

represent about 0.3-7.0 wt %, preferably 0.5-4.0 wt %, more preferably about 0.5-3.0 wt %, most preferably about 0.75-2.0 wt %, of a topically applied formulation or of a drug reservoir of a drug delivery system, or patch.

**[0039]** The aforementioned amounts are particularly applicable to those formulations and patches in which the active agent is (1) an uncharged molecule, e.g., wherein a basic drug is in nonionized, free-base form, (2) a basic salt of an acidic drug, or (3) there are no additional species in the formulation or patch that could react with or be neutralized by the inorganic hydroxide, to any significant degree.

**[0040]** For formulations and patches in which the drug is in the form of an acid addition salt, and/or wherein there are additional species in the formulations or systems that can be neutralized by or react with the inorganic base (i.e., acidic inactive ingredients), the amount of inorganic hydroxide is preferably the total of (1) the amount necessary to neutralize the acid addition salt and/or other base-neutralizable species (i.e., the "acidic species"), plus (2) about 0.3-7.0 wt %, preferably 0.5-4.0 wt %, more preferably about 0.5-3.0 wt %, most preferably about 0.75-2.0 wt %, of the formulation or drug reservoir. That is, for an acid addition salt, the enhancer is preferably present in an amount just sufficient to neutralize the salt, plus an additional amount (i.e., about 0.3-7.0 wt %, preferably 0.5-4.0 wt %, more preferably about 0.5-3.0 wt %, most preferably about 0.75-2.0 wt %) to enhance the flux of the drug through the skin or mucosal tissue. Basic drugs in the form of a neutral, free base or basic salt of acidic drug are usually not affected by a base, and thus for these drugs, the amount in (1) is usually the amount necessary to neutralize inactive components that are acidic. For patches, the aforementioned percentages are given relative to the total weight of the formulation components and the adhesive, gel or liquid reservoir.

**[0041]** Still greater amounts of inorganic hydroxide may be used by controlling the rate and/or quantity of release of the base, preferably during the drug delivery period itself.

#### Inorganic Oxides

**[0042]** Inorganic oxides include, for example, magnesium oxide, calcium oxide, and the like.

**[0043]** The amount of inorganic oxide included in the compositions and systems of the invention may be substantially higher than the numbers set forth above for the inorganic hydroxide, and may be as high as 20 wt %, in some cases as high as 25 wt % or higher, but will generally be in the range of about 2-20 wt %. These amounts may be adjusted to take into consideration the presence of any base-neutralizable species.

#### Inorganic Salts of Weak Acids

**[0044]** Inorganic salts of weak acids include, ammonium phosphate (dibasic); alkali metal salts of weak acids such as sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, sodium phosphate (tribasic), sodium phosphate (dibasic), potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, potassium phosphate (dibasic), potassium phosphate (tribasic); alkaline earth metal salts of weak acids such as magnesium phosphate and calcium phosphate; and the like, and combinations thereof.

**[0045]** Preferred inorganic salts of weak acids include, ammonium phosphate (dibasic) and alkali metal salts of weak acids.

**[0046]** The amount of inorganic salts of weak acids included in the compositions and systems of the invention may be substantially higher than the numbers set forth above for the inorganic hydroxide, and may be as high as 20 wt %, in some cases as high as 25 wt % or higher, but will generally be in the range of approximately 2-20 wt %. These amounts may be adjusted to take into consideration the presence of any base-neutralizable species.

#### **[0047]** B. Organic Bases

**[0048]** Organic bases suitable for use in the invention are compounds having an amino group, amido group, an oxime, a cyano group, an aromatic or non-aromatic nitrogen-containing heterocycle, a urea group, and combinations thereof. More specifically, examples of suitable organic bases are nitrogenous bases, which include, but are not limited to, primary amines, secondary amines, tertiary amines, amides, oximes, cyano ( $-\text{CN}$ ) containing groups, aromatic and non-aromatic nitrogen-containing heterocycles, urea, and mixtures thereof. Preferred organic bases are primary amines, secondary amines, tertiary amines, aromatic and non-aromatic nitrogen-containing heterocycles, and mixtures thereof.

**[0049]** For nitrogenous bases, the amount of enhancing agent will typically represent about 0.5-4.0 wt %, preferably about 0.5-3.0 wt %, more preferably about 0.75-2.0 wt %, of a topically applied formulation or of a drug reservoir of a drug delivery system or a patch. These amounts may be adjusted to take into consideration the presence of any base-neutralizable species.

**[0050]** Still greater amounts of the nitrogenous base may be used depending on the strength of the base and the rate and/or quantity of release of the nitrogenous base preferably during the drug delivery period itself.

**[0051]** Preferred organic bases are those whose aqueous solutions have a high pH or a high pKa (more preferably a  $\text{pKa} > 9$ ), and are acceptable as food or pharmaceutical additives. Examples of such preferred organic bases are those listed below, along with their respective pHs (or pKa values).

Organic base	pH of Aqueous Solution (concentration)
2-amino-2-methyl-1,3-propanediol <sup>1</sup>	10.8 (0.1 m)
2-amino-2-methyl-1-propanol <sup>1</sup>	11.3 (0.1 m)
Diethanolamine <sup>1</sup>	11.0 (0.1 N)
Triethanolamine <sup>1</sup>	10.5 (0.1 N)
Butylamine <sup>2</sup>	pKa = 10.56
Dimethylamine <sup>2</sup>	Strong base, pKa = 10.73
Cyclohexylamine <sup>2</sup>	Strong base, pKa = 10.64
Ethylenediamine <sup>2</sup>	Strong base, pKa = 10.71
Isopentylamine <sup>2</sup>	pKa = 10.6
Monoethanolamine <sup>2</sup>	12.1 (25%), 12.05 (0.1 N), pKa = 9.4
Phenethylamine <sup>2</sup>	Strong base, pKa = 9.83
Piperidine <sup>2</sup>	Strong base, pKa = 11.12
Pyrrolidine <sup>2</sup>	Strong base, pKa = 11.27
Trimethylamine <sup>2</sup>	Strong base, pKa = 9.81

<sup>1</sup>listed in the "Handbook of Pharmaceutical Additives"

<sup>2</sup>listed in the FDA's food additive database

#### Amines

**[0052]** Amines are compounds that include at least one primary amino ( $-\text{NH}_2$ ) group, mono-substituted (secondary) amino group or di-substituted (tertiary) amino group.