**ADHESIVE COMPOSITION WITH ACIDIC ORGANIC ADHESIVE POLYMER AND CATIONIC AMMONIUM-SUBSTITUTED POLYMER**

Cationic ammonium-substituted vinyl polymer is used to improve the performance properties of various adhesives. Adhesives such as the alkyl vinyl ether/maleic acids and various other polymeric adhesives exhibit improved holding properties when combined with the ammonium-substituted polymer, especially in the presence of moisture. Improved bioadhesives, e.g., denture adhesives, are provided.
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ADHESIVE COMPOSITION WITH ACIDIC ORGANIC ADHESIVE POLYMER
AND CATIONIC AMMONIUM-SUBSTITUTED POLYMER

Steven Daryl Smith

TECHNICAL FIELD

This invention relates to improvements in adhesives and, in particular, improved bioadhesives, such as denture adhesives.

BACKGROUND OF THE INVENTION

Ordinary removable dentures, dental plates, and the like, comprise teeth mounted in a suitable plate or base. Dentures function as a substitute for missing teeth and serve as a replacement for all or a portion of the teeth ordinarily found in the oral cavity. Although dentures generally are skillfully prepared, often they do not fit perfectly. Moreover, no matter how satisfactory at first, after a period of time the fit of the denture becomes loose and imperfect due to natural shrinkage and changes in the gums, mucous tissues, and the like. Loose and imperfectly fitted dentures usually are corrected and stabilized by the use of a denture adhesive. Denture adhesives are used to fill the interstices between the denture and the gums or tissues. Prior to placement of the denture in the oral cavity, a denture adhesive is applied to the denture-plate surface which, for a perfect fit, should uniformly contact the gums and mucous tissues. The denture adhesive is formulated not only for its adherent properties, but also to provide a cushion or gasket between the denture and the gums or tissues, thereby positioning the denture securely in the oral cavity.

Requirements and characteristics for a satisfactory denture adhesive composition are many and are dictated by numerous factors. Desirably, one daily application of such a composition should function as an effective means for insulating, cushioning, and securely positioning the denture. The composition should retain its characteristics and properties in the typical powder and cream forms during storage under various climatic conditions such as high temperature and humidity; be readily and easily
capable of application to the denture surface; not be irritating or uncomfortable to the user; have no disagreeable odor or color; have no unpalatable taste; optionally provide antiseptic and germicidal properties for preventing or inhibiting the growth of organisms ordinarily found in the mouth; and function as an agent for prevention of putrefaction or malodorous decomposition of foods or secretions lodging beneath or adjacent to the denture. The adhesive material must be capable of imbibing water and saliva and swelling, so as to fill the interstices between the denture and the gum or mucous tissues. The adhesive should not attack or damage the denture, as by causing a crazing of the denture-plate material. Additionally, the adhesive should be stable to bacteria, molds and enzyme systems found in the oral cavity, and have a pH that is nonirritating to the oral mucosa, generally 5-8.5, preferably a pH around neutrality. The mechanical strength of the adhesive mass, be it gel or colloid, formed by imbibition of water should be great enough to securely maintain the position of the denture under normal use, and not so great as to make denture removal difficult when desired, or as to damage or injure the gums, tissues, or denture upon removal.

As will be seen from the extensive Background Art described hereinafter, there has been a considerable effort made over many years to develop improved denture adhesives. Both synthetic and natural polymers and gums have been used singly, in combination, and in combination with various additives.

Yet, the search continues for denture adhesives that will provide the above-described characteristics and, importantly, will both maintain the secure fit of the denture over prolonged periods (10-16 hours) without the need for reapplication and will be easily removed by the user without the necessity for brushing or scraping substantial amounts of adhesive from the gums or the denture.

It is an object of the present invention to provide denture adhesives that will be stable over prolonged periods in the oral cavity, yet will allow easy removal of the denture on demand.

It is a further object to provide such adhesives using toxicologically-acceptable, palatable materials.
It is another object herein to provide adhesives that perform well in the presence of moisture, particularly in the presence of body fluids such as saliva, perspiration and blood.

These and other objects are secured by the combination of certain anionic adhesives and cationic ammonium-substituted polymers which form gels having specified gel volumes, in the manner disclosed hereinafter.

BACKGROUND ART

A wide variety of materials have been suggested for use in denture adhesives.

U.S. Patent 3,868,432 (Keegan et al., 2/25/75) discloses denture adhesive compositions wherein the anionic component is a polymer of maleic acid and a vinyl-lower alkyl-ether (i.e., Gantrez™) and the cationic material is a copolymer of an acrylamide and a vinyl quaternary ammonium salt or a copolymer of an acrylamide with vinyl and alkyl substituted vinyl pyridinium salts. Similar technical disclosures can be found in U.S. Patent 3,868,340 (Keegan et al., issued 2/25/75), U.S. Patent 3,919,357 (Keegan et al., issued 11/11/75) and U.S. Patent 3,833,518 (Rubin et al., issued 9/3/74). U.S. Patents 3,868,339 (Keegan et al., issued 2/25/75), and 3,936,402 (Keegan et al., issued 2/3/76) disclose denture adhesive preparations comprising Gantrez™-type copolymers and certain ammonium chloride substituted anhydroglucose polymers.

U.S. Patents 3,878,135 (Keegan et al., 4/15/75), 3,878,138 (Keegan et al., 4/15/75), 3,926,870 (Keegan et al., 12/16/75), and 4,001,151 (Keegan et al., 1/4/77) disclose anionic cationic denture adhesive compositions comprising: a) copolymers of acrylamide with vinyl quaternary ammonium salts; and b) protein material, peroxymethylcellulose or cellulose sulfate gum, casein or its alkyl metal salts, or certain gums (karaya, arabic, Shiraz, tragacanth, pectin, pectinates, algin, and alginates), respectively, as the anionic components. U.S. Patents 3,868,259 (Keegan et al., 2/25/75), 3,868,260 (Keegan et al., 2/25/75), 3,919,138 (Keegan et al., 11/11/75), and 3,919,139 (Keegan et al., 2/25/75) disclose ammonium chloride substituted anhydroglucose polymers with carboxymethylcellulose or cellulose sulfates,
natural anionic gum materials (such as gum karaya, gum arabic, gum Shiraz, etc.), protein materials (such as soybean meal, sunflower seed meal, or peanut meal, or combinations thereof, respectively.

U.S. Patents 3,336,269 (Monagle et al., 8/15/67), 3,336,270 (Monagle et al., 8/15/67), and 3,509,113 (Monagle et al., 4/28/70 are cited in the various of the Keegan et al. and Rubin et al. patents discussed above for processes for making acrylamide-type water soluble polymers.

Skeist, HANDBOOK OF ADHESIVES, Reinhold Publishing, N.Y. (1962) at page 127 reports the use of fish glue in conjunction with rubber latex systems.

German 2,408,125 (8/28/75) to G. Seeh relates to the use of dental adhesive compositions containing chewing gum.

German 2,446,449 (6/6/75) assigned to Hydrophilics Int. Inc., based on U.S. priority serial number 435,283 (1/21/74) relates to hydrophilic copolymer salts of aminomethacrylates and a hydrophobic monomer for use in controlled release of agricultural chemicals and as a spray-on adhesive for dentures.

