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Polymer Based Drug Delivery:A Targeted Approach

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ABSTRACT:

In modern era, society is facing various autoimmune, metabolic, cancerous diseases and neurodegenerative disorders. Treatment of such disorders with the help of conventional dosage forms is not effective as majority of such drugs have poor absorption in body and low bioavailability. In the recent past years, huge advancement can be seen in the use of different biopharmaceuticals such as peptides, nucleic acids, proteins and some other related bioactive molecules in the form of novel drugs. If we directly administer such agents through oral route without any proper delivery system, then we have to face various issues related to bioavailability, distribution and stability. A well refined and well researched delivery system is required to improve both pharmacodynamic as well as pharmacokinetic (absorption, metabolism, distribution and elimination) parameters of these novel drugs. The use of polymers in the pharmaceutical dosage form may show various therapeutic, pharmaceutical and pharmacokinetic advantages in comparison to various others conventional dosage forms. Polymer-based delivery approach helps in bioavailability enhancement of these therapeutic agents in the target tissues/cells. In this review article we will discuss about various advantages of using polymers in pharmaceutical dosage forms in order to attain targeted as well as controlled drug delivery. We will also highlight the role of combination (conjugation) of polymers incorporating different drugs to ensure the target release and stability of the drug in the desired organ with apt examples.

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Keywords: polymers, polymeric combinations, targeting, prolonged drug release

1. Introduction:

In the recent past years, huge advancement can be seen in the use of different biopharmaceuticals such as peptides, nucleic acids, proteins and some other related bioactive molecules. These biopharmaceuticals ingredients are used as therapeutic agents for various diagnosing diseases. However, the major problem in using these biopharmaceuticals is their drug delivery system. Like most of the pharmaceuticals drugs like rifampicin, paracetamol, albendazole and many more, we cannot directly deliver peptides [1], nucleic acids [2], proteins [3] directly to the body either by oral or i.v. route. If we directly administer such agents through oral route without any proper delivery system [4], then we have to face various issues related to bioavailability, distribution and drug stability related issues within the body. A well refined and well researched delivery system is required to improve the pharmacodynamic and pharmacokinetic (Absorption, metabolism, distribution and elimination) parameters of these novel drugs [5]. In order to achieve better biocompatibility and specificity with cell/tissue, a well refined delivery system will be required [6]. In order to achieve the well sophisticated drug delivery system, a new generation of drug delivery system has been discovered which has mainly emphasized on the controlled delivery of drug which also helped in increasing the stability of the drugs. The targeted and controlled drug delivery system is one of the highest demanding, progressing and growing scientific area in the pharmaceutical market [7]. The use of targeted and controlled drug delivery system provides the researchers various advantages over the traditional dosage forms. Better biocompatibility, safety from degradation by various enzymes, better cell/tissue specificity, good absorption, controlled release of drug, high circulation time, drug stability and many more advantages can be covered under targeted and controlled drug delivery systems [8].

In modern era, society is facing various autoimmune, metabolic, cancerous diseases and neurodegenerative disorders. Treatment of such disorders with the help of conventional dosage forms failed in giving the adequate treatment benefits as majority of such drugs which are used to treat these disorders have poor absorption in body and low bioavailability which further

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resulted in poor distribution of the drug in the specific site of action. This also resulted in the rapid body clearance of the drug from the body because of high metabolism of drug and its excretion. In the last three decades, huge workis going on some new and novel drug delivery systemsin order to guaranteehigher therapeutic benefits with the least amount of drug and as minimum side effects as possible [9]. The basic concepts which is followed by the different researchersincludes the methods through which one can perform the enhancement in the pharmacological activities of variousactive moieties by modifying theirpharmacokinetic properties like distribution, absorption, metabolism and excretion [10]. This can also be achieved by modifying the pharmacodynamic properties like pharmacological responses, mechanism of drug action,affinity towards the site of action and many more related factors. The use of these novel delivery systems for release of drugs helps in overcoming the drug resistance and also showed better patient compliance [11].

For achievement of targeted and controlled drug delivery, most of researchers usually prefer the use of different polymers. Polymers play a very important role in order to develop a dosage form which has repeated drug release profile with overlapping manner. This is applicable for all types of drugs (lipophilic or hydrophilic), in which drug release is possible in a very synchronized and coordinated manner, with a constant release of dosage form for a longer period of time [12]. These polymers may include long linear type of polymers or large branched type of polymers. Sometimes the polymer is modified by adding and joining with the active moiety with which we get a new type of modified polymer with some bioactive properties. There are many advantages of using polymers in the dosage forms for example by using the polymeric systems there is an increase in permeability and retention factor, drug stability is increased [13], controlled and sustained release of drug can be obtained and many more such advantages [14]. In this review we will discuss various such advantages of using polymers in the pharmaceutical dosage forms.

