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Efficiency estimation of gastroretentive adhesive aids in drug delivery system

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ABSTRACT

Gastro retentive dosage forms have potential for use as controlled-release drug delivery systems. Multiple unit systems avoid the "all-or-none gastric" emptying nature of single-unit systems. Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier. Mucoadhesive polymers increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. The general properties of these polymers for purpose of sustained release of chemicals are marginal in being able to accommodate a wide range of physicochemical drug properties. The aim of this study is to evaluate the mucoadhesive properties between Polycarbophil, Carbopol and Chitosan. Comparability of the results is very difficult due to various parameters for the measurements. Until now, there is no standardized method available for studying mucoadhesion. Chitosan show maximum and prolonged mucoadhesion of 84.11%.

Keywords: Mucoadhesion, Polycarbophil, Carbopol, Chitosan

INTRODUCTION

The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier (Junginger, 1991). Bioadhesion can be defined as a phenomenon of interfacial molecular attractive

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forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to bond with the biological surface for an extended period of time (Webster, 2001; Kaelbe et al., 1997 [1-5]. Robinson et al., 1998; Duchene et al., 1988). The oral human mucosa consists of an epithelium, the lamina propria and the underlying submucosa. The epithelium of the buccal mucosa counts about 40–50 cell layers. The turnover time for the buccal epithelium cells is approximately about 5–6 days. The buccal mucosa is completely covered with the mucus layer consisting of more than 95% water. Thickness of the epithelium as well as keratinisation differs between human and animal mucosa. Thickness of buccal mucosa in humans, dogs and rabbits varies from 500 to 800 μm.

Mucoadhesive polymers are synthetic or natural macromolecules which are capable of attaching to mucosal surfaces. The concept of mucoadhesive polymers has been introduced into the pharmaceutical literature more than 40 years ago and nowadays it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes [6-9]. So far, a considerable number of studies focusing on the mucoadhesive properties of a wide range of polymeric materials have been performed using different in vitro methods and techniques (Peppas et al., 1996).

The polymeric attributes that are pertinent to high levels of retention at applied and targeted sites via mucoadhesive bonds include hydrophilicity, negative charge potential and the presence of hydrogen bond forming groups. Additionally, the surface free energy of the polymer should be adequate so that 'wetting' with the mucosal surface can be achieved. The polymer should also possess sufficient flexibility to penetrate the mucus network, be biocompatible, non-toxic, and economically favorable. Polymers for the use in mucoadhesive preparations can be anionic, cationic or nonionic. Cationic polymers form bonds with the negatively charged mucin chains, whereas anionic polymers have mucoadhesive properties due to hydrogen bonding with the mucus layer. Free thiol groups can also be beneficial to support mucoadhesion due to disulphide bonds.

The process involved in formation of such bioadhesive bonds (Ponchel et al., 1987)

- Wetting and swelling of polymer to permit intimate contact with tissue
- Interpenetration of chains between polymer chain and mucin chain.
- Formation of weak chemical bonds.

Characteristics of polymer for adhesion (Ponchel et al., 1991)

- Sufficient quantities of hydrogen- bonding chemical groups
- Anionic surface charge
- High molecular weight
- High chain flexibility
- Surface tension that will induce spreading into mucosal layer

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Polycarbophil is a high-molecular-weight acrylic acid polymer cross-linked with polyalkenyl ethers or divinylglycol. There is a large number of carboxyl (COOH) on the molecular chain. Polycarbophil have shown high bioadhesive force and prolonged residence time and proved to be non-irritative in in-vivo trials with human buccal mucosa. It is also useful in designing controlled-release formulations (Jain et al., 2002) and for drugs that undergo first-pass metabolism. (Akbari et al., 2004) Polycarbophil buccoadhesive disks have also been developed in formulations increasing the bioavailability and transmucosal absorption of poorly water-soluble drugs. Carbopol is acrylic acid that is crosslinked with either allyl sucrose (Samaligy et al., 2004). Chitosan is a linear polysaccharide, Composed of glucosamine and N-acteyl glucosamine units via β (1 → 4) linkages, randomly or block distributed throughout the biopolymer chain, depending on the preparation method to derive chitosan from chitin. The deacetylation degree is defined as the molar ratio of glucosamine to N-acetyl glucosamine, which is an important parameter determining its properties and applications. After deacetylation process, chitosan is able to dissolve in acidic medium and becomes the only polysaccharide that possesses high density of positive charges, due to the protonation of amino groups on its backbone. Besides this unique

characteristic, chitosan has been proved to have many other intrinsic properties, such as non-toxicity, biocompatibility and biodegradability (Kean et al., 2010).