German 2,558,602 (6/30/77) to T. Pantenge, relates to denture-fixing compositions comprising polyisobutylene and other thickening agents such as natural gums, starch, and the like.

German 2,841,823 (3/27/80) to A. Breuer, relates to denture paste comprising polystyrene, gelatin, polyether resin and hydrogenated hydrocarbon.

German 2,901,661 (1/15/79) to A. Breuer, relates to compositions for improving the fit of dentures using a paste of polystyrene, gelatin, polyether resin, gum arabic, etc.

German 2,932,455 (8/10/79) to L. Frohmueller, relates to denture-securing systems comprising a hardenable fluid substance such as silicone rubber.

German, 3,228,335 (2/9/84) to E. Hofacker, relates to a fixative for dentures comprising an ethanol solution containing untreated polyvinyl-pyrrolidone and densified polyvinylpyrrolidone.

European Patent Application 64,672 to Dhaber and Schmidt, (priority 4/29/81 U.S. 258,562 and 3/26/82 U.S. 361,631) relates to a hydrophilic denture adhesive containing an adhesive polymeric
fraction comprising CMC and poly(ethyleneoxide) in a hydrophilic vehicle.

European Patent Application 140,486 (filed 7/31/84) to A. J. Desmarais, relates to denture adhesive compositions containing a hydrophobically modified water-soluble polymer, alone or admixed with an alkali metal salt of CMC. Hydrophobically modified hydroxyalkyl celluloses and copolymers of ethylene oxide and long chain epoxylkanes are preferred for use in the compositions.

Japanese Patent Document 84/144,708 (8/18/84) to Kureha Chem Ind KK, relates to cavity lining material for dentures that comprises fluorine-containing copolymers and fluorine-containing telomers.

Japanese Patent Document 86/73,648 (4/15/86) to Kobayashi Seiyaku, relates to stabilizers for artificial teeth containing partially saponified vinyl acetate resins, which also can contain water-insoluble inorganic substances such as calcium carbonate, talc or silica.

Japanese 86/87,608 (5/6/86) to Saotome K, relates to denture fixing compositions containing highly "water absorbing" resins, such as N,N'-methylene bisacrylamide, in combination with sodium CMC and polyethylene glycol.

Japanese Patent Document 86/217,153 (9/26/86) to Showa Yakuhin Kako KK relates to a glue for fixing artificial dentures comprising water-soluble high polymers such as gelatin and a binder such as hydroxypropyl cellulose, together with fat-soluble vitamins.

Japanese Patent Document 87/129,210 (6/11/87) to Kobayashi Seiyaku relates to a copolymeric resin containing acetyloxy-substituted repeat units which provide tacky adhesion to false teeth.

U.S. Patent 3,003,988 (10/10/61) to Germann et al, and EPO 0,265,916 (10/27/87) relate to the use of GANTREZTN in denture fixatives.

U.S. Patent 3,440,065 (4/22/69) to A. Laurence, relates to denture adhesives containing wood flour, microcrystalline cellulose or other natural wood pulp derivatives in a gum-petroleum base.
U.S. Patent 3,511,791 (5/12/70) to Puetzer et al., relates to denture adherents having an acrylamide polymer as the principal adhesive component, preferably in combination with some natural gum.

U.S. Patent 3,575,915 (4/20/71) to Novak et al., relates to denture adhesives comprising polyvinyl acetate, a mineral hydrocolloid such as colloidal silicates, and plasticizers.

U.S. Patent 3,736,274 (5/29/73) to Schoenholz et al., relates to denture compositions comprising maleic anhydride and/or acid copolymer, polymeric N-vinyl lactam and CMC.

U.S. Patent 3,740,361 (6/19/73) to O. Altwirth, relates to denture adhesive compositions comprising a mixture of alginate and an ethanol solution of a normally solid polyvinyl acetate resin.

U.S. Patent 3,930,871 (1/6/76) to C. A. Starace relates to thickening compositions, including denture adhesives, comprising a hydrophilic colloid derived from Xanthomonas, in combination with dextrin.

U.S. Patent 4,239,488 (12/16/80) to V. A. Sempler, relates to encapsulated denture adhesives.

U.S. Patent 4,280,936 (7/28/81) to Dhabhar, Heyd and Schmidt, relates to improved denture adhesives containing a specified ratio of CMC and poly(ethyleneoxide) in a mineral oil base.

U.S. Patent 4,318,742 (3/9/82) to O. Lokken, relates to denture adhesives containing a major amount of gum base and a quantity of hydrophilic polymer to modify the adhesive properties of the gum base.

U.S. Patent 4,373,036 (2/8/83) to Chang et al., relates to denture fixative compositions containing various cellulose derivatives and polymers such as partially neutralized alkylvinylether-maleic acid or anhydride copolymers, optionally with crosslinking agents. See also U.S. Patent 4,470,814 (9/11/84) to Chang et al.

U.S. Patent 4,474,902 (10/2/84) to Dhabbar and Schmidt, relates to improved denture adhesives containing karaya gum in a hydrophilic vehicle. See also U.S. Patent 4,514,528 (4/30/85) and U.S. Patent 4,518,721 (5/21/85) to these same inventors, relating, respectively, to improved denture adhesives containing adhesive polymeric fractions consisting of admixtures of partial salts of
lower alkylvinyl ether maleic anhydride-type copolymers with CMC or poly(ethylene oxide), as well as denture adhesives containing CMC and poly(ethylene oxide). See also U.S. Patent 4,522,956 (6/11/85) to Dhabhar and Schmidt relating to improved denture adhesives containing poly(ethylene oxide) as the sole adhesive component in a hydrophilic vehicle comprising certain polyethylene glycols.

Other denture adhesives are described in U.S. Patents 4,530,942 (7/23/85); 4,542,168 (9/17/85); and 4,569,955 (2/11/86).

U.S. Patent 4,529,748 (7/16/85) to H. G. P. Wienecke, relates to dental prosthesis adhesives formed from film-forming substances such as various cellulose derivatives, acrylate polymers, methacrylate polymers, and other film-providing substances.

U.S. Patent 4,608,088 (8/26/86) to O. Lokken relates to dental adherents containing a dental adhesive, an alginate, and a setting agent for the alginate.

U.S. Patent 4,664,630 (5/12/87) to O. Lokken, relates to denture adherents comprising a dental adhesive and a gel-forming mixture of a water-soluble alginate, together with a setting agent for said alginate. The compositions are said to be useful as denture adhesives, and also as a depot formulation for delivery of therapeutic agents to the oral cavity.

U.S. Patent 4,504,618 (3/12/85) to Irvine et al, relates to aqueous dispersions of film-forming addition polymers said to be useful as components of adhesives.


**SUMMARY OF THE INVENTION**

The present invention encompasses adhesive compositions, comprising an intimate mixture of: (a) from about 10% to about 90%, by weight, of an acidic organic adhesive polymer, preferably
selected from the poly(lower alkyl vinyl ether/maleic acid); (b) from about 10% to about 90%, by weight, of an organic cationic ammonium-substituted vinyl-polymer; and (c) the balance (0% to about 80%), if any, comprising pharmaceutically acceptable carrier and adjunct materials. Adjunct materials can include pharmacologically active compounds for delivery to the oral cavity or skin.

