Bioadhesive Nano particulate Drug Delivery System

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ABSTRACT

Mucoadhesion is defined as a condition in which two elements, one of which is biological in origin, are bound together for a long time via interfacial adhesion. The study aims to shed some light on the fundamentals of mucoadhesion, including the advantages of bioadhesive systems, characteristics of bioadhesive polymers, theories of bioadhesion, factors affecting bioadhesion, mechanism of bioadhesion and the polymers and systems employed in the design of bioadhesive delivery systems with key outcomes.

Key words: Mucoadhesion, Polymers, Bioadhesion, Bioactive molecules

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INTRODUCTION

The remarkable progress of nanotechnology in recent years has resulted in revolutionary developments in the sector due to potential technological developments and their applicability in industry [1]. In this context, research on bioadhesive systems has received much interest because of their long-term adherence to mucus, which is a constituent of every organ in the human body and leads to increased systemic and local drug bioavailability. Bioadhesion may be defined as the binding of a natural or synthetic polymer to a biological substrate. Bioadhesive polymeric-based systems play an important role in delivering various bioactive molecules and drugs. A bioadhesive delivery system residing on a biological surface allows site specific drug delivery by releasing bioactive molecule in the specific site, hence increases bioavailability of drug. Nanoparticles (NP) are colloidal particles that are entrapped, encapsulated, or adsorbed with therapeutic agents. When incorporated in to formulation, they can target a molecule to a specific site, modify drug release pharmacokinetics, and improve drug efficacy and safety [2,3]. Drugs linked to polymeric bioadhesive nanoparticulate systems help to overcome the limitations of conventional drug delivery techniques.

ADVANTAGES OF BIO-ADHESIVE DRUG DELIVERY SYSTEM

- A prolonged residence time at a site of absorption or action.
- A localization of the Drug Delivery System (DDS) at a given target site.
- Possible by pass of first pass effect.
- Reduction in dosing frequency of bioactive molecules due to increased residence time and controlled release at target site.
- Improved bioavailability of bioactive molecules at lower concentration due to prolonged contact time [4].
- Characteristics of bioadhesive polymers and theories of bioadhesion.

CHARACTERISTICS OF BIOADHESIVE POLYMERS AND THEORIES OF BIOADHESION

There are various bioadhesive polymers which are used in various delivery systems based on bioadhesion. Following is the list of few bioadhesive dosage forms developed with one or more bioadhesive polymers along with key findings of the work (Figures 1 and 2) (Tables 1 and 2).

Figure 1: Characteristics of bio adhesive polymers.

Figure 2: Theories of bio adhesion.

Table 1: Factors affecting bio adhesion.

Polymer related factors	Environment related factors	Physiological factors
• Molecular weight • Concentration of active polymer • Degree of hydration • Charge on polymer • Flexibility of polymer chain • Spatial confirmation • Swelling • Presence of functional group	• pH • Applied strength • Initial contact time • Swelling	• Mucin turnover • Disease state

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Table 2: List of various bio adhesive systems developed with key findings.

Drug	Delivery system	Bio adhesive system	Bio adhesive polymer	Key findings
Povidone iodine	Tablets		Polyvinyl pyrrolidone	Release of polymer complex with iodine for 8 h along with rapid disintegration and good bio adhesive strength [5].
Itraconazole	Vaginal film	For Vaginal delivery	Hydroxypropyl methylcellulose E15	Bio adhesive polymer retained film up to 7 h on the vaginal mucosa of rat and showed improved therapeutic benefits of drug against Candida albicans vaginitis [6].
5-Fluorouracil	Bio adhesive gel	For buccal delivery	Poloxamer 407, HPMC K 15 M, Gantrez S-97 (poly methyl vinyl etherco-maleic anhydride)	Bio adhesive strength of gel increased with increasing concentration of HPMC K 15 M and Gantrez S-97 and gel showed sustained release of the drug up to 8 h along with high buccal mucosal permeability [7].
Ondansetron hydrochloride	Tablets		Carbopol (CP 934), sodium alginate, sodium carboxy methyl cellulose low viscosity (SCMC LV), hydroxypropyl methylcellulose (HPMC 15 cps)	Bio adhesive tablets showed high drug permeation through the bovine buccal mucosa and sustained the release up to 500 min *in vitro*. Tablets show high stability in human saliva [8].
Etodolac	Thermogel		Poloxamer, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, methyl cellulose, hydroxyethyl cellulose, carbopol	Prepared thermogel showed good bio adhesive strength, drug release through the Fickian diffusion, and no morphological damage to rectal tissues of rats [9].
Epirubicin (Epi)	Liquid and solid suppository	For rectal drug delivery	Pluronic (Plu) and pH-sensitive polyacrylic acid (PAA	Prepared suppositories showed high *in vitro* bio adhesive strength, higher value of relative bioavailability and AUC along with efficient reduction in tumour cells in Balb/c mice [10].
Zolmitriptan	Nasal inserts		Chitosanchondroitin sulphate	Results of *in vitro* and in situ showed that formulations having drug: polymer in 1:10 ratio gave 90% and 98% zolmitriptan release over a period of 8 h [11].
Azithromycin	Ocular inserts	For ocular drug delivery	Alginate, carbopol, and hydroxyl propyl methylcellulose (HPMC)	Tensile strength and elasticity of the alginate-based insert was higher compared to carbopol inserts; and insert containing carbopol and HPMC in the ratio 30:70 sustained the drug release for 6 h [12].
Brimonidine	Nanoparticles		Sodium alginate, chitosan	Nanoparticles prepared from both polymers showed sustained drug release for approximately 10 h and effectively reduced intraocular pressure compared to marketed eye drops of the drug [13].
Lafutidine	Tablet	For gastrointestinal drug delivery	Sodium alginate, xanthan gum, karaya gum	Optimized formulation showed a muco adhesive strength >35 g and X-ray analysis suggested that tablet was well adhered for >10 h in rabbit's stomach [14].
Acyclovir	Microspheres		Sodium alginate	Optimized formulation showed high muco adhesive strength (66.42 ± 1.01%) and Gamma scintigraphy result showed gastric retention of formulation for more than 4 h *in vivo* [15].