The polymers although have various advantages but there are multiple disadvantages too of using polymers which should not be ignored. Polymers can be natural as well as synthetic type. Most commonly the naturally occurring polymers are usually biodegradable in nature. However,

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the one which are synthetic in nature are non-biodegradable in nature [15]. Hence, the use of biodegrable natural polymers is the most common practice in the pharmaceutical dosage forms. Moreover most of these natural occurring polymers are hydrophilic in nature with least side effects. But still we are unable to use these natural polymers in most of the pharmaceutical dosage forms because although they are abundant in nature and very easy to found but purification of these natural polymers and reproducibility is very difficult task for the researchers. Various researches are going on in order to achieve the purification of these natural polymers without affecting the physical and chemical properties of these polymers. On the other hand the synthetic polymers are easy to purify and modify as per pharmaceutical dosage form requirements [16] but there non-biodegradability make it challenging to use within the polymers. Moreover, the synthetic polymers have high immunogenic nature which prevents the use of synthetic polymers for longer time.

2. Advantages of Polymers in Drug Delivery:

Polymers afford various therapeutic, pharmaceutical and pharmacokinetic advantages in comparison to various others conventional dosage forms. Polymeric helps in enhancement of the bioavailability of therapeutic agentsin the target tissues/cells [17]. Polymers have a feature to compress and relaxation. When the polymers get compressed then the polymeric pores get closed because of which the drug present in the polymers remain inside it. However, if the conditions of the polymers changes (with the change in the external environmental conditions) the polymeric pores become opens with relaxation and hence the drug trapped within the polymers releases out and can reach the target tissues/cells. These external environmental conditions changes can be the presence of certain metabolic enzymes such as amylase,lipase, and protease, etc or change in the pH or temperature and other conditions like magnetic field extra[18-19].This resulted in achieving the targeted drug delivery of the drug through the polymeric systems which itself reduces the side effects or toxic effects in nontarget organs [20].

Polymers also helped in enhancing the permeability and retention (EPR) effect [21].The polymeric systems help in achieving the passive tumor targeting. The circulation time of the drugis increased within the body. This is because the polymers have high large molecular

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weights. Polymers are basically made with the combinations of various monomers resulting in high molecular weight [22]. The polymers can be linear and branched which further increase the size of the polymers. Due to this the polymeric system remains inside the body and do not get opsonized by the macrophages present inside the body. High molecular weight does not allow the macrophages to perform any phagocytosis or opsonisation [23]. Hence the drug in release only where the environmental conditions is as per the requirement of the dosage from where the drug is released further.

Polymeric also help in achieving controlled or sustained release of drug from the polymeric dosage forms which further is useful in maintaining the rate, onset and duration of the drug release. This helps in maintaining the steady state concentration of drug within the required therapeutic window. The maintenance of therapeutic concentration of drug in the body is very important in order to achieve effective treatment. The low concentration of drug from the therapeutic window will show no result and the high concentration of drugfrom the therapeutic window will be toxic in nature. The use of polymers also increases the stability of drug by avoiding the deactivation or degradation of the drug [24] from various circulating antigen/antibody reactions, enzymes, macrophages, defense cells extra. This also leads to favor low immunological response against the drug**.**

Some polymers also have tendency to show drug targeting. Some polymers directly attach themselves on the targeting organ and show the drug release in that organ. Despite of current advancements and researches in the polymeric systems, it is still unclear to predict the tendency and ability of different polymers to attach specifically to different organs [25, 26]**.**The physical and chemical properties of naturally occurring polymersis maintained in such a way that when it flow through nephrons of the kidney [27]and also passes through liver [28-30], it do not show any filtered out phenomenon because of which more effective use of drug can be possible. The filtration of polymer from kidneys depends upon the size and shape of polymer. The unique size and shape of polymers such as polymers used in carbon nano-tubes may enhance the clearance of the drug from the body after filtering out from kidneys because of favorable orientation with respect to the blood flow.Polymers show different advantages as shown in Figure 1.

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3. Drug Release from Polymer-based Drug Delivery Systems:

Various drugs which have low aqueous solubility, instability at various physiological pH, high systemic toxicity with lesser cellular uptake ability are considered as ideal candidates for delivering in the form of polymeric combinations. Prolonged drug delivery can be achieved with the synthesis or preparation of polymeric formulations. The pattern of drug release depends upon the nature of polymer used. The chemical structural design and chemical properties of different polymers used can affect the pattern of drug release from the polymeric systems. Some polymers have the ability to show changes in their shape, size, structure and its physical and chemical nature which further perform the changes in their pore sizes and permeability which further results in release of drug trapped or conjugated within the polymer. Some polymers have a feature to compress and relaxation.

