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purpose of validating the theoretical approach. The expected peak location and width of the bolus (introduced 10 cm into the duodenum) is indicated in the figure. The peak of the bolus is exactly 10 cm beyond the distance ($\sqrt{D * t}$ from the entrance to the duodenum, reflecting the fact that the bolus was introduced 10 cm into the small intestine. Also, the width of the peak corresponds to the theoretical expectation ($\sqrt{D * t}$).

Theoretical serum concentrations were compared with experimental data in various cases. Figure 2 shows a comparison between experimental data and theoretical predictions for the case of ibuprofen, administered orally in humans (5). Total predicted absorption is 51%, near the experimental estimate. The good match of the data is obtained upon assuming an epithelial permeability of 7.8×10^{-6} cm/s.

Fig. 2 Comparison of experimental (symbol) and predicted (solid curve) serum concentration profiles for ibuprofen following oral administration to humans.

Figure 3 shows a comparison between experimental data and theoretical predictions for the case of GHRP-1, administered orally in humans (6). Theoretical absolute bioavailability is approximately 0.1%. The theoretical prediction is obtained upon assuming an epithelial permeability of 6×10^{-7} cm/s.

Fig. 3 Comparison of experimental (symbol) and predicted (solid curve) serum concentration profiles for GHRP-1 following oral administration to humans.

The proposed theoretical model can be used to predict the absorbed systemic concentrations of therapeutics ranging from small lipophilic molecules to macromolecules.

REFERENCES

1. Kreydiyyeh, S.I., Bitar, K.M., Bikhazi, A.B. J. Pharm. Sci., 79, 494 (1990).
2. Adson, A., Raub, T.J., Burton, P.S., Bartuhn, C.L., Hilgers, A.R., Audus, K.L., Ho, N.F. J. Pharm. Sci., 83, 1529 (1994).
3. Brenner, H., Edwards, D.A. Macrotransport Processes. Boston: Butterworth-Heinemann (1993).
4. Stoll, B., Batycky, R., Leipold, H., Milstein, S., Edwards, D. Submitted (1997).
5. Dressman, J.B., Bass, P., Ritschel, W.A., Friend, D.R., Rubinstein, A., Ziv, E. J. Pharm. Sci., 82, 857 (1993).
6. Bowers, C.Y. J. Ped. Endocrin. 6, 21 (1993).

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WATER SOLUBLE FILM FOR ORAL ADMINISTRATION

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Introduction

Mucoadhesive dosage forms for application to the oral cavity which are designed to deliver therapeutic and/or cosmetic agents to the oral mucosa are known in the art. Sanvordeker and Leung (1) described a mucoadhesive carrier allowing the controlled release of a therapeutic agent via the mucosal tissue comprising an anhydrous but hydratable polymer matrix and amorphous fumed silica. An optional water-insoluble film can be added to provide a non-adhering surface. They also disclosed a bilaminate film suitable for prolonged delivery of an active ingredient in the oral cavity (2). In a similar way, Mizobuchi, et al. (3) disclosed a sheet-shaped adhesive preparation comprising an adhesive layer containing certain water-soluble and water-insoluble polymers and a water-insoluble carrier which can adhere to the oral mucosa thereby releasing an active agent to the oral cavity. A number of attempts have been made to reduce the adverse feeling in the oral cavity caused by the rigidity and inflexibility of the support layer by introducing soft film supports(4-6). However, these devices still leave the patient with a considerable amount of residue from the water-insoluble support film thereby still causing a feeling of discomfort. The obvious solution to overcome this problem was to develop mucoadhesive films which completely disintegrate, or even completely dissolve in the saliva.

