**Physiological considerations for the formulation and evaluation of mucoadhesive in situ forming oral gels**

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**Purpose**
Presently, most of the reported formulation characterization techniques that can be used for mucoadhesive in situ forming oral gels fail to account for physiological factors such as the shape of the oral cavity, the effect of gravity, and the presence of saliva. However, inconsideration of these factors may lead to overestimation of formulation critical quality attributes leading to clinical failure. The main objective of this study was to investigate the impact of physiological factors on the in vitro performance of in situ forming oral gels prepared with different mucoadhesive polymers.

**Methods**
Four different poloxamer based mucoadhesive in situ forming oral gels (F1, F2, F3, F4) were prepared, each containing a different mucoadhesive polymer using bupivacaine HCl as a model drug. The in situ forming gels were characterized using different in vitro techniques. Furthermore, the effect of physiological factors on mucoadhesion (measured using a texture analyzer) and on gelation were evaluated by comparing previously reported methods with revised methods designed to mimic the effect of gravity and the presence of artificial saliva in the oral cavity.

**Results**
The formulations exhibited higher gelation temperatures and a lower mucoadhesion using the revised methods. Furthermore, the rheological time sweeps conducted at 35 °C demonstrated a higher gelling time for formulations diluted with artificial saliva than the undiluted formulations. Polymers such as PVP, sodium alginate, and sodium CMC showed Fickian diffusion at normal pH and non-Fickian diffusion kinetics at a lower pH. In contrast, chitosan exhibited first-order release kinetics for all the dissolution media. The % drug release is correlated with the gel consolidation behavior. Except for sodium CMC, which is highly soluble (leading to a faster drug release), higher gel consolidation led to slower drug release.

**Conclusion**
Comparison of the previously reported techniques to the revised methods emphasizes the importance of considering the physiological factors for the formulation characterization of in situ forming oral gels. The drug release kinetics of the formulations were dictated by the nature of the mucoadhesive polymer, the release medium, and the gel consolidation behavior of the formulations. Hydrophilic polymers, lower gel consolidation, and a lower media pH led to faster drug release.

**Keywords:** Mucoadhesion, in situ forming gels, rheology, oral cavity, salivary flow, in vitro release