EXHIBIT 1

United States Patent [19]

Makino et al.

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[54] STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

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[58] Field of Search 514/970, 338, 155, 156, 514/157, 394, 395, 925, 927; 424/475, 495, 683, 686, 692

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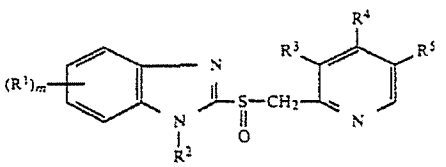
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Attorney, Agent, or Firm—Wegner, Cantor, Mueller & Player

[57] ABSTRACT

The pharmaceutical composition of the invention, which comprises a benzimidazole compound of the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylaklyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, is physically stable.

3 Claims, No Drawings

STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

This invention relates to a pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulphinyl]-benzimidazole or a derivative thereof (hereinafter sometimes referred to collectively as "benzimidazole compounds"), which is useful as an antiulcer agent, as stabilized by incorporation of a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium and its production.

Certain benzimidazole compounds are recently under clinical study as gastric acid secretion inhibitors. They serve as therapeutic agents for digestive ulcer. Their principal pharmacological effect consists in gastric acid secretion suppression based on $(H^+ + K^+)$-ATPase inhibition and is more potent and durable as compared with histamine H_2 receptor antagonists such as cimetidine and ranitidine. They also have gastric mucosa protecting activity. Therefore, they have attracted attention as next-generation potent therapeutic agents for digestive ulcer.

Those benzimidazole compounds which are described in Japanese Unexamined Patent laid open Nos. 62275/77, 141783/79, 53406/82, 135881/83, 192880/83 and 181277/84, corresponding to U.S. Pat. No. 4,045,563, U.S. Pat. No. 4,255,431, European Patent Publication No. 45,200, U.S. Pat. No. 4,472,409, European Patent Publication No. 5,129 and G.B. Patent Publication No. 2,134,523A, respectively, among others are known to have antiulcer activity.

These compounds, however, are poor in stability. In solid state, they are susceptible to heat, moisture and light and, in aqueous solution or suspension, their stability decreases with decreasing pH. In dosage forms, i.e. tablets, powders, fine granules, granules and capsules, said compounds are apt to interact with other components contained in said dosage forms and accordingly are in less stable state as compared with the case where they occur alone. Thus, the content decreases and the color changes significantly in the manufacturing process of dosage form and with the lapse of time. Microcrystalline cellulose, polyvinylpyrrolidone (PVP), carboxymethylcellulose calcium, polyethylene glycol 6000 and Pluronic F68 (polyoxyethylenepolyoxypropylene copolymer), for instance are dosage form components adversely affecting the stability of said compounds. Furthermore, in the case of coated tablets and coated granules among the above dosage forms, enteric coating bases such as cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate and Eudragit (methacrylic acid-acrylic acid copolymer) have poor compatibility with said compounds and cause content decrease and color change. Nevertheless, one or more of these components or ingredients, which, as mentioned above, can produce adverse effects on the stability of said compounds, are essential in the manufacture of oral preparations and therefore difficulties are inevitably encountered in dosage form manufacture.

The prior art avoids the above-mentioned stability problem by using said benzimidazole compounds in a salt form, say in the form of a lithium, sodium, potassium, magnesium, calcium or titanium salt [Japanese Unexamined Patent laid open No. 167587/84 (European Patent Publication No. 124,495A)]

However, the above prior art method requires, for the stabilization of the benzimidazole compounds, a step

of converting said compounds to such a salt form as mentioned above in advance.

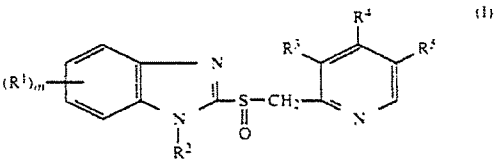
In view of the above, the present inventors made investigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

Thus, this invention relates to

(1) A pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and

(2) A method of producing a stabilized pharmaceutical composition which comprises incorporating a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium in a pharmaceutical composition containing 2-[(2-pyridylmethylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity.

The benzimidazole compounds having an antiulcer activity which are to be used in the practice of the invention are those compounds which are described in the above-cited laid-open patent specifications, for instance and are represented by the formula



(I)

wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

The compounds of the formula(I) can be produced by the methods described in the above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is made of the substituents in those compounds which have the formula (I) and are already known.