MATERIALS AND METHODS

Repaglinide was received as a gift sample from Gensynth fine chemicals Pvt Ltd. Hyderabad, India. Polycarbophil, Carbopol 934p, Chitosan, Calcium chloride, acetic acid and ethanol was received as a gift samples from Research laboratories, Hyderabad, India.

Preparation of Mucoadhesive Nanoparticles (Harshad et al., 2010)

Repaglinide nanoparticles were prepared by Ionotropic gelation method. Different formulations of Polycarbophil, Carbopol and Chitosan were prepared.

Table.1: Composition of formulations

Formulation	Drug (mg)	Polymers (mg/ml)			Calcium chloride (mg)
		Polycarbophil	Carbopol	Chitosan	
F1	6.0	1.0	1.0	1.0	6.75
F2	6.0	2.0	2.0	2.0	6.75
F3	6.0	3.0	3.0	3.0	6.75
F4	6.0	4.0	4.0	4.0	6.75
F5	6.0	5.0	5.0	5.0	6.75
F6	6.0	6.0	6.0	6.0	6.75

Weighed amount of polycarbophil dissolved in deionized water, carbopol dissolved in distilled water and chitosan dissolved in 1% acetic acid separately with sonication for 1 hour. Calcium chloride was dissolved in water. Repaglinide was dissolved in 1:1 ethanol water mixture and then added in calcium chloride solution at once. The mixture of drug and calcium chloride solution was added drop wise into polymeric solution, over the period of 1 hour at stirrer rate of 150 rpm. The suspension was allowed overnight and then probe sonicatedfor 3 min. the above suspension was kept for freeze drying for 24 hours as shown in **Table.1**

Shape and surface morphology

Surface and shape characteristics of the prepared nanoparticles were evaluated using scanning electron microscopy (SEM). The scanning electron microscopy samples were prepared by lightly sprinkling the granules powder on a double adhesive tape, which was stuck on an aluminum stub. The stubs were then coated with gold using a sputter coater, and the photographs of the samples were taken for shape and surface morphology.

Effect of polymers on Mucoadhesion (Chien, 1992)

Mucoadhesion of different nanoparticles was assessed using the method reported with little modification. A strip of rat intestinal mucosa was mounted on a glass slide and accurately weighed bioadhesive nanoparticles in dispersion form was placed on the mucosa of the intestine. This glass slide was incubated for 15 min in desiccators at 90 % relative humidity to allow the polymer to interact with the membrane and finally placed in the cell that was attached to the outer assembly at an angle 45º. Phosphate buffer saline (pH 6.8), previously warmed to 37±0.5 ºC, was circulated to the cell over the microspheres and membrane at the rate of 1 mL/min. Washings were collected at different time intervals and microspheres were separated by centrifugation followed by drying at 50ºC. The weight of nanoparticles washed out was taken and percentage mucoadhesion was calculated by the following formula:Percentage mucoadhesion = Wo. −Wt. / Wo. × 100Where Wo. = weight of nanoparticles applied; Wt. = weight of nanoparticles leached out.

RESULT AND DISCUSSION

Nanoparticles Shape and surface morphology

The average particle size(s) of the prepared nanoparticles was found to be 300-400 nm (**Figure 1**).