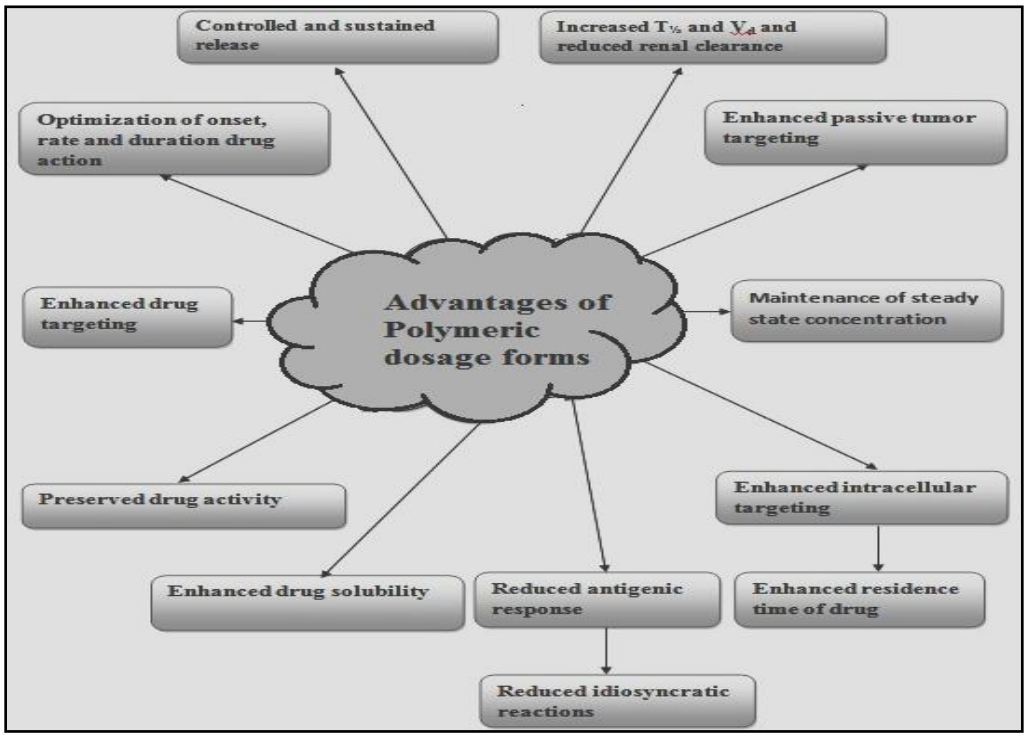

Figure 1: Different advantages of Polymeric Dosage Forms.

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When the polymers get compressed then the polymeric pores get closed because of which the drug present in the polymers remain inside it. However, if the conditions of the polymers changes (with the change in the external environmental conditions) the polymeric pores become opens with relaxation and hence the drug trapped within the polymers releases out and can reach the target tissues/cells. Figure 2 shows how the drug gets released from the increase size of pores of the polymer. Such type of polymers isalso named as "*Smart Polymers"* [31-34]. Various external environmental factors which impact the release ofdrug from the polymeric drug delivery system can be divided into various types like light, pH, Magnetic field, Glucose concentration, Electric field, urea concentration, ultrasound, redox potential, temperature and many more. All such external environmental factors, due to which the changes in polymers are possible,have been listed in below table I. In this some examples of polymers have also been shown whose shape, size can be changed with the change in external conditions**.**

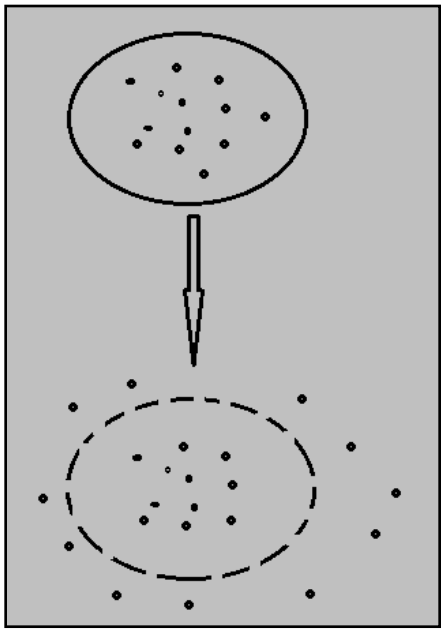

Figure 2: Release of drug from polymeric system when external stimulus is applied