Special case of nanoparticles as bioadhesives

Oral administration of polymeric nanoparticle suspensions leads to mucoadhesion of a significant fraction of the particles. Parts of the particles are received by the mucus gel layer while the remaining particles undergo unmodified transit. Process of mucoadhesion of nanoparticles can be described as administration of the suspension of particles, which comes immediately in contact with the portion of oral mucosa. From this moment, the suspension acts as a reservoir of particles and very rapidly, an adsorption process takes place that leads to the adsorption of some amount of the available particles. Adsorption occurs in the mucus layer and is an irreversible process. The particles present in the lumen travel through the intestine, sweeping progressively the whole mucosa. Simultaneously, the absorption of these particles takes place resulting in a progressive covering of the intestinal mucosal. Eventually, the particles begin to detach from the mucosa in the proximal to the distal region. Non-adherent particles from the lumen pool and detached particles from the mucoadherent pool are finally removed with feces [4]. The mechanism of drug absorption from muco adhesive systems is depicted in Figure 3.

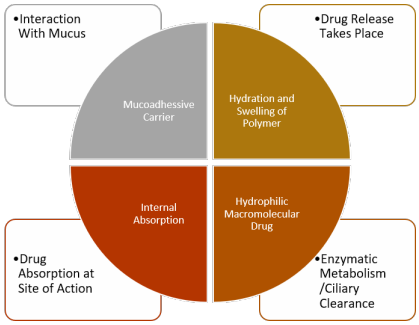

Figure 3: Mechanism of drug absorption from bio adhesive systems.

EVALUATION OF BIOADHESIVE DRUG DELIVERY SYSTEMS

In-vitro evaluation parameters

Measurement of detachment force: This test involves measurement of the force required to separate two parallel glass slides covered with polymer and mucus layer respectively [16-19].

Tensile strength measurement: Aqueous dispersion of a bioadhesive polymer is placed between two discs made up of polyoxy methylene. The upper disc shows movement while the lower disc is stationary, as it is fixed on a stationary frame of the machine. After application of the tensile force, maximum force required for detaching next to the fracture is calculated by using a force displacement curve.

Measurement of adhesion strength: Adhesion strength measurement can be carried out by using the fluorescent probe method. Probes are used to analyse the polymer and mucin interaction.

Falling liquid film technique: This method involves in situ quantification of adherence of particles on a mucosal surface. Briefly, a particulate system allowed flowing down through an inclined plastic slide covered with mucosal membrane.

Colloidal gold staining technique: This technique is used for quantitative comparison of bioadhesive properties of various hydrogels.

In-vivo evaluation parameters

Gamma scintigraphy technique: *in-vivo* distribution pattern of any dosage form is confirmed by using gamma scintigraphy technique.

Isolated loop technique: In this technique, the bioadhesive property of microspheres was calculated in terms of mean residence time, followed by injection into the in situ perfused gut segment.

X-ray studies: GI transit time of bioadhesive formulations can be confirmed through X-ray inspection by coating the formulations with radio-opaque markers like barium sulphate.

CONCLUSION

Now-a-days bio adhesive drug delivery system is becoming a promising approach to achieve a targeted and sustained release of drug and maintaining patient compliance. Mucoadhesive nanoparticulate systems are potentially helpful in delivering active drug molecule at required site of action and these systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bio-adhesive component.

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