineties then a stationary drug level will be established. The stationary level can be kept extremely low if the delivery device is placed close to the target organ. Recently they are increasingly included in dosage forms to fulfil specialised functions for improved drug delivery because many new drugs have unfavourable physicochemical and pharmacokinetic properties.

ABBREVIATIONS

PCL- Poly caprolactone, PLGA-Poly lactic glycolic acid, HA-Hyaluronic acid, SEM- Scanning electron microscopy, PGA- Poly glycolic acid, PLA- Poly lactic acid

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