Mucoadhesion for Enhanced Drug Delivery

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BACKGROUND

Mucoadhesion is a state where two materials, at least one of which is a mucous membrane are held together for extended periods of time by interfacial forces (Figure 1).

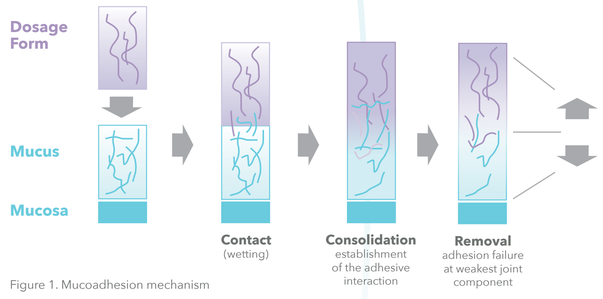

Figure 1. Mucoadhesion mechanism

Mucoadhesive dosage forms can be designed to ensure prolonged contact with mucosal membranes present in the human body (buccal, nasal, ophthalmic, intestinal, rectal, vaginal), providing increased efficacy, patient compliance and product differentiation (Figure 2).

The design of such formulations requires the use of an excipient that imparts mucoadhesive properties and ensures prolonged contact between the drug product and the mucosa.

Polymers with mucoadhesive properties are hydrophilic molecules containing functional groups that could interact with the mucin glycoproteins via non-covalent bonds such as hydrogen bonds, van der Waals forces and ionic interactions. Examples include carbomers (e.g., Carbopol® polymers), xanthan gum, sodium carboxymethylcellulose, and carrageenan.

Efficacy	• Enhanced systemic delivery – Mucosa permeability – By-pass GI-route/first hepatic pass • Localized – dosage form at site of action • Tailored duration
Patient Compliance	• Noninvasive • Convenient (administration/removal) • Reduced drug side-effects
Differentiation	• Mucoadhesion can be used to provide product innovation and new label claim opportunities

Figure 2. Benefits of mucosal drug delivery

OBJECTIVE

Compare the in-vitro mucoadhesive properties of various polymers in pharmaceutical formulations and their application in designing patient compliant dosage forms.

MATERIALS

Carbopol® 971P NF and 974P NF polymers; xanthan gum; carrageenan; copolymer of methyl vinyl ether and maleic anhydride (PVM/MA); hydroxypropyl cellulose (HPC); sodium carboxymethylcellulose (NaCMC); polyvinyl alcohol (PVA); FD&C Blue No. 1.

METHODS

in-vitro oesophageal retention model

Lubrizol Life Science Health has developed a method based on the in vitro oesophageal retention (IVOR) model that allows for mucoadhesion evaluation in a dynamic environment.[1] The dosage form is subjected to continuous fluid flow during testing. The device is depicted in Figure 3.

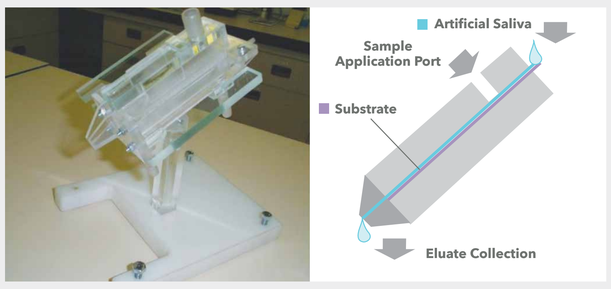

Figure 3. In-vitro oesophageal retention model used to test mucoadhesive properties of formulations

Preparation of 1% gel of various polymers

Typically, the polymer was dispersed at desired concentration in deionized water. For Carbopol® polymers the dispersion was followed by neutralization to pH of ~ 7.0 according to recommended procedures.[2] To the resulted dispersion an aqueous solution of FD&C Blue No. 1 was added such that the final concentration of the blue marker in the formulation was ~ 0.03%.

Preparation of cold/cough formulations containing Carbopol® polymers

Cold/cough liquid formulations were prepared by dissolving the acetaminophen, dextromethorphan and sweetener, followed by mixing with dispersion of Carbopol® polymer. The inclusion levels of the mucoadhesive polymer in the formulation were 0, 0.3, 0.5 and 1.0%.

Preparation of films containing Carbopol® polymers

Film formulations containing Carbopol® polymer and PVA (1:2) were prepared by solvent casting from aqueous/ethanolic gels. Typically, the Carbopol® polymer was dispersed at the desired concentration in water/ethanol mixture. An aqueous PVA solution and plasticizer were added to the Carbopol® polymer dispersion. Films of various thickness were cast from the resulted gels on high density polyethylene using an automated film applicator.

