HYDROCOLLOIDAL SYSTEMS BASED ON POLYMERIC MATERIAL FOR DRUG TARGETING – A REVIEW

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ABSTRACT
Targeted drug delivery, sometimes called smart drug delivery which can deliver the drug to specific site of the body. Hydrocolloids based polymeric materials represents one of the most rapidly advancing research areas and established itself as an integral part of targeted drug delivery systems. This review focused the development of hydrocolloids particularly on targeted drug delivery applications such as oral delivery, ocular delivery, chrono drug delivery etc. The application of hydrocolloids mainly drug delivery system based on properties of polymeric materials that are used in the pharmaceutical field.

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INTRODUCTION

In recent years drug delivery technologies are now considered an equivalent component in drug development. Drug delivery technologies allow for effective use of existing drugs and successful development of new drug candidates. Therefore, developing new drug delivery technologies and utilizing them in product development is crucial for improving patient compliance. Hydrocolloidal based drug delivery system have become an incredibly prolific area of research in the field of drug targeting, because of their high water content, mechanical similarity to natural tissues, and ease of surgical implantation, hydrocolloids are at the forefront of drug carrier design. Hydrocolloids are polysaccharides of high molecular weight and it is mostly available from natural resources like plants and seaweeds or produced by microbial synthesis. Hydrocolloids, as the name suggests are the hydrophillic materials that are used as rheology control and suspending agents to provide many attractive features to the pharmaceutical formulations.[1] Hydrocolloids are classified on the basis of their origin, natural polysaccharides, semi or synthetic polymers. The examples of natural hydrocolloids are alginic acids (alginate), amylose, arabinogalactans, chitosan, chondroitin sulfate, cyclodextrin, dextran, galactomannans, gellan, konjac, guar gum, inulin, karaya gum, laminarin, locust bean gum, pectins, pullulan, rice bran, scleroglucan, tragacanth, wheat starch, and xanthan. Semi synthetic hydrocolloids like cross-linked polyacrylic acid, polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethylcellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene oxide, superporous hydrogels, polyacrylamide, polyisopropyl acrylamide, crosslinked starch, cross-linked hyaluronic, carboxymethyl guar have been studied to a great extent. [2, 3] Hydrocolloids are used as carrier for localized drug delivery because they are hydrophilic, biocompatible, and their drug release rates can be controlled by adjust swelling rate. Macromolecular drugs, such as proteins or oligonucleotides that are hydrophilic, are inherently compatible with hydrocolloids. The drug release rate form hydrocollaidal formulations mainly depend upon controlling the degree of swelling, crosslinking density, and degradation rate of the hydrophilic polymers. [4, 5] Hydrocolloids have been extensively used for target drug delivery system. Figure 1 is represented advantages of hydrocolloidal system based on polymeric materials for drug targeting.

**Figure 1** is represented advantages of hydrocolloidal based target drug delivery system.

Hydrocolloids are utilized in the majority of target drug delivery system including oral, transdermal, Protein and peptides (macromolecules) and tissue engineering etc., and shown in Figure 2.

**Figure 2** Illustrated Hydrocolloids are utilized in the various Target Drug Delivery Systems.
Oral delivery

Chitosan, a polysaccharide obtained by N-deacetylation of chitin, has been investigated as a drug carrier in hydrocolloids and gels. It has ability to become hydrated and form gels in acidic aqueous environments and is thus used to prepare sustained release drug delivery systems. The possible mechanism of retarding drug release may be a stagnant gel layer controls the diffusion initially, but after some time, the network of the gel structures starts to disintegrate and thus diffusion is facilitated.[6] Chitosan based formulations can be improved oral absorption/bioavailability and might be valuable for delivery of drugs to specific regions such as stomach, buccal mucosa. Other good characters of chitosan such as biodegradable, mucoadhesive, gel forming capacity at lower pH, permeation enhancement and all these properties makes chitosan a good candidate for the development of drug delivery system.

Hydrocolloids have been used for formulation of gatroretentive drug delivery system which is enhancing Mean residence Time (MRT) of the drug in gastrointestinal tract. Effervescent floating dosage forms are matrix types of systems, which may be volatile liquid containing systems or gas-generating Systems, prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescents compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. When the formulations contact with the acidic gastric liquid, carbon dioxide is liberated and entrapped in swollen hydrocolloids polymer which provides buoyancy to the dosage forms. Non-effervescents type floating drug delivery systems are used gel forming or swellable cellulose type hydrocolloids polymer and matrix-forming polymers like polycarbonate, polycrylate, polyacrylamide, and polystyrene. After oral administration this dosage form swells in contact with gastric fluids (pH 2) and attains a bulk density less than one (d<1). The air entrapped within the swollen hydrophilic matrix conveys buoyancy to these dosage forms. The results of swollen gel-like structure act as a reservoir and controlled the drug release. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polycrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.[7, 8]