Without intending to limit the invention, it is believed that the organic adhesive, being acidic in character, interacts with the organic cationic ammonium-substituted polymer in such a way in the presence of water to form a water-insoluble gel. The organic adhesive and cationic ammonium-substituted polymer are selected such that the gel formed from the components and water is characterized by a Gel Volume (as determined according to the procedure described hereafter) between about 0.5 and about 10.0 g water/g acidic organic adhesive polymer and cationic ammonium-substituted polymer (combined), preferably between about 0.5 and about 4.0 g/g, more preferably between about 1.0 and about 3.0 g/g.

The invention provides improved adhesives which are particularly useful for application as bioadhesives, i.e., for adherence to human and animal tissue. The adhesive compositions hereof can be provided in various forms, including powder, paste, and gel. The bioadhesives are especially useful for denture adhesive compositions. Paste compositions herein can be conveniently packaged in a tube or pump dispenser.

The invention also provides adhesive tape comprising an adherent amount of the adhesive composition on a solid backing material. An adherent medical dressing comprises such tape, in combination with an absorbent material to imbibe blood or other body fluids.

The adhesive compositions herein also provide a depot which can be used, for example, to deliver pharmacologically active materials to the oral cavity or skin over extended periods. Such pharmacologically active substances include, for example: fluoride ion (anticaries); antimicrobial agents (antiplaque/antigingivitis); antidepressants; antifungals; antihypertensives; pain
remedies, and the like, where gradual, prolonged release is beneficial.

The invention is described with more particularity below. All ratios, proportions and percentages herein are by weight, absent water or other polar solvents, unless otherwise specified.

**DETAILED DESCRIPTION**

**Cationic Ammonium-Substituted Polymer**

The organic cationic water soluble polymers used in the present invention comprise water soluble ammonium-substituted vinyl and water soluble salts thereof. The cationic polymers hereof should have a molar ratio of ammonium-substituted monomeric units to total monomeric vinyl units of at least about 60%, preferably at least about 75%, more preferably at least about 85%, most preferably at least about 90%. It is believed that reduced levels of substitution results in compositions having lower degrees of cohesion, water insolubility, and in-use periods of effectiveness for bioadhesive applications (e.g., denture adhesives).

The number average molecular weight of the cationic ammonium-substituted polymer should be at least about 2,000. Typically the molecular weight will range from about 2,000 to about 1,000,000, preferably average from about 20,000 to about 200,000, more preferably from about 75,000 to about 150,000. Without intending to necessarily limit the invention, it is believed that increasing molecular weight, with other factors being constant, will slow dissolution and increase gel strength.

Preferred starting monomers for polymerization to form ammonium-substituted vinyl polymers include vinyl compounds of the general formula:

\[ \text{H}_2\text{C} = \text{C}(\text{R}_1)(\text{R}_2) \]

wherein: \( \text{R}_1 \) is hydrogen or an alkyl, preferably hydrogen or a short chain alkyl, e.g., \( \text{C}_1-\text{C}_5 \) alkyl; and \( \text{R}_2 \) is a moiety having an amine or ammonium functionality. Preferred \( \text{R}_2 \) moieties are:

\[ \text{R}_2 = -\text{C}-\text{O}-\text{R}_3-\text{N}-(\text{R}_4)_2 \]

and
(III) $R_2 = \text{C-NH-R}_5\text{-N-}(R_6)_2$

wherein: $R_3$ and $R_5$ are alkyls, preferably short chain alkyls, more preferably $C_2$-$C_7$ alkyls; and each $R_4$ and $R_6$ are, independently, alkyls, preferably short chain alkyls such as $C_1$-$C_7$ alkyls. By "independently" what is meant is that for any $R_2$, each of the $R_4$ or $R_6$ alkyl moieties can be different chain length alkyls.

The vinyl monomer (I) can be polymerized in an amine-substituted form, as exemplified wherein $R_2$ is as set forth above in (II) and (III), and then have the amine converted to an ammonium by a quaternization reaction. Alternately, the monomer can be converted to an ammonium-substituted form prior to polymerization.

Amine functionalities can be quaternized by reaction with a salt of the formula $R'X$ wherein $R'$ is a short chain alkyl, preferably a $C_1$-$C_7$ alkyl, more preferably $C_1$-$C_3$ alkyl, and $X$ is an anion which forms a water soluble salt with the quaternized ammonium formed as a result of reaction between $R'X$ and the amine functionality. $X$ is preferably a halide, such as chloride, bromide, iodide, or fluoride, more preferably chloride, bromide, or sulfate. Suitable water soluble salts of the ammonium substitutions include, but are not limited to, alkyliodide, alkylchloride, alkylbromide and alkyl sulfate salts wherein the alkyl group is a lower alkyl group containing from one to seven carbon atoms, preferably one to three carbon atoms. The preparation of quaternary ammonium from tertiary amines moieties, e.g., $-N(-R_4)_2$ and $-N(R_6)_2$ of Formulas II and III, respectively, is well known to those skilled in the art and is further discussed in the Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, (1982) Volume 19 at pp 521-531, incorporated by reference herein.

Suitable starting monomers include dialkylaminoalkyl acrylate, dialkylaminoalkyl methacrylate, dialkylaminoalkyl acrylamide, dialkylaminoalkyl methacrylamide, dialkyldiallylammonium salts, and vinylloxylalkyltrialkylammonium salts, wherein the alkyl groups are preferably 1 to 7 carbon alkyls, more
preferably 1 to 3 carbon alkyls. Thus the preferred polymers will comprise at least about 60% vinyl monomeric units of the formula:

\[(IV) \ (-\text{CH}_2 \text{-C(R}_1 \text{(R}_2 \text{)})\]

wherein \(R_1\) is as defined above and \(R_2\) is

\[0\]

\[(V) \ -\text{C-O-R}_3 \text{-N-(R}_4 \text{)}_2 \text{R}'\]; or

\[0\]

\[(VI) \ -\text{C-NH-R}_5 \text{-N-(R}_6 \text{)}_2 \text{R}'\];

wherein \(R_3, R_4, R_5, R_6,\) and \(R'\) are as defined above.

Polymerization techniques for vinyl monomers are well known in the art. Free radical polymerization is preferred. Suitable free radical polymerization processes include solution polymerization. A variety of free radical initiators can be used. e.g., azo compounds, peroxides, persulfates, redox couples, etc. Polymerization of acrylamide monomers, for example is discussed in Encyclopedia of Polymer Science and Engineering, Vol. 1, John Wiley & Sons, Inc. (1985) at pages 176-186, incorporated by reference herein. Polymerization of acrylates and the ammonium salts of acrylamides monomer can be performed utilizing free radical polymerization, although polymerization of the acrylamide or amino-substituted acrylates followed by quaternization is preferred.

The amine- and ammonium-substituted monomers can be co-, ter-, etc. polymerized with spacer monomers. The spacer monomer chosen should be of a type and used in an amount such that the polymer is water soluble. Also the spacer monomer used should readily polymerize with the amine- or ammonium- substituted monomer. Exemplary spacer monomers include, but are not limited to, acrylamide, methacrylamide, alkyl and dialkyl acrylamides, alkyl and dialkyl methacrylamides, alkyl acrylate, alkyl methacrylate, and N-vinyl pyrrolidone. The alkyl and dialkyl substituted monomers preferably have C1-C7 alkyl groups, more preferably C1-C3 alkyl groups.