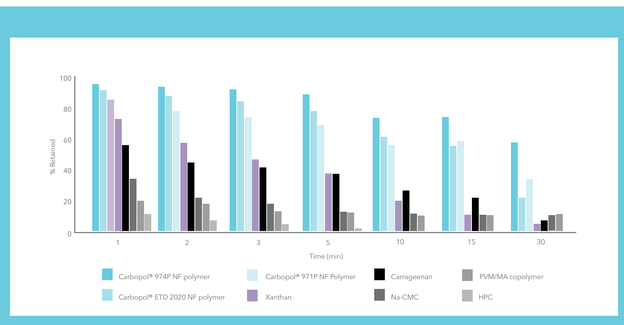

Figure 4. In-vitro mucoadhesion of dispersions made from various polymers (1.0% w/w)

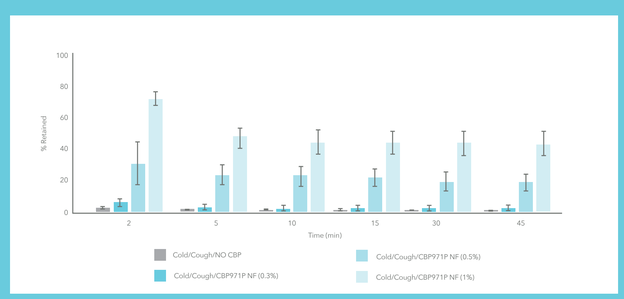

Figure 5. Impact of Carbopol® 971P NF polymer (CBP971P NF) on mucoadhesion in oral liquids

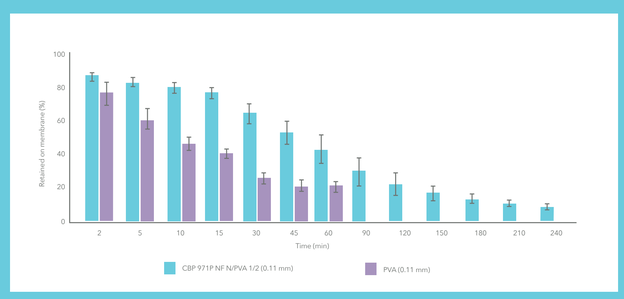

Figure 6. Mucoadhesion enhancement of films containing Carbopol® polymer

RESULTS and DISCUSSIONS

Mucoadhesive properties of polymer semisolid formulations

The mucoadhesive properties of Carbopol® polymers were compared in vitro with other materials, including xanthan gum, carrageenan, sodium carboxymethylcellulose (NaCMC), copolymer of methyl vinyl ether and maleic anhydride (PVM/MA), and hydroxypropyl cellulose (HPC). The aqueous dispersions of the materials (1% w/w) were evaluated using the IVOR model to simulate oral/peroral conditions. **Compared to other materials, Carbopol® polymers provided the longest retention over time, with more than 20% retained on the substrate even after 30 minutes** (Figure 4).

Liquid cold and cough formulation

The in-vitro mucoadhesive properties of a commercial liquid cold & cough formulation was evaluated in the presence or absence of Carbopol® polymer. Carbopol® polymer inclusion level was varied to determine the effect on retention of the formulation over time. **Formulations containing Carbopol® polymer had significantly higher retention than formulations that did not contain Carbopol® polymer** (Figure 5). Additionally, higher retention was achieved with higher polymer concentration.

Mucoadhesion enhancement of films containing Carbopol® polymers

Polyvinyl alcohol is known in pharmaceutical formulation as a film former, while Carbopol® polymers have demonstrated mucoadhesive properties. The mucoadhesion of the films was influenced by Carbopol® polymer degree of crosslinking, longer retention being ensured by films containing Carbopol® 971P NF polymer. Film thickness impacted mucoadhesion as expected, thicker films showing better retention. At similar thickness, PVA films containing Carbopol® 971P NF polymer showed longer retention when compared to benchmark PVA films (Figure 6). After 90 minutes, the PVA film was almost entirely washed off, whereas the Carbopol® polymer containing PVA film was retained to some extent even at 240 minutes (Figure 7).

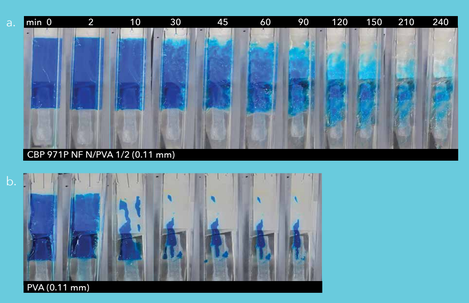

Figure 7. IVOR of films a. CBP971P NF/PVA 1/2 (0.11 mm); b. PVA (0.11 mm)

The presence of Carbopol® polymers enhanced mucoadhesive properties of the films, offering flexibility of formulation.

CONCLUSION

The in-vitro mucoadhesion studies conducted demonstrated that:

- Introducing mucoadhesive excipients in drug formulations facilitated enhanced contact time with the target membrane
- Excipient selection greatly impacted the level and effectiveness of mucoadhesion in a formulation
- Carbopol® polymers (carbomers) have proven to exhibit higher retention times in formulation compared to other polymers
- Mucoadhesion can be used to provide product innovation and new label claim opportunities

REFERENCES

[1] Young, S. A. and Smart, J. D. A novel in-vitro apparatus for evaluating the mucoadhesion of liquid and semi-solid formulations, J Pharm. Pharmacol. 50, 167 (1998)

[2] https://www.lubrizol.com/Life-Sciences/Literature/Pharmaceutical-Literature Technical Data Sheets TDS-103 and TDS-237

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