Gastro retentive floating drug delivery systems are improve the oral absorption of the drug by making the drug available in gastric region for longer time. Alginate, is a natural, hydrophilic, high molecular weight, linear anionic heteropolysacharide extracted from surface of sea weeds like marine brown alga, tangle weed, agar-agar etc. Among the various floatable multiple-unit dosage forms, calcium alginate gel beads have been developed in recent years as a unique vehicle for multiple-unit drug delivery systems. It has many advantages like biocompatibility, biodegradability, reproducibility, simple method of preparation, abundant sources, low cost and minimal processing requirements. Alginate and Calcium ion is rapidly formed by gelation of alginic acid in the presence of calcium ions and is able to incorporate some compounds such as drugs or polysaccharides in the gel matrix.[9] Gel beads of calcium alginate can be produced by extruding sodium alginate solution as droplets into calcium chloride solution. Sodium bicarbonate was used as gas forming agent. The hydrogel properties of calcium alginate beads have been proposed for controlling the release of various drug molecules and floating ability of the beads were increased gastro retention time significantly.

Colloidal gel barrier system

Colloidal gel barrier system consist of high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydroxethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbofil, polycrylate and polystyrene.[10] Hydration of hydrocolloids polymer occurs when contact with gastric fluid and forms a colloid gel barrier around its surface and controlled the drug release. Freichel have formulated oral hydrocolloid drug delivery system with a late burst in the release profile by using methylhydroxy ethylcellulose, MHEC 10000 B, was used as the basis polymer and hydroxypropyl methylcellulose acetate succinate, HPMCAS HF, as release modifier. The mechanism of the final burst at pH values >5.7 could erosion of the gel layer surrounding the tablet core was reported.[11]

Protein and peptide delivery

Recent years, there are growing numbers of peptide and protein based drugs available for various therapeutic use. The delivery of therapeutic peptide and proteins remain a priority for many pharmaceutical companies and researchers. From a recent review on delivery strategies for peptide and proteins, it is evident that over 40% of all pharmaceutical companies are active in this area. This has resulted from the advances in molecular biology and biotechnology, which identified and made commercially available many peptide and proteins with valuable therapeutic properties. The delivery systems have been designed to a) protect protein and peptide from coming in contact with proteases, primary in the lumen and b) release the protein only up on reaching a favourable area for absorption. Several formulations tested include emulsion, liposomes, nanoparticles and soft gelatine coated capsules. Novel bioadhesive drug carrier system and chitosan-EDTA-protease inhibitor conjugate have also been used to deliver many other biological active peptide and protein molecules through oral route by shielding them enzymatic attack. There is increasing interest in exploiting the combined advantages of proteins and hydrocolloids as functional ingredients via the development of protein–polysaccharide complexes as carrier for drug delivery.[12, 13] The protein and polysaccharide components may be joined together by either (i) covalent bonding or (ii) electrostatic interactions. Guar gum microspheres prepared by ionic gelation of cationic guar gum have been explored for application as a protein drug delivery systems. Microspheres were shown good loading capacity of bovine serum globulin at various concentrations. Chitosan phthalate and chitosan succinate polymers were synthesized by phthalyation and succinyllation of native chitosan molecules. Microspheres of chitosan phthalate and chitosan succinate were prepared by emulsion phase separation technique. The swelling index of the microspheres in pH 7.4 was higher than in pH 2.0. From swelling character of the microspheres it was concluded that the insulin loaded in to the chitosan phthalate and chitosan succinate microspheres can be protected from the hostile environment of stomach which has acidic pH and releases insulin at colonic pH. Chitosan phthalate and chitosan succinate microspheres have the potential to serve as oral insulin carriers, improving oral stability and bioavailability of insulin. It provides therapeutic equivalency to the current therapies and the ability to provide better control of blood glucose levels in diabetics.[14] The
favourable properties like biocompatibility, biodegradability, pH sensitiveness, mucoadhesiveness, etc. has enabled these polymers to become the choice of the pharmacologists as oral delivery matrices for proteins.[15]

Ocular delivery

Bioadhesion refers to the process of attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue, or it can be the mucous coat on the surface of a tissue. The capacity of the polymers is to adhere to the mucin coat of the eye by forming non-covalent bonds. These bioadhesive polymeric systems significantly prolong the drug residence time.[16] Mucoadhesives thus increase the residence time of the drug in cornea. It is also enhanced contact between the drug and the absorbing tissue which may result in a high drug concentration in the local area and hence a high drug flux occurred through the absorbing tissue.

