Re-profiling of Polymeric Excipients as Active Entities: A Review[1]

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ABSTRACT

The re-profiling of polymeric excipients as active entities is a fascinating area of research that has garnered significant attention in recent years. This review aims to provide a comprehensive overview of the current advancements in this field. Polymeric excipients, traditionally used as inert components in drug formulations, have proven to possess inherent therapeutic properties that can be harnessed for various therapeutic applications. By modifying the chemical structure or altering the physical properties of these excipients, researchers have successfully transformed them into active entities with enhanced functionalities. the use of polymeric excipients as active entities opens up new avenues for the development of novel drug delivery systems, including nanomedicine, microspheres, and hydrogels. These innovative systems have the potential to revolutionize the field of drug delivery by improving therapeutic efficacy, reducing toxicity, and enhancing patient compliance. Despite the immense potential, there are still challenges that need to be overcome, such as the optimization of formulation parameters, understanding the mechanisms of action, and ensuring the safety and stability of these re-profiled polymeric excipients. Nevertheless, the re-profiling of polymeric excipients as active entities holds great promise in the development of personalized medicine and targeted therapies, paving the way for a new era in pharmaceutical research and development.

INTRODUCTION

According to IPEC (International Pharmaceutical Excipients Council) America and IPEC Europe, an excipient is “These are the substance(s) other than the API which has been appropriately evaluated for safety and is included in a drug delivery system to either aid processing of the system during manufacturing or protect, support or enhance stability, bioavailability or patients compliances or assist in product identification and enhance any other attributes of overall safety and effectiveness of drug product during storage or use “[1].

By definition, a pharmaceutical excipient is a material or combination of substances that fills the volume of an agglomerating mixture, acts as a carrier, and contains active medicinal ingredients(APIs)[2]. Excipients are thoroughly studied for both their compatibility with the active component and their safety for usage in humans before being universally accepted as safe[3].

Excipients help with production, administration, or absorption[1]. Excipients also used to ensure, support, or improve the formulation's stability[4]. Pharmaceutical excipients may be categorized based on:

1) origin like plant (acacia, cellulose, starch), animal (gelatin, lactose, lanolin), synthetic (PEGs, polysorbates), minerals (calcium carbonate, kaolin)[5,6].

2) Their function in dosage form such as binders, preservatives, bulking agents, etc.

3) chemical composition like alcohols, acids, polymers[7].

Excipients can alter a drug's bioavailability and pharmacokinetics, hence during the drug development process, careful consideration and testing of these materials are crucial[8].

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Regarding safety aspect, excipients are closely monitored and subject to quality control during the pharmaceutical manufacturing process. A strategy to ensure and guarantee the quality and safety of excipients should be based on a strict risk assessment, and its results shall be documented and controlled during regulatory inspections by the authorities, according to the current regulations of the European Union's Good Manufacturing Practice of Medicinal Products (EU GMP)[9]. Excipients undergoes several toxicity studies in order to considered safe for longer-term use in humans[10].

It is widely known that the process necessary to develop a medicine is drawn out and frequently tiresome. As a result, our focus is more broadly focused on the potential of repurposing of pharmaceutical excipients as active therapeutics. Excipients have historically been undervalued in pharmaceutical formulations since they were considered to be inexpensive substances that served just as inactive carriers for medications. In fact, excipients play a crucial role in pharmacological preparations, and attitudes toward their use have changed significantly. In fact, excipients are neither inert nor inactive component. Excipients may possess extra applications aside from their primary use as pharmaceutical additives. The use of various excipients as unusual active pharmaceutical components, either by itself or in combination with other active pharmaceutical ingredients, has come to light in recent years[11]. “Atypical Actives” is a term used to describe an excipient that serves as the formulation's active medicinal ingredient[12]. These agents are available in a range of dosage forms that can be taken orally, topically, parenterally, or ophthalmologically.

Several types of excipients have been shown to be effective as therapeutics[12]. Polymers are used in a variety of pharmaceutical applications, including complex drug delivery systems and inert bulk excipients. At pH levels close to 7, positively-charged chitosan derivatives outperform unmodified chitosan in terms of both water solubility and bacterial activity[8]. Polymers utilized as prodrugs, conjugates, complexes with biopolymers that have essential medical applications, and direct therapies in and of themselves.