Invention

The present invention contemplates a rapidly dissolving film which can be adhered to the oral cavity thereby releasing a pharmaceutically or cosmetically active agent, said film comprising water-soluble polymers, a combination of certain surfactants, one or more polyalcohols, and one or more pharmaceutically or cosmetically active ingredients. Optionally the formulation may contain colorants, sweetening agents, flavors, flavor enhancers, or other excipients commonly used to modify the taste of formulations intended for application to the oral cavity. The resulting film is characterized by an instant wettability which causes the film to soften immediately after application to the mucosal tissue thus preventing the patient from experiencing any prolonged adverse feeling in the mouth.

The film is manufactured using conventional coating and drying techniques, cut into pieces of a shape and size that meet the requirements of the specific application, and packaged into suitable containers.

Experimental

The mucoadhesive film of the present invention contains as essential components a water-soluble polymer or a combination of water-soluble polymers, a combination of surfactants, one or more polyalcohols, and a pharmaceutically or cosmetically active ingredient. The polymers used for the mucoadhesive film include polymers which are hydrophilic and water-dispersible. The combination of surfactants used for the mucoadhesive film is a mixture of nonionic surfactants. The amount of drug to be incorporated into the film depends on the kind of drug and is usually between 0.01 and 20% (w/w). Cosmetically active agents may include breath freshening compounds like menthol, other flavors or fragrances commonly used for oral hygiene, and/or

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actives used for dental and/or oral cleansing like quarternary ammonium bases. The mucoadhesive film according to the present invention can be prepared as follows: The active ingredient, surfactants, polyalcohol, and possible other ingredients except the water-dispersible polymer are dissolved in a sufficient amount of a solvent which is compatible to them. After a clear solution has been formed, the water-dispersible polymer or mixture of water-dispersible polymers is slowly added under stirring until a clear and homogeneous solution has been formed. The solution is coated onto a suitable carrier material and dried to form a film. The carrier material must have a surface tension which allows the polymer solution to be spread evenly across the intended coating width. The coating of the solution onto the carrier material can be performed using any conventional coating equipment.

The films with desired thickness were cut or punched out for the disintegration and tensile strength tests. The tensile strength of the films was assessed using Erichsen (Model 474, A. M. Erichsen GmbH, Germany) and was expressed as the maximum force (N) (Figure 1). A 25-cm² film was placed in the peri dish which was filled with deionized water, and the time for the film to totally disintegrate was recorded (Figure 2). The decrease of integration time of formulations A to E was accompanied by the decrease of tensile force of the formulations. This correlation indicated that the choice of the most optimal formulation could be decided by using either the tensile strength or the disintegration test.

Conclusion

A composition containing therapeutic agents and/or breath freshening agents for use in the oral cavity is disclosed. The carrier comprises water-soluble polymers in combination with certain ingredients and provides a therapeutic and/or cosmetic effect. The film is coated and dried utilizing existing coating technology and exhibits instant wettability followed by rapid dissolution/disintegration upon administration in the oral cavity.

References

(1) Sanvordeker, D.R. and Leung, S-H. S. US patent 5,047,244, 1991.
(2) Sanvordeker, D.R. and Lenug, S-H. S. WO patent 91/06270, 1991.
(3) Mizobuchi, T., Ohji, A., Sakoh. S, and Muguruma, Y. US Patent 4,876,092, 1989
(4) Kuroya, T. and Inoue, Y. European Patent 0-381-194-B1, 1990.
(5) Blank, R.G., Mody, D.S., Kenny, R.J. and Aveson, M.C. US Patent 4,946,684, 1990.
(6) Inoue, T., Maeda, K. and Eguchi, Y. US Patent 5,206,010, 1993.

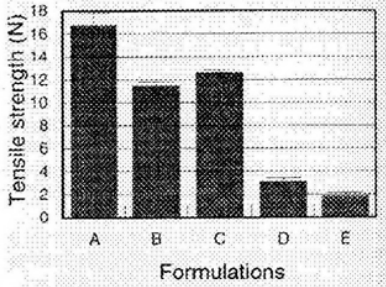

Figure 1: The tensile strength of polymer films.