The most commonly used bioadhesives are macromolecular hydrocolloids with numerous hydrophilic functional groups such as carboxyl, hydroxyl, amide and sulphate. It has capable of forming hydrogen bonds to tissues. Typically, these polymers have high molecular weight molecules which cannot cross biological membranes. The bioadhesive polymers can be natural, synthetic or semi-synthetic in nature. Further, they can be either water soluble polymers with linear chains or water insoluble polymers that are swellable networks joined by cross-linking agents. Commonly used polymers under the various groups include -hydroxypropyl cellulose and hydroxypropyl methylcellulose as the non ionics; chitosan and DEAE-dextran as the polycationics; and the polyacrylic acid derivatives e.g. carbopol, polycarbophil and carboxymethylcellulose (CMC) etc. as the polyanionics. Cationic and anionic polymers bind more effectively than the neutral polymers. The bioadhesive power of a polymer is affected not only by the nature of the polymer but also by the nature of the surrounding media. The polymer related factors include the molecular weight, concentration of the active polymer, flexibility of the polymer chains and their spatial conformation. While the pH, initial contact time, swelling etc. form the environment related factors, the physiological variables include mucin turnover and diseased state.[17]

The ocular concentration of timolol improved 3 to 9 fold in the presence of sodium CMC compared with non-viscous eyedrops. Acetazolamide formulated in CMC when compared with the saline solution of the drug in patients with unilateral open-angle glaucoma, was found to have a longer duration of action.[18, 19]

Dermal delivery

Transdermal route is an alternative choice of route of administration of such drugs which shows poor patient compliance due to low bioavailability, short plasma half-life and leading to increased frequency of administration. This originates the need of an alternate route of administration. Transdermal route offers many advantages over oral dosage form such as, improved patient compliance in long-term therapy; bypassing first pass metabolism; sustained drug delivery, maintenance of constant and prolonged drug level in plasma; minimization of inter and intrapatient variability and interruption (or) termination of treatment when necessary.

Chitosan is a cationic polymer derived from the exoskeleton of crustaceans (such as crabs) and it contains copolymers of glucosamine and N-acetyl glucosamine. Chitosan has been extensively studied in the biomedical field. The uses of chitosan in pharmaceutical field have increased due to antimicrobial and antifungal properties. The ability of chitosan is to retain high amounts of water and high degree swelling capacity, which could be of particular value in relation to slow-release formulations.

Martin has developed patches containing either NaCMC 39% or pectin 39% showed that there was a significant difference in the rates of hydration of the two types of patch (p < .005).[20] An increase in application time of the hydrocolloid patches allowed more Triamcinolone acetonide to be released, which was illustrated by an increase in both the maximum percentage total possible score (%TPS) values and AUC, although changes in the hydrocolloid composition did not significantly alter the blanching response. All of the patches adhered well, were unobtrusive to the normal activity of the wearers, and showed great potential for the convenient, localized, prolonged delivery of the drugs. Also reported epidermal diffusion rates were, however, similar, both showing a 3-4-fold enhancement over unoccluded conditions. The increase in Triamcinolone acetonide diffusion with the patches can be explained by the increase in skin hydration that occurs during occlusion.[21] Differences in transepidermal water transfer through the epidermal membranes between two types of hydrocolloid patch were observed, however, this level of stratum corneum hydration was apparently similar. Hydrocolloid patch component and hydrophobic component of the patch matrix may also influence the level of skin hydration and consequent drug diffusion. Queen et al., was studied occlusive effect of Actiderm® (hydrocolloid dermatological patch) on the percutaneous penetration of several drugs including corticosteroids.[22] Hydrocolloid dermatological patch was found to be effective in controlling and sustaining the localized delivery of the steroid into the skin and enhancing the healing of dermatological disorders.[23]

Tissue engineering

Hydrocolloidal gel system due to their unique biocompatibility, flexible methods of synthesis, range of constituents, and desirable physical characteristics, have been the material of choice for many applications in regenerative medicine.[24] They can serve as scaffolds that provide structural integrity to tissue constructs, control drug and protein delivery to tissues and cultures, and serve as adhesives or barriers between tissue and material surfaces. This expanse of hydrogel knowledge allows for scaffold properties, such as cellular uptake, molecular response, structural integrity, biodegradability, biocompatibility. Hydrocolloidal chitosan shell may provide the possibility to bioconjugate various bioactive ligands, e.g. sugars, antibodies or peptides, to the surface via covalent coupling. The coupling of biotin via a NHS-PEG linker showed that the amino groups of chitosan represent suitable sites for covalent bioconjugation of different ligands. The process was allowed the production of particles with a mean diameter between 1 and 10 mm, a useful size range for the phagocytosis by phagocytes like dendritic cells or macrophages.[25] Hydrocolloidal based delivery system may enhance cellular uptake of the drug molecules.
Colon delivery