In the present study we will try to focus on the benefits of pharmaceutical polymers wherein the polymer itself is regarded as the active pharmaceutical component and a polymeric species directly affects the desired pharmacology. During the Second World War, synthetic polymers were first utilized as parentral healthcare aids[13]. Since then, all polymers have been introduced to the market as polymeric pharmaceuticals. The majority of bioactive macromolecules' current and future uses depend on their propensity to tenaciously bind various types of substances. The repetitive nature of recognition moieties, the flexibility and modular structure, and the compatibility with a wide variety of recognition moieties are all characteristics of polymers. Compared to monovalent systems, the high valency given by each chemical unit in polymer encourages enhanced binding[14].

A very broad and diverse range of chemicals are referred to as polymeric excipients, including macromolecular molecules of natural origin, semi-synthetic polymers, and synthetic polymers[15]. Due to their biocompatibility and acceptable mechanical qualities, polymeric materials have been used in therapeutic applications such as medication administration and tissue regeneration for decades. Selected polymer-drug conjugates have also been exploited as bioactive medicines because they have better therapeutic effectiveness, solubility, and target selectivity[16]. While the majority of research on the therapeutic use of polymeric materials concentrates on the polymer's function as a carrier, recent studies have turned their attention to the use of polymers as standalone therapeutic agents[17]. Drug-free macromolecular therapies was first proposed by Wu and colleagues in 2010[18]. The development of a polymer with biological activity without the use of a low molecular weight drug was described by the authors.

For thousands of years, natural polymers have been employed as part of herbal treatments. It has long been recognized that natural polymers derived from plants, animals, and seaweed have antiviral and antitumor action[19].

It is crucial to stress that this review serves more as an overview of the past, present, and potential applications of polymer-based treatments than as an exhaustive description of all currently available and emerging technologies.

Antibacterial polymers

Antibacterial polymers can be divided into the following groups depending on the type of polymeric system:

- Polymers with inherent antimicrobial activity or,

- Polymers with an antimicrobial function acquired by conjugating antibacterial functions to the polymer backbone or adding antibacterial filler to the polymer matrix.

Cationic natural and synthetic polymers are among those that have attracted growing interest. While synthetic polymers provide exact control of their features and modifications, including the molecular weight distribution, polarity, and chain degradability, natural cationic polymers typically have a high degree of biocompatibility[20].

Cationic polymers are extremely effective against bacteria and have decreased susceptibility to resistance among microorganisms emerging[21]. The antibacterial polymer is first adsorbed on the surface of the bacteria, which is followed by diffusion through the cell wall and breakdown of the cytoplasmic membrane as the primary mechanisms by which cationic polymers kill bacteria[22].

Natural chitosan is one of the cationic polymers that are frequently studied. In addition to fungi, chitosan possesses potent antibacterial properties against both Gram-positive and Gram-negative bacteria[23]. Molecular weight (MW) of chitosan is one of the crucial elements that affect the antibacterial activities of chitosan[24]. According to Zhong et.al, when chitosan's MW is less than 305 kDa, the antibacterial impact was boosted as the concentration rose. This applies to both S. aureus and E. coli[25]. Chitosan with MW less than 2.2 kDa, on the other hand, was said to have no impact on microbial growth[26]. Chitosan, however, has weak mechanical qualities, is insoluble in water and most organic solvents, and these drawbacks make it difficult to use in practical applications[27]. Several chemical alterations are made to it to enhance its quality[28]. At ph levels close to 7, positively-charged chitosan derivatives outperform unmodified chitosan in terms of both water solubility and bacterial activity[29]. Carboxyl alkyl derivatives of chitosan has inhibitory, antibacterial, and antifungal properties[30]. Compared to unmodified chitosan, quaternary chitosan derivatives have stronger antibacterial activity[31]. Ahmad et al. assessed various chitosan derivatives and looked at the impact of various variables on their antibacterial activity[32]. The findings showed that chitosan had significant antibacterial action. As it directly inhibits the growth, chitosan is thought to be more fungistatic than fungicidal[33]. Due to its non-specific manner of pathogen suppression, chitosan is regarded as a good choice for antifungal treatment. It primarily targets the cell walls and membranes of microorganisms and has a lower propensity to lead to the emergence of drug resistance[34]. Several studies have been published about the antifungal activity of chitosan. Ing et.al studies the inhibitory effect of chitosan on Candida albicans, Aspergillus niger, and Fusarium. Solani[35]. In a paper of Hongpattarakere et al. chitosan samples were evaluated against C. albicans with varying molecular weights and levels of deacetylation [36]. Li et al. proved the effectiveness of chitosan against three different fungi at various molecular weights [37].