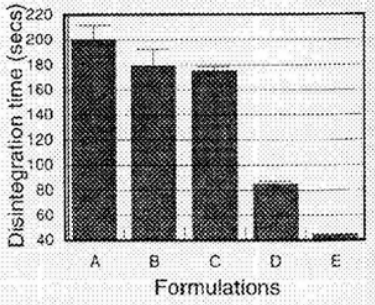

Figure 2: The disintegration time of polymer films.

Water Soluble Polycations for Controlled Delivery Systems

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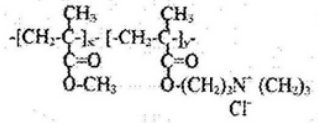
Introduction

Drug delivery systems using ion exchange resins are one of the oldest processes [1]. Commercially available ion exchange resins are based on highly cross-linked poly(styrene/divinyl benzene) (sulfonated and quaternized) or cross-linked poly(methacrylic acid). Highly cross-linked gel type resins (negligible swelling) significantly sustain the release of a drug in the gel matrix, which yields $\sqrt{t}$ release kinetics with a tailing.

Recently, swellable polyelectrolyte gel matrices have been extensively investigated as drug delivery systems. By varying the ionic pendant groups and the degree of cross-linking of the polymer chains, the degree of swelling of charged polyelectolytes may be tailored. Several investigators used cationic and anionic hydrophobic polymers consisting of tertiary amine and methacrylic acid or acrylic acid groups, respectively, for the release of drugs [2-4]. However, due to the pH dependent swelling characteristics of charged polymers containing tertiary amine or carboxylic acid pendant groups, it was not feasible for these ionic gels to be employed as oral delivery systems, because the pH condition changes as a dosage form travels along the gastro-intestinal (GI) tract. Nujoma and Kim [5] demonstrated a (pseudo) linear release of water soluble drugs from erodible, drug/resin complex, gel tablets using noncross-linked poly(sulfopropyl methacrylate potassium -co- methyl methacrylate) (PSPMK/MMA). Drug release from drug-PSPMK/MMA, which has a drug loading of greater than 40 wt%, maintains zero-order release kinetics for a long period of time because the drug in the matrices is bound to the polymer side chain until the complex is dissociated by incoming counter ions. It was found that drug release was independent of the pH of the dissolution medium as long as the ionic strength was higher than 0.1 M which is commonly observed in the GI fluid [6]. In addition, tablets, which are a common extended release dosage form were successfully prepared from these drug/resin complexes.

In this study, we present the zero-order release kinetics of water soluble anionic drugs from erodible, drug/polycationic, matrices (tablets) using poly(trimethylaminoethyl methacrylate chloride -co-methacrylate) (PTMAEMC/MMA):



Experimental Methods

Synthesis of PTMAEMC/MMA and Preparation of Drug Resinate Tablets

PTMAEMC/MMA was prepared by the free-radical solution polymerization of PTMAEMC (40%) and MMA (60%) as reported earlier [7]. The polymer was dissolved in de-ionized water, and a drug solution was added to the polymer solution. The complexes precipitated in water were recovered and washed several times before being dried. The dried drug-resinates were crushed in a mortar and pestle to obtain powders. Tablets with drug-resinates and dextrose were fabricated in 9.0 mm diameter die and a flat surface punch with a Carver press.

Drug Release Kinetics Tests

The drug release kinetics from drug-resinate tablets were carried out in 0.01 M phosphate buffer containing different amounts of NaCl at 37°C by the USP basket method at 100 rpm, unless otherwise noted. Drug release was monitored on a HP8452A diode-array spectrophotometer at 250 nm and 290 nm for diclofenac Na and sulfathiazole Na as model drugs, respectively.

Results and Discussion

The effect of ionic strength on diclofenac Na release from drug-PTMAEMC/MMA complex tablets at pH 7 is shown in Figure 1. Tablets of 200mg weight were formulated with 20 % dextrose as a tablet binder. The buffer contained 0.01 M phosphate and NaCl ranging from 0.05 M to 0.2 M