The cationic polymers hereof can be copolymers, terpolymers, etc. which have ammonium-substituted vinyl monomer units, non-ammonium-substituted vinyl units, as well as other monomer units. Exemplary copolymers include copolymers of the above
starting ammonium-substituted monomers with acrylamides, such as, but not limited to, acrylamide and dimethylacrylamide, and vinyl monomers such as, but not limited to, N-vinylpyrrolidinone. U.S. Patent 3,868,432, issued 2/25/75, to Keegan, et al. discusses copolymers with vinyl and acrylamide monomeric units and and U.S. Patents 3,336,269 and 3,336,270, issued 8/15/67 to Monagle disclose processes which can be used for making them. These patents are incorporated herein by reference. The copolymers contemplated in U.S. Patent 3,868,432 are not directly applicable to the present invention, however, because they are limited to 50% or less of ammonium-substituted vinyl units. However, the process developed in said patent for making the same can be modified by those skilled in the art to make polymers with higher percentages of ammonium-substituted vinyl units without undue experimentation. This can be done by polymerizing ammonium substituted monomers with the spacer monomers at ratios corresponding to that desired in the final product.

Methods for forming the ammonium-substituted vinyl polymers are well known to those skilled in the art. Suitable methods include free radical polymerization processes such as solution polymerization and are described, for example, in Principles of Polymerization, 2nd edition, George Odian, John Wiley & Sons, Inc. (NY, 1981) pp 179-318 and 423-507, and Encyclopedia of Polymer Science and Engineering, 2nd edition, executive editor Jacqueline Kroschwitz, Volume 13, pp 708-867, "Radical Polymerization", John Wiley & Sons, Inc. (New York, 1988), each of which are incorporated herein by reference.

Commercial sources of ammonium-substituted organic polymers useful for the present invention include, but are not necessarily limited to, Merck & Co., Inc. (Rahway, New Jersey, U.S.A.), for their acrylamide/dimethylallyl ammonium chloride copolymer series marketed under the MERQUAT trademark and GAF Corp. (New Jersey, U.S.A.) for their GAFQUAT series of quaternized copolymers of vinylpyrrolidone and dimethylaminoethyl methacrylate.

Slow dissolution of the ammonium-substituted polymer may be disadvantageous in certain applications wherein the polymer can be washed away prior to gel formation (e.g., in a powder denture
adhesive composition formulated for in situ formation of the gel in the mouth of the user). Under circumstances wherein increased gel strength is nevertheless desired, the ammonium-substituted polymer can be pre-hydrated to facilitate fast dissolution and gel formation.

Acidic Organic Adhesive Polymer

The acidic organic adhesive polymers used in the practice of this invention can be any of the tacky or pressure-adherent gums, resins, polymers, and the like, both synthetic and naturally-occurring, which are well known for their adherent properties. The selection of acceptable adhesives for use in sealing/adhering dentures to oral tissues is readily made by referring to the above-noted patents, or to standard texts. In general, the adhesive will comprise from about 10% to about 90% by weight of the compositions herein.

There can be mentioned by way of exemplification, but not limitation, the following acidic adhesive polymers useful in the practice of the present invention: alkyl vinyl ether-maleic anhydride or -maleic acid copolymers, polyacrylic acid, polymethacrylic acid, salts thereof, and combinations thereof. Suitable salts include, but are not limited to, inorganic salts such as metal salts (e.g., sodium, zinc, calcium, strontium) and ammonium. The salt form of the polymer should remain soluble in the polar solvent to be used. Preferred are alkyl vinyl ether-maleic acid copolymers. A particularly preferred adhesive polymer herein is GANTREZ Resin (TM GAF Corporation, N.J.) which can comprise a poly(lower alkyl vinyl ether/maleic anhydride and acid) material; See GANTREZ AN Tech. Bulletin 7543-017. The acid form of the maleic monomer of the copolymer, and salts thereof, is preferred for use herein for reason of better solubility in polar solvent.

The lower alkyl vinyl ether-maleic anhydride and acid (GANTREZ-type) copolymers are readily obtained by copolymerizing a lower alkyl vinyl ether monomer, such as methyl vinyl ether, ethyl vinyl ether, divinyl ether, propyl vinyl ether and isobutyl vinyl ether, with maleic anhydride to yield the corresponding lower alkyl vinyl ether-maleic anhydride copolymer, which is readily
hydrolyzable to an acid copolymer. Both anhydride and acid forms are also available from commercial suppliers. For example, the GAF Corporation, Wayne, New Jersey, provides both the polymeric free acid form and the corresponding anhydride form under its GANTREZ trademark as the "GANTREZ S Series" and "GANTREZ AN Series". The lower alkyl vinyl ether-maleic anhydride (GANTREZ-type) copolymers are readily obtained by copolymerizing a lower alkyl vinyl ether monomer, such as methyl vinyl ether, ethyl vinyl ether, divinyl ether, propyl vinyl ether and isobutyl vinyl ether, with maleic anhydride to yield the corresponding lower alkyl vinyl ether-maleic anhydride copolymer, which is readily hydrolyzable to an acid copolymer. Both anhydride and acid forms are also available from commercial suppliers. For example, the GAF Corporation, Wayne, New Jersey, provides both the polymeric free acid form and the corresponding anhydride form under its GANTREZ trademark as the "GANTREZ S Series" and "GANTREZ AN Series", respectively. In the former acid series, the GANTREZ S-97 (M.W. = 50,000) is particularly suitable, and, in the latter anhydride series, the GANTREZ AN-149 (M.W. = 50,000), the GANTREZ AN-169 (M.W. = 67,000) and the GANTREZ AN-179 (M.W. = 80,000) copolymers are particularly suitable. Said acid and anhydride forms of such copolymers have an average molecular weight of from about 50,000 to about 80,000 (as measured by membrane osmometry in 2-butanol 1-10 grams/1000 ml solution). When the anhydride copolymer dissolves in water, the anhydride linkage is cleaved so that the highly polar, polymeric free acid is formed. Accordingly, the anhydride form, which is relatively less expensive than the acid form, may be used as a convenient and cheaper precursor for the acid. Elevated temperatures may be advantageously employed to enhance the rate of anhydride-to-acid hydrolysis.

The GANTREZ materials and their use for preparing denture adhesives are described in detail in U.S. Patent 3,003,988 (Oct. 10, 1961) and EPO 0,265,916, filed October 27, 1987, to Shah, Gounaris and Holeva, incorporated herein by reference. Detailed disclosure regarding the use of this adhesive in the manner of the present invention is also provided hereinafter. Mixtures of GANTREZ with other materials, especially carboxymethylcellulose
(generally, at a weight ratio GANTREZ:CMC in the range of 5:1 to 1:5) is especially preferred.

The salts of GANTREZ can also be used herein. These can be prepared by dissolving the acidic GANTREZ polymer in water and neutralizing it with the appropriate bases. However, the desired salts in a form suitable for use as denture adhesives advantageously can be prepared by reacting the alkyl vinyl ether and maleic anhydride used to make GANTREZ and the bases in a slurry in a mixture of a lower aliphatic alcohol and water. Advantageously this process utilizes smaller amounts of liquid medium than other processes and permits separation of the salts by relatively simple procedures. This permits savings. Additionally the improved process avoids the use of excessive amounts of cation materials and consistently produces the desired GANTREZ-type salts with the requisite physical characteristics and properties.