Chitosan may potentially have antitumor properties, which are shown more frequently in low-molecular-weight polymer forms. According to a study by You-Jin et al., chitosan significantly reduced the metastatic spread of cancer[38]. Chitosan is thought to boost immunity as suggested by some researchers[39,40].

Chitin and chitosan both have analgesic effects, according to numerous researchs. Studies conducted by Ohshima et al. demonstrated that chitosan has analgesic effects in burn patients[41]. The Elieh-Ali-Komi et al. study's findings indicated that chitosan had a stronger analgesic effect than chitin[42].

Bacterial infection during the infectious phase of a burn wound may hinder healing and almost certainly result in significant complications. In order to accomplish both wound healing improvement and antibacterial properties, chitosan is combined with antibiotics[43].

During the proliferative stage of wound healing, chitosan is known to speed up granulation and its use in wound healing has been examined[44,45]. Numerous studies were conducted on the chitosan/heparin combination to demonstrate its interaction with growth factors, which are crucial to the healing of wounds. Chitosan effectively supports cell development due to its positive surface charge [46]. Additionally, the structural similarity between chitosan and heparin as well as the precise interactions with different growth factors led to identical bioactivity and biocompatibility[47,48]. Chitin oligosaccharides have been investigated for their possible application in the treatment of chronic bowel disease and wound healing. Chitin oligomers have been found to have a mucin- stimulating effect in an ex-vivo model for the first time[49].

Due to its biodegradability and biocompatibility in physiological conditions, gelatin, a natural polymer generated from collagen, is frequently used in pharmaceutical and medical applications[50]. Gelatin solution increased plasma volume for shock patients, according to studies[51]. The most sought-after colloidal plasma expanders following serious injuries with significant blood loss are those that contain gelatine as the active ingredient [52]. By accelerating the formation of thrombus and giving it structural support, gelatin does enhance the hemostatic process[53]. Currently, a number of gelatin-based medical products are being marketed by businesses across the globe with the intention of serving as hemostats during various surgical procedures[54]. Şelaru et al. concentrated on gelatin scaffold's capacity to speed up the vascularization of freshly designed tissues and to confirmed its suitability as a candidate for nervous tissue engineering [55]. There have been numerous scientific studies on the efficiency of gelatin in skin wound healing to date. Akhavan et al.'s research shown that gelatin improved fibroblast adhesion, cell survival, and proliferation[56].The results of several *in vivo* investigations show high and considerable contraction levels in wounds treated with gelatin scaffolds, which may be related to gelatin's hydrophilic property and retention of wound hydration, which promoted healing[57,58]. Gelatin matrices can also promote the development of new tissue and offer structural

and mechanical support[59]. In a study by Enrione et al., the effectiveness of fish gelatin for rabbit wound healing was investigated [60]. The outcomes demonstrated good wound healing with full re-epithelialization and granulation.

Marine polysaccharides

Micro- and macroalgae were among the earliest sources of natural chemicals with in vitro antibacterial activity. The first record of an aquatic microalga's antibacterial activity dates back to 1940 [61]. Algal extracts contain substances that are active in vivo or in vitro against a variety of retroviruses [62]. Thirumurugan et al. recommended using these agents for conditions that are chronic in character and for which the modification of signaling pathways may show gradual and long-lasting positive effects[63].

Carrageenans, commonly used as pharmaceutical thickening and gelling agents, a family of high molecular weight sulphated polysaccharides derived from specific kinds of red seaweed [64]. A variety of DNA and RNA viruses could not replicate when carrageenan was present. A number of diseases, primarily those brought on by enveloped viruses, are thought to be preventable with the usage of carrageenan and its depolymerized derivatives, oligosaccharides[65]. Early researchs revealed that carrageenan had antiviral properties against herpes and hepatitis A viruses[66-68]. Zhou et al studied the potential effect of carrageenan on immunity[69]. The results of the trial showed that giving carrageenan to mice that had been given an antitumor drug considerably improved their immune system. Carrageenans may be used as models for creating new anti-HIV drugs after having their therapeutic qualities enhanced chemically[70].

Brown seaweed is the source of the anionic, naturally occurring biopolymer known as alginate[71]. Alginate-based therapeutics that control bacterial responses and treat infections of multi-drug resistant bacteria were developed by Khan et al.[72]. In a variety of multi-drug resistant organisms studied, a 512-fold reduction in the MIC values of Gram-negative infections was recorded. Asadpoor et al. found that exposure to alginate oligosaccharides(2–16%) significantly reduced the growth of Group B Streptococcus[73]. The promise of alginate nanoscale biosensor-based diagnostics for the identification of potentially fatal bacterial infections has been recognized by earlier researchers[74]. Alginate has been utilized to reduce the harmful effects of Salmonella infection through an immunomodulation-based approach [75].