Referring to R^1 in the above formula, C_{1-7} alkyls may be mentioned as the alkyl represented by R^1; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxyalkyl and C_{1-4} alkyls as the alkyl moiety; C_{1-4} alkyls as the alkyl moiety of the carbamoylalkyl; C_{1-5} alkoxys as the alkoxy; C_{1-7} alkyls as the alkyl moiety of the hydroxyalkyl; C_{1-4}alkanoyls as the acyl; phenyl as the aryl; phenyl as the aryl moiety of the aryloxy; C_{1-6} alkyls as the alkyl moiety of the alkylthio; and C_{1-6} alkyls as the alkyl moiety of the alkylsulfinyl.

Referring to R^2, C_{1-5} alkyls may be mentioned as the alkyl represented by R^2; C_{1-4} alkanoyls as the acyl; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkyls as the alkyl moiety of the alkylcarbamoyl; C_{1-4} alkyls as each of the alkyl moieties of the dialkylcarbamoyl; C_{1-4} alkyls as the alkyl moiety of the alkylcarbonyl-

methyl; C_{1-4} alkoxys as the alkoxy moiety of the alkoxycarbonylmethyl; and C_{1-4} alkyls as the alkyl moiety of the alkylsulfonyl.

Referrring to R^3, R^4 and R^5, C_{1-4} alkyls may be mentioned as the alkyl represented by any of them; C_{1-8} alkoxys as the alkoxy; and C_{1-4} alkoxys as each of the alkoxy moieties of the alkoxyalkoxy.

Referring to R^4, C_{1-8} alkoxys may be mentioned as the alkoxy, which may optionally be fluorinated.

Among those compounds of the above forumula (I), (1) the compounds of which R^1 is hydrogen, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 and R^5 are the same or different and each is hydrogen or methyl, R^4 is fluorinated C_{2-5} alkoxy and m is 1, (2) the compounds of which R^1 is hydrogen, fluorine, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 is hydrogen or methyl, R^4 is C_{3-8} alkoxy, R^5 is hydrogen and m is 1, and (3) the compounds of which R^1 is hydrogen, fluorine, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 is C_{1-8} alkoxy, R^4 is C_{1-8} alkoxy which may be fluorinated, R^5 is hydrogen and m is 1.

Detailed mention is now made of the substituents in such novel compounds.

Referring to R^3, the lower alkyl represented thereby is preferably C_{1-8} lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy and more preferably C_{1-4} lower alkoxy.

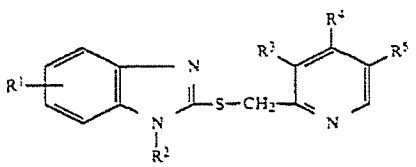
Referring to R^4, C_{1-8} lower alkoxys may be mentioned as the lower alkoxy, which may optionally be fluorinated, and preferred examples are as mentioned above for R^3. As the fluorinated lower alkoxy, there may be mentioned, for example, 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy and 2,2,3,3,4,4,5,5-octafluoropentoxy, and fluorinated C_{2-4} lower alkoxys are preferred.

The position of R^1 is position 4 or position 5, preferably position 5.

Some methods of producing the above novel compounds [hereinafter referred to as "compounds of formula (I')"] are described below.

Said compounds can be produced by subjecting a compound of the formula

(II)



wherein R^1–R^5 are as defined above, to oxidation.

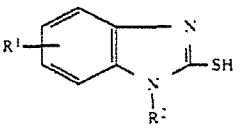
The oxidizing agent to be used is, for example, metachloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, permaleic acid or the like peracid, sodium bromite or sodium hypochlorite. Examples of the solvent to be used in carrying out the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, and water. These solvents may be used either singly or in admixture. Said oxidizing agent is used preferably in an amount approximately equivalent or slightly excessive relative to the compound (II). Thus, said agent is used in an amount of about 1–3 equivalents, more preferably about 1 to 1.5 equivalents. The reaction is carried out at a temperature from about 0° C. (ice cooling) to around the boiling point of the solvent used, generally at a temperature from about 0° C. (ice cooling) to room temperature, preferably at a temperature of about 0° C. to 10° C. The reaction time is generally about 0.1 to 24 hours, preferably about 0.1 to 4 hours.

The desired novel compounds (I') produced by the above reaction can be isolated and purified by conventional means such as recrystallization, chromatography and so on.

Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

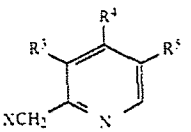
The novel compounds (II) can be produced by reacting a starting compound of the formula

(III)



wherein R^1 and R^2 are as defined above, with a starting compound of the formula

(IV)



wherein R^3–R^5 are as defined above and X is a halogen atom.