Whereas in prior adhesive compositions comprising GANTREZ materials intended for use as denture adhesives have advantageously included divalent salts of GANTREZ or mixed salts of GANTREZ including the divalent salts in order to improve the cohesive properties of the composition in use, it is a benefit of the present invention that levels of cohesion can be obtained without resort to such divalent salts that significantly exceed such prior-known compositions. Although resort to the use of divalent salts may not be necessary when practicing the present invention, such salts nevertheless can be used effectively in the present compositions. A more detailed description of divalent salts, e.g., zinc and strontium salts of alkylvinylylether/maleic acid copolymers, can be found in U.S. Patent 4,758,630, Shah et al., issued July 19, 1988, incorporated herein by reference.

In a preferred process for the manufacture of GANTREZ salts, a slurry is prepared of a suitable lower alkyl vinyl ether-maleic anhydride copolymer in a lower aliphatic alcohol (i.e., containing less than 5 carbon atoms). Calcium cations, preferably in the form of calcium hydroxide (Ca(OH)₂), in the amount desired in the product are added to this slurry with the addition carried out at room temperature. An aqueous solution containing the amount of the particular alkali metal cation (preferably by solution of the
particular hydroxide [e.g., NaOH] in water] that is desired in the product is then added with stirring. Calcium and alkali cations are utilized in substantially the same equivalent ratio and amounts as desired in the product (e.g., equivalent ratio Ca/Na from 2:1 to 10:1). The overall alcohol-water ratio, after addition of the aqueous alkali cation solution, should be between 60:40 to 80:20 with a 70:30 ratio by volume preferred. The resulting slurry is heated with stirring until the pH levels off near neutrality. The resulting mass is then filtered, dried and ground. The resulting product consists essentially of the particular mixed calcium-alkali partial salt of the partial ester of the copolymer.

In a preferred embodiment of the process, the alcohol is isopropyl alcohol and the ratio of alcohol to water is between 60:40 and 80:20 by volume, with the preferred ratio about 70:30. A higher water content causes coagulation of the slurry, while a substantially lower water content provides an adhesive having an apparent bulk density below about 0.5 gram per cubic centimeter. Denture-adhesive characteristics of the mixed salts of the GANTREZ seem to depend on their apparent bulk densities, with the lower apparent bulk densities providing inferior adhesive characteristics. Bulk densities higher than 0.7 gram per cubic centimeter are preferred. A significant decrease in adhesive characteristics is obtained with apparent bulk densities less than 0.5 gram per cubic centimeter. Slurry temperatures should not exceed about 60°C. The preferred and optimum slurry temperature is less than 50°C, and is generally from 40°C to 50°C. While lower slurry temperatures are operable, an increase in reaction time is required.

Cations utilized in the processes for preparation of the partial, mixed salts of the invention may be provided by a number of various materials. Generally, the cations are obtained from compounds which contain the particular cations and are at least soluble in part in water, and, more particularly, from the more common salts or hydroxides containing the particular cations. Salts and alkalis which are particularly suitable are those that are completely soluble or soluble to a significant degree in
water, or water-alcohol mixtures. Suitable compounds include calcium hydroxide, calcium acetate, calcium halides, calcium lactate, calcium gluconate, sodium hydroxide, sodium acetate, sodium carbonate, sodium halides, sodium potassium carbonate, sodium sulfate, potassium hydroxide, potassium halides, quaternary ammonium hydroxides, etc. The compounds used should be substantially pure to assure obtaining pure, white or colorless, partial, mixed salts. Salts having anions that form toxic or irritating by-products should be avoided, or special precautions and treatment provided to assure the removal and absence of such by-products from the partial, mixed salt product. Some by-products in various amounts may be tolerated without a detrimental effect on the stabilizing properties and characteristics of the mixed, partial salt.

As can be seen from the foregoing, the GANTREZ-type resin is used, in this embodiment, in the form of its mixed calcium/alkali metal salt. These mixed, partial salts have a pH within the range of 5 to 8.5, with those having a pH between 6 and 7 preferred. The mixed, partial salts are frangible so that appropriate particle size and bulk density can be obtained. For best results the particles should be capable of passage through a 150-mesh sieve (U.S.B.S. series) and preferably are less than 0.74 millimeter in their largest dimension. These salts consist of mixed, partial salts containing calcium cations and alkali cations selected from the group consisting of sodium, potassium, and quaternary ammonium cations at an equivalent ratio of calcium cations to the alkali cations in the mixed salts in the range from 2:1 to 10:1 and preferably between 3:1 and 7:1 (on a mole ratio basis, the range of calcium to alkali cations is from 1:1 to 5:1). The sum total of cations in the partial, mixed salt should be sufficient to give a neutralization of from 0.5 to 0.95 and preferably 0.7 to 0.9 of the total initial carboxyl groups in the GANTREZ-type copolymer. (In determining the total initial carboxyl groups in the copolymer, the anhydride radical is considered as containing two initial carboxyl groups.) The GANTREZ adhesives include mixed salts of the specific copolymers that have less than about one-third of the total initial carboxyl groups esterified. Preferably, the total
initial carboxyl groups neutralized by salt formation, or by salt formation and esterification, do not exceed 95% of the total of the initial carboxyl groups of the specific copolymer. The mixed salts of copolymers containing about 5% to 15% of the total initial carboxyl groups as unreacted acid groups, rather than salts or esters thereof, provide particularly superior properties in the practice of this invention.

The following illustrates the foregoing principles as they apply to the preparation of a mixed Ca/Na GANTREZ-type adhesive for use in the practice of this invention.

Preparation of GANTREZ-Adhesive (Ca/Na)

A reaction kettle is charged with 825 parts of anhydrous isopropyl alcohol. 234 parts of a methyl vinyl ether-maleic anhydride copolymer (PVM/MA), having a specific viscosity of between 2.5 and 3.5, and 66.6 parts of calcium hydroxide are added to the isopropyl alcohol slowly, with good agitation, to form a slurry. A solution of 12.0 parts of sodium hydroxide dissolved in 450 parts of water is added slowly to this slurry, with good agitation. The resulting slurry has an isopropyl alcohol-to-water ratio of from 70:30% by volume. The resulting slurry is heated to a temperature of about 45°C and held at this temperature until the pH of the slurry levels off at about 6.6 (approximately 1-1/2 hours). The slurry is then cooled to room temperature and filtered. The filter cake is dried in an air-circulating oven at 65°C and then ground and screened through a 200-mesh sieve (U.S.B.S. sieve series).

More than 90% of the theoretical yield of a white powder is obtained consisting essentially of the calcium-sodium partial salt of an isopropyl partial ester of the methyl vinyl ether-maleic anhydride copolymer with a calcium-to-sodium equivalent ratio of 0.6:0.1 per initial carboxyl group in the copolymer and with the balance of the initial carboxyl groups present as unreacted acid and isopropyl ester groups. The product is an apparent bulk density of 0.80 gram per cubic centimeter and, at a concentration of 1% by weight in water, has a pH of 6.7.