Plant polysaccharides

Pectin: The majority of plant cell walls contain pectins, which are hydrophilic polysaccharides with a linear chain[76]. Pectin taken orally has been demonstrated to prevent the development of intestinal wall inflammation in test animals[77]. The anti- inflammatory effect of pectin, which is determined by its galacturonan backbone, has been established by Markov et al. [78]. Applications for wound healing are thought to be very well suited for pectin and its derivatives. Cipriani et al. have created pectin derivatives with beneficial antithrombogenic properties that could be applied to wound treatment[79]. When pectin was employed as the basis for a papin gel, healing was shown to be quicker than when water was used as the vehicle[80]. Pectin, a natural anti-glycation substance, has been used successfully to treat wounds that have trouble healing[81]. Hydrogels made of chitosan and pectin that showed excellent exudate uptake have application as bandages for the management of chronic wounds[82]. An interactive wound care system with antioxidant characteristics that aid in removing free radicals from the injury site was created using pectin[83].

Mokady was the first to write on how pectin lowers cholesterol levels in animals[84]. Several researches that discussed pectin's capacity to reduce blood and liver cholesterol in various animals came after that. Pectin is thought to bind to cholesterol and bile acids in the gut, preventing absorption and encouraging excretion [85]. Another explanation of pectin hypocholesterolaemic effect proposes interferance with the creation of micelles, which prevents cholesterol absorption [86]. Pectin soluble fibers may reduce total and LDL cholesterol in human, according to qualitative reviews [87]. Examples of physical and chemical aspects of pectin that affect cholesterol reduction include degree of esterification and molecular weight [88]. According to the European Panel on Dietetic Products, Nutrition, and Allergies, consuming 6 g of pectin daily helps to maintain normal cholesterol levels[89].

Cellulose derivatives

In the pharmaceutical industry, cellulose derivatives serve a crucial role as pharmaceutical excipients and are widely employed in the manufacture of already-available drugs, the development of innovative dosage forms, and cutting-edge pharmaceutical manufacturing procedures. One benefit of utilizing cellulose in wound care is that it can manage wound secretions and fosters a moist environment for ulcers, which promotes wound healing more quickly[90]. One of the most widely used hydrophilic cellulose derivatives in pharmaceutical manufacturing is hydroxypropyl

methylcellulose (HPMC). Both the FDA and the EMA have designated HPMC as a safe excipient (Generally Recognized as Safe, or GRAS)[91,92]. Because of its cellulose backbone, HPMC cannot be digested[93]. The viscosity of utilized HPMC and the hypocholesterolaemic impact of bile acid and cholesterol excretion have been linked in animal research[94]. In this study, the relationship between HPMC's influence on intestinal viscosity and its hypocholesterolemic effect was examined. Two theories have been put forth to explain this phenomena. The first one assumes that a barrier will form and reduce permeability while the second theory contends that direct adsorption is present and is what reduces cholesterol absorption [95,96].

In a clinical investigation on volunteers, it was discovered that HPMC powder had the same anti-allergic rhinitis effects as the powerful corticosteroid budesonide[97]. In addition to protecting against inhaled allergens, HPMC is also thought to protect against noxious substances and environmental dust that could irritate the nasal mucosa [97]. Al kotaji et al studied the effect of HPMC nasal gel as a protective tool against allergic rhinitis and the results were promosing [98].

CONCLUSION

In conclusion, the review on the re-profiling of polymeric excipients as active entities sheds light on the immense potential and versatility of these materials in the field of pharmaceutical sciences. The exploration of polymeric excipients as not merely passive carriers, but rather as active components, has opened up new avenues for drug delivery systems and therapeutic interventions. Moreover, the ability to tune the biocompatibility and biodegradability of these polymers has further expanded their applicability in various biomedical applications. However, despite the tremendous progress made in this field, several challenges still need to be addressed, such as ensuring the stability and reproducibility of these modified excipients, understanding their pharmacokinetics and pharmacodynamics, and optimizing their formulation and manufacturing processes. Nonetheless, the re-profiling of polymeric excipients as active entities presents a promising approach that holds great potential for the development of innovative and effective drug delivery systems, ultimately leading to improved patient outcomes in the realm of pharmaceutical sciences.

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