There has been growing interest in developing site-specific formulations for targeting drug delivery to the colon due to both local and systemic delivery of drugs can take place in the region. Report suggested that treatment could be made more effective if it were possible for deliver the drugs to be targeted on the colon. Colon is a promising site for those drugs which are poorly absorbed from upper GIT and small intestine and targeting of the drugs to a particular part of the GIT will improve the bioavailability, which will in turn reduce dose frequency, increase patient compliance and reduce several toxic effects of the drugs. Colon specific systems might also allow oral absorption of peptide and protein drugs, which are normally inactivated in the upper parts of the gastrointestinal tract. Colon-specific systems could also be used in diseases like diurnal rhythms, which is defined as a variable night time exacerbation of the underlying asthma condition associated with increased airway responsiveness and worsening of lung functions. The lung function (peak expiratory flow rate, FEV1) is usually highest at 4 pm and lowest at 4 am. Generally, asthma attacks are more prevalent in early morning and its inconvenient for a patient to take medicine at midnight. Management of such type of disease can not be possible by simple drug delivery system. Special drug delivery system needs to develop which can release the drug at a predetermined time. Pulsed release system capable of delivering the drug at the required time after a well-defined lag time.[29] Qureshi et al., was developed pulsed release dosage form contains an insoluble cross-linked capsule body filled with drug-loaded pellets sealed with hydrocolloid plug and a soluble capsule cap. Various hydrocolloid polymers, namely, hydroxypropyl methylcellulose, (HPMC), hydroxypropyl cellulose (HPC), sodium alginate, polyethylene oxide (PEO) and guar gum were used as plug component system in order to adjust lag period time.[30] The study concluded that hydrocolloids based delivery system capable of well controlled drug release rate from the dosage forms.

CONCLUSION

Hydrocolloids have become most important pharmaceutical excipients for conventional and controlled drug delivery dosage forms. Hydrocolloids biopolymer systems that are abundant, low-in-cost, compatible with human digestibility and able to controlled drug release would be the best carrier for drug delivery system. Among many novel delivery systems investigated so far delivery of drugs for targeting particular site, the hydrocolloidal system showed the great potential for the selectively delivering the drug to target site. Future advances in hydrocolloids will require thoughtful integration of polymeric materials to ensure targeted drug delivery lives up to its true clinical potential.

<table>
<thead>
<tr>
<th>Target Delivery System</th>
<th>Hydrocolloidal System Used</th>
<th>Embedded Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral delivery</td>
<td>Agarose, Alginate (both 3%, w/w), or Gellan Guar gum</td>
<td>Diltiazem hydrochloride</td>
<td>[9]</td>
</tr>
<tr>
<td>Protein and peptide delivery</td>
<td>Pectin:Gellan:Alginate, Polyionic hydrocolloids (Chitosan and Alginate)</td>
<td>Casein and Hydrogenated vegetable fat Protein</td>
<td>[12]</td>
</tr>
<tr>
<td>Ocular delivery</td>
<td>sodium CMC</td>
<td>Timolol</td>
<td>[19]</td>
</tr>
<tr>
<td>Colon delivery</td>
<td>Pectin and Pectin (10%) and in combination with hydroxypropyl methyl cellulose and hydroxyethyl cellulose</td>
<td>Vancomycin</td>
<td>[26]</td>
</tr>
<tr>
<td>Gastro retentive delivery</td>
<td>Hydroxypropyl methyl cellulose (HPMC) and Carbopol 934P</td>
<td>5-flourouracil</td>
<td>[7]</td>
</tr>
<tr>
<td>Chronopharmaceutica l delivery system</td>
<td>Mixture of sodium alginate and ethyl cellulose as plug</td>
<td>Salbutamol</td>
<td>[30]</td>
</tr>
<tr>
<td>Dermal delivery</td>
<td>Pectin or carmellose sodium</td>
<td>Triamcinolone acetoneide</td>
<td>[21]</td>
</tr>
<tr>
<td>Nutraceutical delivery systems</td>
<td>Iota-carrageen</td>
<td>Curcumin</td>
<td>[31, 32]</td>
</tr>
</tbody>
</table>

Table 1. Summarized hydrocolloidal drug delivery systems used for drug targeting.
REFERENCES