In an alternate mode, cations other than Ca/Na can be used advantageously to prepare the GANTREZ-type adhesive. In
particular, zinc (preferred) and strontium salts of alkyl vinyl ether (AVE)-maleic acid copolymers (MA) such as GANTREZ can be used. See U.S. Patent 4,758,630; July 19, 1988 to Shah, Gounaris and Holeva.

Such polymeric salts are advantageously prepared by the interaction of the AVE/MA copolymer with a cationic zinc or strontium compound, such as, for example, the hydroxide, acetate, halide, lactate, etc., salts, in an aqueous medium. Since zinc hydroxide is not commercially available, its use as a reactant is readily and more economically accomplished by employing an aqueous slurry of particulate zinc oxide which, although practically insoluble in water, provides hydration to zinc hydroxide on the particulate surface. Strontium hydroxide, on the other hand, is available in either crystalline or powder form and is soluble in about 50 parts water. Aqueous solutions of strontium oxide, however, which forms the hydroxide when treated with water (caution: heat evolution), may also be used.

As before, anions that form toxic, irritating or contaminating by-products should be avoided, or special precautions and treatment provided to assure the removal and absence of such by-products from the polymeric salt end-product. The particular compound used should be substantially pure to assure obtaining a substantially pure, substantially white or off-white polymeric salt end-product.

In general, the lower AVE/MA copolymer, or its corresponding anhydride, is added to water preheated to about 70-80°C with vigorous stirring to form a homogeneous mixture. If the anhydride precursor is utilized, it is recommended that the aqueous mixture be further heated to about 90°C with stirring to ensure complete hydrolysis of the anhydride to the acid form. Heating is then discontinued although mixing is continued until the batch turns clear with a simultaneous decrease in viscosity (about 65-75°C). An aqueous solution of the cationic zinc or strontium salt forming compound, or, for example, an aqueous dispersion of particulate zinc oxide in the form of a slurry, in an amount sufficient to provide the desired cationic content desired in the end-product, is separately prepared at ambient temperature and slowly added to
the hot polymeric acid solution with continuous vigorous mixing so as to prevent localized precipitation of the cationic polymeric salt. After addition is complete, mixing is continued to ensure that all the salt forming compound is reacted with the copolymer.

The sum total of zinc or strontium cations in the resultant unmixed partial salts of AVE/MA copolymers should be sufficient to give a neutralization of from about 10 to about 60% and preferably from about 40 to about 50% of the total initial carboxyl groups in the copolymer.

The reaction batch is then transferred to shallow drying trays in a convection oven maintained at about 70°C with hot air circulation to evaporate the water content and recover the polymeric salt product in dry form. If necessary, the reaction solution may be treated according to conventional purification methodology to remove or minimize any contaminants occasioned by anionic functions in the aforementioned cationic zinc or strontium salt-forming compound.

After drying, the resultant product, which consists essentially of the particular zinc or strontium unmixed partial salt of the AVE/MA copolymer, is then ground or milled to the desired mesh size for providing the satisfactory denture-adhering properties. Said salts are frangible so that appropriate particle size and bulk density can be obtained. For best results, particles should be capable of passage through a 140- to 20-mesh sieve (0.105 to 0.074 mm sieve opening) (U.S.B.S. series) and preferably are less than 0.074 mm in their largest dimension.

The zinc and strontium GANTREZ-type AVE/MA copolymer salts have exceptional adhesive qualities when contacted with water or saliva such that they are extremely useful as denture adhesive materials. For such use, the salt in particulate form is preferably characterized by a particle size of at least 140-mesh U.S.B.S. sieve; a bulk density greater than 0.5 gram per cubic centimeter and preferably higher than 0.7 gram per cubic centimeter; and a pH between 3 and 4.7, the pH being determined on a 1% by weight dispersion in water.
The following illustrates the foregoing principles as they apply to the preparation of a Zn GANTREZ-type adhesive for use in the practice of this invention.

**Preparation of GANTREZ-Adhesive (Zn)**

Into a reaction vessel equipped with a high speed stirrer and containing 73.5 parts (29.9 kg) of purified water heated to 70°C, is slowly added 3.87 parts (1.58 kg) of methyl vinyl ether-maleic anhydride copolymer having a specific viscosity of about 2.5. After addition is complete, the temperature of the aqueous copolymer dispersion is raised to 90-95°C with high speed mixing. At such temperature, hydration of the anhydride copolymer continues, marked by a significant increase in batch viscosity. Further heating is then discontinued and the mixture is gradually cooled to about 70°C with continued mixing. Complete hydrolysis of the anhydride copolymer to the corresponding methyl vinyl ether-maleic acid (MVE/MA) copolymer is observable when the batch turns clear with a substantial and simultaneous decrease in viscosity.

In a separate vessel 1.04 parts (422.7 grams) of zinc oxide is thoroughly dispersed in 21.6 parts (1.58 kg) of purified water. The aqueous zinc oxide dispersion is added slowly to the hot MVE/MA copolymer solution in small quantities. Vigorous stirring of the MVE/MA copolymer solution is required to prevent localized precipitation of the zinc MVE/MA copolymer salt. After addition of the zinc oxide dispersion is complete, mixing is continued for about another two hours to ensure completion of the reaction.

The resultant solution of the zinc salt of methyl vinyl ether-maleic acid (MVE/MA) copolymer is then transferred to shallow stainless steel drying trays and the trays placed in a hot air convection oven at 70°C for a sufficient time to evaporate the water content (about 16-18 hours). The dried zinc MVE/MA copolymer salt is then ground in a milling apparatus and screened through a 140-mesh sieve and then through a 200-mesh sieve (U.S.B.S. sieve series). The powder has an apparent bulk density of about 0.9-1.1 gram per cubic centimeter, and a pH of 4.6 for a 1% solution in water. The salt has about 50% neutralization (with
zinc) of the total initial carboxyl groups in the original copolymeric salt molecule.

Compositions

The adhesive compositions of the present invention comprise, as described above, from about 10% to about 90% of the acidic organic adhesive polymer, from about 10% to about 90% of the organic cationic ammonium-substituted polymer, and from 0% to about 80% of a pharmaceutically acceptable carrier or adjunct materials. The weight ratio of acidic organic adhesive polymer to ammonium-substituted polymer should be from about 9:1 to about 1:9, preferably from about 5:1 to about 1:5, more preferably from about 4:1 to about 1:1. The preferred compositions will comprise poly(alkyl vinyl ether-maleic acid) copolymer (or salts thereof) as the organic adhesive polymer and an ammonium-substituted vinyl polymer as in Formula I, or co-, ter-, etc. polymer thereof having a degree of ammonium substitution of at least about 60%, preferably at least about 75%, more preferably at least about 90%, most preferably essentially 100%, and will have a molecular weight of from about 20,000 to about 200,000, preferably about 75,000 to about 150,000. Also, as described above, these compositions are characterized by having a Gel Volume (as determined according to the following procedure) of between about 0.5 and about 10.0 g water/g acidic organic adhesive polymer and cationic ammonium-substituted polymer (combined), preferably from about 0.5 to about 4.0 g/g, more preferably from about 1.0 to about 3.0 g/g. The preferred and more preferred Gel Volumes are especially desirable for bioadhesive applications such as, but not limited to, denture adhesives. The above percentages of acidic organic adhesive polymer, organic cationic ammonium-substituted polymer, and optional carrier and adjunct material are calculated on a weight basis exclusive of water or other polar solvent.