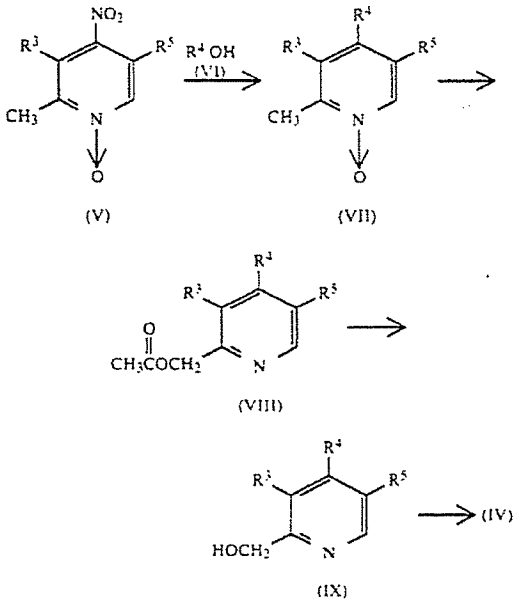
The halogen atom represented by X is, for example, chlorine, bromine or iodine.

The reaction is carried out advantageously in the presence of a base. As said base, there may be mentioned alkali metal hydrides such as sodium hydride and potassium hydride, alkali metals such as metallic sodium, sodium alcoholates such as sodium methoxide and sodium ethoxide, alkali metal carbonates such as potassium carbonate and sodium carbonate, and organic amines such as triethylamine, among others. As the solvent to be used in carrying out the reaction, there may be mentioned, for example, alcohols such as methanol and ethanol, and dimethylformamide. The base is used generally in an amount slightly excessive relative to the equivalent amount but may also be used in large excess. Thus, it is used in an amount of about 2–10 equivalents, preferably about 2–4 equivalents. The above reaction is carried out generally at a temperature of about 0° C. to around the boiling point of the solvent used, preferably at about 20° C. to 80° C., for a period of about 0.2–24 hours, preferably about 0.5–2 hours.

Some methods of producing the starting compounds (IV) are described below.

Among the compounds (IV), those compounds wherein R^3 and R^5 are the same or different and each is hydrogen or methyl and R^4 is fluorinated C_{2-5} alkoxy or C_{3-8} alkoxy can be produced by the following process:

Process (1)



A nitro compound of the formula (V), wherein R^3 and R^5 are as defined above, is reacted with an alcohol derivative of the formula R^4OH (VI) wherein R^4 is fluorinated C_{1-5} alkyl or C_{3-8} alkyl, in the presence of a base to give an alkoxy derivative of the formula (VII) wherein R^3, R^4 and R^5 are as defined above. The base to be used in carrying out the reaction includes, among others, alkali metals such as lithium, sodium and potassium, alkali metal hydrides such as sodium hydride and potassium hydride, alcoholates such as potassium t-butoxide and sodium propoxide, alkali metal carbonates and hydrogen carbonates such as potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate. and alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. The alcohol derivative to be submitted to the reaction includes, among others, propanol, isopropanol, butanol, pentanol, hexanol, 2,2,2-trifluoroethanol, 2,2,3,3,3-pentafluoropropanol, 2,2,3,3-tetrafluoropropanol, 1-(trifluoromethyl)-2,2,2-trifluoroethanol, 2,2,3,3,4,4,4-heptafluorobutanol and 2,2,3,3,4,4,5,5-octafluoropentanol. While R^4OH itself may be used as a solvent in carrying out the reaction, ethers such as tetrahydrofuran and dioxane, ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide, for instance, may also be used as solvents. An appropriate reaction temperature may be selected within the range of about 0° C. (ice cooling) to around the boiling point of the solvent used. The reaction time is about 1–48 hours.

Heating (about 80°–120° C.) of the thus-obtained compound (VII) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid gives an 2-acetoxymethylpyridine derivative of the formula (VIII) wherein R^3, R^4 and R^5 are as defined above. The reaction period is generally about 0.1–10 hours.