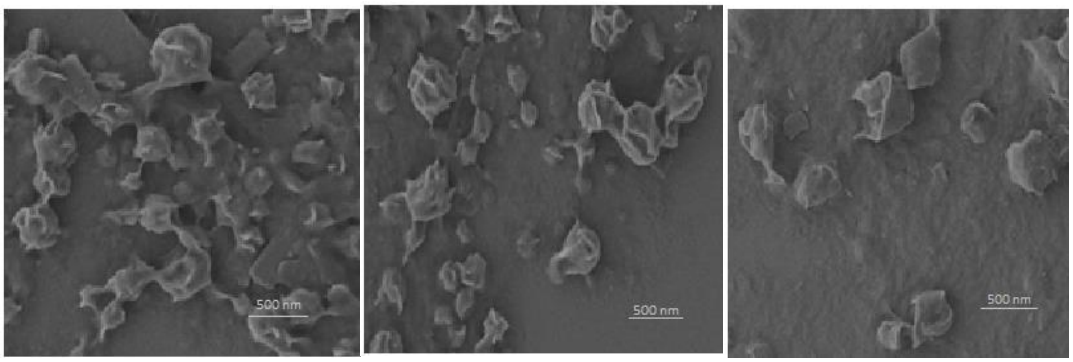

Figure 1: SEM images of nanoparticles (Polycarbophil, Carbopol and Chitosan respectively)

Effect of polymers on Mucoadhesion

It can be seen that the Chitosan nanoparticles had good mucoadhesive properties and could adequately adhere to intestinal mucosa. The results also showed that with change in polymer to drug ratio, the % mucoadhesion also varies. The maximum and prolonged mucoadhesion (84.11%) was observed with the formulation 6 as shown in **Table.2**.

Table.2: Percentage mucoadhesion

Formulation	Chitosan	Carbopol	Polycarbophil
F1	74.30±0.8	68.20±0.6	20.4±2.0
F2	77.21±0.5	71.45±1.0	21.8±0.9
F3	79.80±1.2	73.28±0.9	23.7±1.6
F4	80.12±1.0	76.40±0.8	25.6±0.9
F5	82.32±1.4	79.38±1.2	27.1±1.6
F6	84.11±1.1	81.10±1.6	19.6±0.9

- Chitosan has an excellent bioadhesive, prolonged residence time and proved to be non-irritant in vivo trails with human buccal mucosa (Nafee et al., 2004).
- Chitosan swells in water 1000 times their original volume to form gel.
- The presence of greater amine and hydroxylic groups in chitosan than carbopol and polycarbophil.
- The molecular chain length determines the strength of mucoadhesive bonds; it is believed that high molecular weight corresponds to maximum adhesiveness in chitosan than carbopol and polycarbophil.
- Interpenetration was considered highly when partial hydration of hydrogel resulted from a balancing of the chemical potential throughout the system, chitosan has average pore diameter of 2.3 nm where as for carbopol 3.4 nm and polycarbophil3.7 nm.
- The salic acid of mucin is in cationic form. The stronger interaction of mucin at Ph> 5.5
- Survey of mucoadhesive properties of various polymers as shown in **Table.3.**

Table.3. detachment force

Polymer	Detachment force (Mn/Cm^2)
Chitosan (low viscosity)	13.9
Chitosan (high viscosity)	16.7
Chitosan (sigma)	16.6
Carbopol	11.8
Polycarbophil	7.6

- The Chitosan is potent inhibitors of proteolytic enzymes.
- Among all the polymeric hydrogels used polysaccharide (chitosan) derivatives are good mucoadhesives.
- After deacetylation process, chitosan is the only polysaccharide that possesses high density of positive charges, due to the protonation of amino groups on its backbone.
- Chitosan has the highest value for various properties such as Adhesion, Swelling, Humidification and biocompatible with both healthy and infected skin (Gooday, 1986).
- The sequence of Adhesion force Chitosan>Xanthum gum>Carbopol 1342p>Carbopol 974p>Polycarbophil> HPMC>CMCNa> Gelatin> Acacia gum.

CONCLUSION

The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility. Now researchers are looking beyond traditional polymers, in particular next-generation mucoadhesive polymers (Chitosan, Carbophil, Polycarbophil etc.); these polymers offer greater attachment and retention of dosage forms. However, these novel mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases. From the results Chitosan shows highest mucoadhesion than carbophil and polycarbophil.

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