This invention also encompasses the gel compositions comprising the above cationic ammonium-substituted polymers and acidic organic adhesive polymers, and optional carriers and adjunct materials in the above ranges on a weight basis exclusive of water or other polar solvent, and from about 0.5 g water or other polar solvent/g polymer (combined) to about 10.0 g water or
other polar solvent/g polymer (combined), preferably from about 0.5 g/g to about 4.0 g/g, more preferably from about 1.0 g/g to about 3.0 g/g. Water is the preferred polar solvent. Additionally, it is not meant to exclude from the scope of this invention gels made from the cationic ammonium-substituted and acidic organic adhesive polymers hereof and polar solvents other than water. Other suitable polar solvents include, but are not limited to, methanol, ethanol, and propanol.

The compositions of this invention can contain pharmaceutically acceptable carriers and adjunct materials. Without limiting the invention, the compositions can be provided to the user in the form of powder, paste, or gel. Powders preferably comprise an intimate mixture of the ammonium-substituted and acidic adhesive polymers. The powders can be first hydrated with water or otherwise formed into a gel with another polar solvent and then used. Alternately, the powder can be applied directly to a surface, which is to be adhered to tissue, such as a denture, and be subsequently hydrated after being placed into position, such as in the oral cavity, where sufficient water is present to hydrate the composition to form the gel. Gels comprise the polymers, as described above, and water or other polar solvent. Pastes can be formed by including a carrier such as mineral oil, petrolatum, or other paste-forming carriers known in the art. The pastes can be hydrated or otherwise formed into contact with the gel before or after contact with the surface or surfaces to which it is to adhere. Adjunct materials included will depend upon the intended use of the composition, and can include any compatible pharmacologically active compounds for delivery to human or animal tissue, e.g., delivery to the oral cavity or the skin. Such pharmacologically active substances include, for example: fluoride ion (anticaries); antimicrobial agents (antiplaque/antigingivitis); antidepressants; antifungals; antihypertensives; pain remedies, and the like, where gradual, prolonged release is beneficial.

The invention also provides adhesive tape comprising an adherent amount of the adhesive polymer compositions hereof on a solid backing material, such as a textile fabric or thermoplastic
film, as are well known in the art. An adherent medical dressing comprises such tape, in combination with an absorbent material to imbibe blood or other body fluids.

**Gel Volume Determination**

Gel Volume for the compositions of the present invention is calculated as the ratio of grams of distilled water absorbed per gram of gel-forming polymers (combination of acidic organic adhesive and the cationic ammonium-substituted polymer, dry weight basis). A known amount of the gel-forming polymers is mixed in a beaker with an excess of distilled water and allowed to swell for a period of 24 hours with gentle stirring. An excess of distilled water will vary dependent upon the Gel Volume of sample, but ten to twelve times the weight of the gel-forming polymers will typically provide an excess of distilled water for the compositions of the present invention. Upon saturation, the polymer gel is removed from the excess distilled water. This can be done by pouring the contents of the beaker into a tea bag and allowing the fluid to drain away. The tea bag utilized should be grade 1234, obtainable from C. H. Dexter Division of the Dexter Corp., Windsor Locks, Connecticut, USA, or equivalent. The sample is then weighed. The polymer gel is then dried to completion under reduced pressure in an environment having no greater than 6.0% relative humidity and again weighed. Gel Volume is calculated by dividing the difference between the polymer gel weight and the dried polymer gel weight by the weight of the dried polymer gel.

Having thus described the basic cationic ammonium-substituted polymers and the acidic organic adhesive materials used in the practice of this invention, the following examples illustrate their conjoint use in the preparation of improved adhesive compositions.

**EXAMPLE 1**

This example exemplifies production of ammonium-substituted vinyl polymer having a degree of ammonium substitution of 100% which is suitable for use in the adhesive compositions of the present invention.
250 ml roundbottom flask is charged with 100.0 ml of degassed toluene. 30.0 g of N,N-dimethylaminoethyl methacrylate and 0.3 g of azoisobutylnitrile are also added to the flask and the contents are mixed. The flask is then purged with nitrogen gas, to remove ambient air, and sealed. The contents of the flask are then heated at 65°C for 30 hours. A viscous reaction product containing poly (N,N-dimethylaminoethyl methacrylate) forms. The reaction product is stripped under vacuum to remove the solvent (toluene) and unreacted monomer. The poly(N,N-dimethylaminoethyl methacrylate) is dissolved in 300 ml methanol and is quaternized by reaction with butyl iodide (34.8 g) to form the butyl iodide salt of poly(N,N-dimethylaminoethyl methacrylate). This solution is then evaporated under vacuum and ground into a powder. Confirmation of conversion of amine groups to ammonium salts can be obtained by IR (Infra-red) analysis. Number average molecular weight, as determined by Gel Permeation Chromatography (GPC) analyses, will typically be about 150,000.

A denture adhesive composition in dry powder form is prepared by admixing the GANTREZ-adhesive (Ca/Na) prepared in the above-described manner with the poly(N,N-dimethylaminoethyl methacrylate) butyl iodide salt prepared in the above-described manner, at a weight ratio of GANTREZ: cationic polymer (solids) of about 3:1 to about 4:1.

In use, the above powder (typically 2-10 g) is placed on a premoistened denture, allowed to hydrate briefly, and the denture is inserted in the mouth and pressed into place, all in the manner of denture adhesives well-known in the art.

EXAMPLE II

The powder denture adhesive composition of Example I is modified by blending it with mineral-oil/petrolatum to provide a denture paste. A typical composition is as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Parts by Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GANTREZ Adhesive (Ca/Na)</td>
<td>40</td>
</tr>
<tr>
<td>poly(N,N-dimethylaminoethyl methacrylate) butyl iodide salt</td>
<td>40</td>
</tr>
<tr>
<td>Heavy Mineral Oil</td>
<td>7</td>
</tr>
<tr>
<td>Petrolatum</td>
<td>13</td>
</tr>
</tbody>
</table>
In use, the paste is placed on a premoistened denture.

**EXAMPLE III**

A denture adhesive is prepared in the manner of Example I, using a 1:1 mixture (solids basis) of a mixed Ca/Na salt of GANTREZ Adhesive (Ca/Na) and organic cationic ammonium-substituted polymer of Example I. Aqueous dispersions of the polymers are then mixed and freeze-dried. Alternately, the mixture can be drum-dried. After freeze-drying, the composition can be used in powder form or, optionally, blended with oleaginous materials to form a paste. The paste can be packaged in a tube or pump, of the type used with dentifrices.

Alternately, the GANTREZ adhesive and ammonium-substituted polymer can be mixed together and ground, such as with a mortal and pedestal in the laboratory (or, for example, by using pinmills or hammermills on an industrial scale) to form a powder. The powder can then be used directly or formed into a paste, as described above.