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S.No.	External Stimulus	Polymers
1	Magnetic field [35]	Poly (ethylene-co-vinylacetate)
2	Ultrasound [36]	Polyanhydride, Polylactide, Polyglycolide**.**
3	Electric Field [37]	Poly (Dimethyl Siloxance), Poly (Methacrylic acid)
4	Temperature [38]	Poly(methacrylic acid), Poly(acrylamide), Poly (N-isopropyl acrylamide)**,** Poloxamers 188 and 407, Poly(N,N'-diethylacrylamide)**,** N,N'-methylene-*bis*-acrylamide.
5	Concentration of Glucose [39]	Poly (methacrylic acid-co-butyl methacrylate), Polyacrylamide, Poly Polyacrylic acid**,**copolymers of Hydroxy-ethyl methacrylate
6	Redox potential [40]	Polyanhydrides, poly (β-aminoesters), Poly(lactic/glycolic acid)
7	pH [41]	Poly(methacrylic-g-ethylene glycol), Poly(methacrylic acid)**,** Poly(orthoesters), Poly(acrylic acid)
8	Concentration of Morphine [42]	Methyl vinyl ether co-anhydride maleic copolymer
9	Dual sensitive(pH and temperature)polymers [43]	Poly (N, N – dimethyl amino ethyl methacrylate)**,** N-ethylpyrrolidine methacrylate, Poly (acrylo-N-propyl piperazine).
10	Mechanical stress [44]	Dihydrazide - cross linked poly guluronate, poly (methyl methacrylate)
11	Concentration of Urea [45]	Methyl vinyl ether co-anhydride maleic copolymer

Table 1: Enlist polymers affected by external stimulus

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Release of drug from polymeric systems with the change in external stimuli (pH, temperature, Light and Redox potential):

3.1. pH:

With the change in the environmental pH we can see the change in chemical and physical properties of different polymers. These changes may include either the degradation of the concerned polymer or it may cause the swelling of the polymer depending upon the swelling index of polymeric system. All the polymers which have acidic groups in their structure, they swell more in the basic pH. These acidic groups mainly include like COOH, SO_3H etc. Similarly, all those polymers which have basic groups, they swell better in the acidic pH. The groups like NH_2 make the polymers basic in nature. This type of property is due to ionization of the functional groups at different pH [46]. When the charged polymeric groups repel each other then swelling of the polymer occurs which further resulted in the increase in the pores size. When the pore sizes of the polymers swell then the drug trapped within the polymers release out from the polymeric pores. For example; the acidic polymer, poly-acrylic acid have the ability to swell in the basic pH on the other hand the basic polymer chitosan have ability to swell in the acidic pH.

3.2. Redox potential:

Various types of polymers like polyanhydrides, poly(lactic/glycolic acid) and poly (B-amino-esters) extra may change in their properties with the change in the outer redox potential. All the polymers which have disulfide linkage in their structure are readily cleaved in a reductive environment [40]. These polymers show high drug release (reductive amino-acids) in presence of cysteine or glutathione.

3.3. Temperature:

Different polymers have the ability to show phase transition which further depends on the temperature change. The change in temperature result in the phase transition in the polymers which further changes the different properties of the polymers and hence the polymers shows change in their geometric shapes and drug entrapped within it get released [47]. Ideally, below

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lower critical solution temperature (LCST-32°C), the polymer known as PNIPAA (Poly N-iso-propyl-acryl-amide) acts as a hydrophilic polymer however, above LCST (lower critical solution temperature), it acts like hydrophobic natured polymer. This may be due to the continuous disruption as well as formation of different intra-molecular and inter-molecular electrostatic interactions.

3.4. Light:

In the presence of different chromophores, both natural and synthetic polymers have ability to undergo discoloration caused by UV chromophoric groups. These UV chromophoric groups have ability to efficiently absorb the Ultra Violet radiations. For example the polymer, polycarbonates have the ability to show photo-Fries rearrangement when the polycarbonates are kept in the UV environment. In the presence of UV-B and UV-C radiations polymeric properties changes which further leadin drug release from polymer [48].

A drug can be combined with either one extreme or in both the extremes of the polymeric chain as shown in figure number 3. The replacement of hydroxyl end group in the PEG (Polyethylene glycol) chain can influence the site of conjugation. Moreover the molecular weight of the polymer has also been changed. Some other examples of such polymeric combinations can be seen in Table 2.