**EXAMPLE IV**

A denture adhesive comprises a freeze-dried or drum-dried mixture, as follows.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percent (Wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GANTREZ Adhesive (Ca/Na)</td>
<td>45</td>
</tr>
<tr>
<td>Sodium Carboxymethylcellulose</td>
<td>10</td>
</tr>
<tr>
<td>poly(N,N-dimethylaminoethyl methacrylate) butyl iodide salt</td>
<td>45</td>
</tr>
</tbody>
</table>

**EXAMPLE V**

An improved denture adhesive comprises the following:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percent (Wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene Powder (200 mesh)</td>
<td>10</td>
</tr>
<tr>
<td>CMC (Na salt)</td>
<td>20</td>
</tr>
<tr>
<td>Gum Arabic</td>
<td>20</td>
</tr>
<tr>
<td>poly(N,N-dimethylaminoethyl methacrylate) butyl iodide salt</td>
<td>20</td>
</tr>
<tr>
<td>Gelatin</td>
<td>10</td>
</tr>
<tr>
<td>GANTREZ Adhesive-179 (Zn salt), as described above</td>
<td>20</td>
</tr>
</tbody>
</table>
EXAMPLE VI

An adhesive suitable for use on tapes, envelope flaps, stamps, and the like, comprises a 1:1:1 mixture (by weight of solids) of Ca/Na GANTREZ:organic ammonium-substituted polymer (of Example I):gelatin.

The adhesives of the above-disclosed type can be affixed to bandages, catamenials, or other absorbent structures to provide self-adhering medical dressings.

The adhesives can also be used to deliver pharmacologically active agents to the oral tissues.

EXAMPLE VII

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Parts by Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denture adhesive composition of Example I</td>
<td>500</td>
</tr>
<tr>
<td>Sodium Fluoride (impalpable)</td>
<td>10</td>
</tr>
<tr>
<td>Cetyl Pyridinium Chloride*</td>
<td>50</td>
</tr>
</tbody>
</table>

*Antimicrobial

The ingredients are dry-blended, then moistened to provide a 2 g bolus which is placed in the oral cavity between the cheek and gums. The bolus remains in place and slowly exudes the fluoride ion and the antimicrobial. After 2-3 hours, the bolus is removed and discarded.

EXAMPLE VIII

This example exemplifies production of an ammonium-substituted vinyl co-polymer having a degree of ammonium-substitution of about 60 mole percent suitable for use in the adhesive compositions of the present invention.

A 250 ml roundbottom flask is charged with 100.0 ml of degassed water. 25.3 g (0.15 moles) of N, N-dimethylaminopropyl methacrylamide, 9.9 g (0.1 moles) of N, N-dimethylacrylamide, and 0.35 g of 2,2'-azobis (2-aminopropane) dihydrochloride (1.0% aqueous solution) are then added to the flask and the contents are mixed. The flask is purged with nitrogen gas, to remove ambient air, and sealed. The contents of the flask are heated at 65°C for 30 hours. A viscous reaction product containing poly (N, N-dimethylaminopropyl methacrylamide- co- N,N-dimethyl acrylamide) forms. The product will typically have about 60 mole % dimethylaminopropyl methacrylamide monomeric units. Confirmation
of the mole percent N-dimethylaminopropyl-methacrylamide monomeric units in the polymer can be obtained by Infra-red (IR) and Nuclear Magnetic Resonance (NMR) analysis. The reaction product is dried to remove solvent by evaporating the solvent under vacuum, and then dissolved in methanol (150 ml) and reacted with 27 grams (0.15 moles) iodobutane to quaternize the amine-substituted monomer units in the polymer product. The reaction mixture is stripped under vacuum to remove methanol and any unreacted monomer and iodobutane. Number average molecular weight, as determined by Gel Permeation Chromatography (GPC) analyses, will typically be about 150,000. Conversion of the amine substituents to ammonium salts can be confirmed by IR analysis. The product is ground into a fine powder and admixed with GANTREZ adhesive and formulated as in Examples I through VII. Higher mole percentages of ammonium-substituted polymer can be obtained by increasing the starting N,N-dimethylaminopropyl-methacrylamide:N,N-dimethylacrylamide molar ratio.

WHAT IS CLAIMED IS:
CLAIMS:

1. An adhesive composition comprising a mixture of:
   (a) from 10% to 90%, weight basis exclusive of water or other polar solvent, of an acidic organic adhesive polymer; and
   (b) from 0% to 80%, total composition weight basis, of a pharmaceutically acceptable carrier or adjunct material, characterized in that said composition additionally comprises:
   (c) from 10% to 90%, weight basis exclusive of water or other polar solvent, of an organic cationic ammonium-substituted vinyl polymer having a degree of ammonium substitution of at least 60%; or
   (d) from 10% to 90%, weight basis exclusive of water or other polar solvent, of an organic amine-substituted vinyl polymer;
   said composition having a Gel Volume of between 0.5 and 10.0 g water/g (acidic organic adhesive polymer and cationic ammonium-substituted polymer combined).

2. An adhesive composition according to Claim 1, wherein said Gel Volume is between 0.5 and 4.0 g/g and the weight ratio of said acidic organic adhesive polymer to said ammonium-substituted vinyl polymer or amine-substituted vinyl polymer is from 5:1 to 1:5.

3. An adhesive composition according to Claim 2, wherein said organic adhesive (a) comprises poly(lower alkyl vinyl ether-maleic acid), polyacrylic acid, polymethacrylic acid, salts thereof, or combinations thereof.

4. An adhesive according to Claim 3 wherein said ammonium-substituted vinyl polymer (c) has a degree of ammonium-functionality from at least 75% to at least 90%.
5. An adhesive according to Claim 3 wherein said amine-substituted vinyl polymer (d) has a degree of amine-functionality from at least 25% to at least 75%.

6. An adhesive gel composition comprising the composition of Claim 1 and a polar solvent, especially water.

7. An adhesive gel composition according to Claim 6, wherein said polar solvent comprises water, and said gel composition comprises from 0.5 g to 10.0 g water per gram of composition.

8. An adhesive gel composition comprising the composition of Claim 3 and water.

9. An adhesive gel composition according to Claim 8, comprising from 0.5 to 4.0 g water per gram of composition.
**INTERNATIONAL SEARCH REPORT**

International Application No

**I. CLASSIFICATION OF SUBJECT MATTER**

(If several classification symbols apply, indicate all)

- IPC (5): C08K 3/20; C08J 3/02; C08J 39/04; A61K 6/00; C09J 139/04
- U.S. Cl. 523/120; 524/457, 461, 516, 521; 525/203, 217, 218

**II. FIELDS SEARCHED**

Minimum Documentation Searched

- Classification System
- Classification Symbols

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

**III. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y US, A, 4,504,618 (TRIVNF ET AL.) 12 MARCH 1985; See entire document.</td>
<td>1-9</td>
<td></td>
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<tr>
<td>Y US, A, 3,868,432 (KEEGAN ET AL.) 25 FEBRUARY 1975; See entire document.</td>
<td>1-9</td>
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</tbody>
</table>

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referred to on oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

**IV. CERTIFICATION**

- Date of the Actual Completion of the International Search 17 JUNE 1991
- Date of Mailing of this International Search Report 16 JUL 1991
- International Searching Authority 1 ISA/US
- Signature of Authorized Officer: Tom McDonald, Jr.

Form PCT/ISA/210 (second sheet) (May 1986)