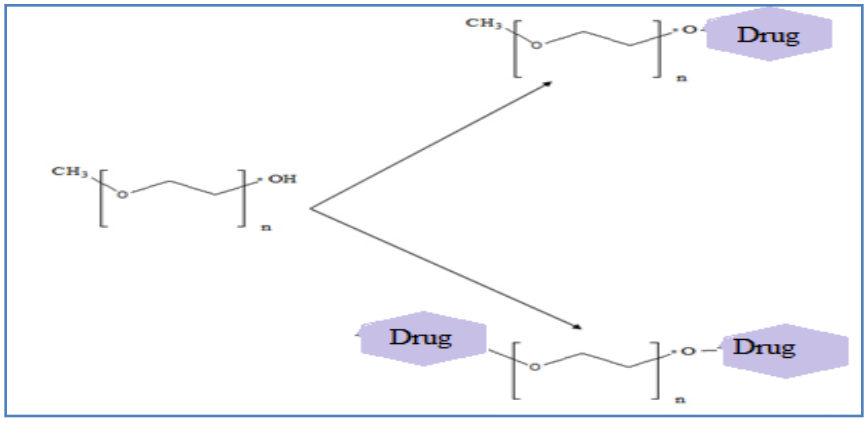

Figure 3.Conjugation of drug in single and both extremes of polymeric chain

Table 2: Different combinations of Polymers and drugs in order to treat different diseases

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S.No.	Name	Indication	Reference
Polymer combined with DRUGS			
1	PEG-Camptothecin	Anticancer	[49]
2	PEG-gentamicin	Anti-inflammatory	[50]
3	PEG-amphotericin B	Antimicrobial	[51]
4	PEG-tacrolimus	Immunosuppressant agent	[52]
5	PEG-acyclovir	Antiviral	[53]
6	PEG-curcumin	Antioxidant	[54]
Polymer combined with HORMONES			
7	PEG-growth hormone antagonist	Acromegaly	[55]
8	PEG-human thyroid stimulating hormone	Thyroid related disorders	[56]
9	PEG-calcitonin	Hypocalcemic effect	[57]
10	PEG- human growth hormone	Acromegaly	[58]
Polymer combined with ENZYMES			
11	PEG- Uricase	Gout	[59]
12	PEG-Methioninase	Anti-cancer	[60]
13	PEG-arginine deiminase	Hepatitis C	[61]
14	PEG-asparaginase	Acute lymphoblastic leukemia	[62]
Polymer combined with CYTOKINES			
15	PEG-Interferon-α-2a	Hepatitis C	[63]
16	PEG-Interferon-α-2b	Hepatitis C	[63]
17	PEG-Interferon-β-1a	Anti-cancer activity	[64]
18	PEG-Interleukin 6	Thrombolytic disorders	[65]
19	PEG-TNF α^{c}	Anti-cancer activity	[66]
Polymer combined with NUCLEIC ACIDS			
20	PEG-antisialoadhesion monoclonal antibodies	Blood related disorder	[67]
21	PEG-Fab' fragment	Tumor necrosis factor	[68]

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22	PEG-Anti TNF α Fab' (Certolizumab)	Rheumatoid Arthritis	[69]

4. Conclusion and Future Perspectives:

Treatment of various autoimmune, metabolic, cancerous diseases and neurodegenerative disorders with the help of conventional dosage forms failed in giving the adequate treatment benefits because of their poor absorption in body and low bioavailability. In the last three decades, various researchers have worked on some new and novel drug delivery systems in order to ensure higher therapeutic benefits with the least amount of drug and as minimum side effects as possible The basic concepts which is followed by the different researchers includes the methods through which one can perform the improvement in the pharmacological activities of different drugs by modifying the absorption, distribution, metabolism and excretion.

Development of polymeric combinations occurs in four different generations. In the first generation design of novel concept of polymer combination was described, in the second generation use of combination therapy is described, in the third generation improvement of polymer chemistry is well explained, and in the fourth generation clinical risk benefits and the new possibilities in polymeric combinations are discussed**.** There are various concept of using polymeric combinations which are under study and can be considered as valuable and ideal candidates for treatment of various dreadful diseases. Some of these concepts and their future prospective are discussed below:

1) Concept of using polymeric dosage forms whose main site of action will be stem cells and they show their action at stem cells only**.**
2) Novel concept of using polymeric prodrugs in which the antibodies are conjugated in order to treat cancer.
3) Concept of using polymeric systems as therapeutic vaccines**.**
4) Design of polymeric combinations as antiangiogenic agents

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5) Concept of using polymeric pharmaceutical systems which have ability to target at sub-cellular level**.**
6) New concept of using polymeric systemsas biochemical, chemical and optical sensors.

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