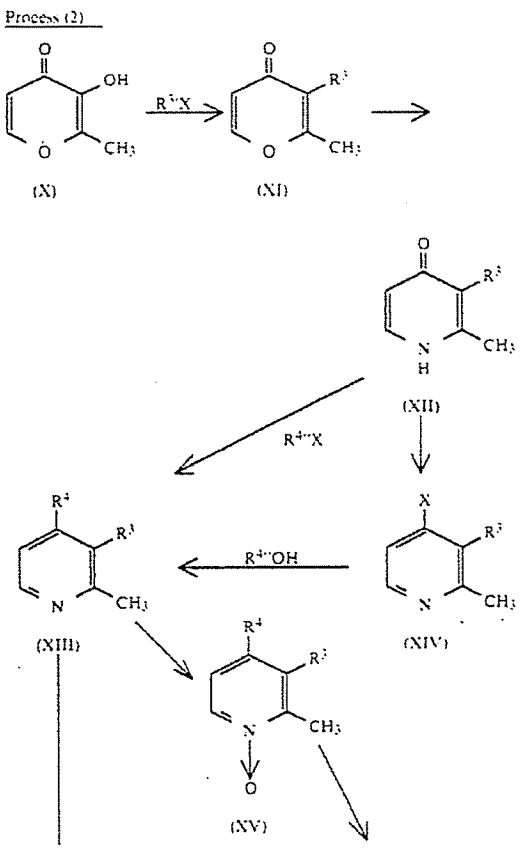
The subsequent alkaline hydrolysis of the compound (VIII) gives a 2-hydroxymethylpyridine derivative of the formula (IX). Sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate, for instance, are usable as alkalis, and methanol, ethanol and water, among others, are usable as solvents. The reaction is generally conducted at about 20°–60° C. for about 0.1–2 hours.

The compound (IX) is further halogenated with a chlorinating agent such as thionyl chloride to give a 2-halomethylpyridine derivative of the formula (IV) wherein R^3, R^4 and R^5 are as defined above and X is chlorine, bromine or iodine. Usable as solvents are, for example, chloroform, dichloromethane and tetrachloroethane. The reaction is generally carried out at about 20–80° C. for about 0.1–2 hours.

The compound (IV) thus produced occurs in the form of a salt of hydrohalogenic acid corresponding to the halogenating agent used and it is generally preferable to subject said compound to reaction with the compound (III) immediately.

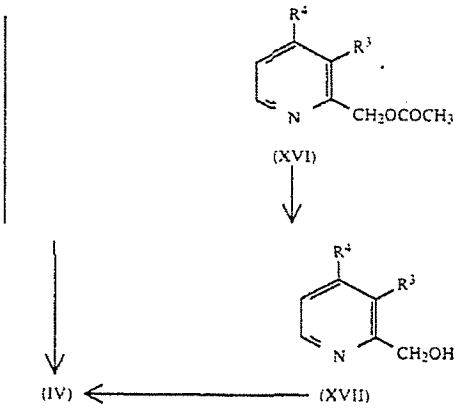
Among the compounds (V), those compounds wherein R^3 is C_{1-8} lower alkoxy, R^4 is alkoxy which may optionally be fluorinated, and R^5 is hydrogen can be produced by the following process:

Process (2)



-continued

Process (2)



Thus, maltol (X) is reacted with a alkyl halide of the formula R^3X in the presence of silver oxide, for instance, to give a compound of the formula (XI). Reaction of (XI) with aqueous ammonia gives a pyridone derivative of the formula (XII). Direct alkylation of the compound (XII) with an alkyl halide, or halogenation of (XII) with a halogenating agent such as phosphorus oxychloride followed by reaction of the resultant halo derivative (XIV) with a lower alcohol of the formula R^4OH in the presence of a base gives a compound of the formula (XIII). The compound (XIII) can be converted to the compound (IV) by direct halogenation with N-bromosuccinimide or chlorine, for instance. The compound (XIII) may also be converted to the compound (IV) by oxidizing the same with an oxidizing agent such as m-chloroperbenzoic acid, reacting the resulting compound (XV) with acetic anhydride, hydrolyzing the resulting comppund (XVI) and halogenating the resulting compound (XVII) with a halogenating agent such as thionyl chloride.

The alkyl halide to be used in the production of the compound (XI) includes, among others, methyl iodide, ethyl iodide, propyl iodide, isopropyl iodide, butyl iodide, pentyl iodide and hexyl iodide, and the alkyl halide to be used in the production of the compound (XIII) further includes, in addition to those mentioned above for use in the production of the compounds (XI), 2,2,2-trifluoroethyl iodide, 2,2,3,3,3-pentafluoropropyl iodide, 2,2,3,3-tetrafluoropropyl iodide, 1-(trifluoromethyl)-2,2,2-trifluoroethyl iodide, 2,2,3,3,4,4,4-heptafluorobutyl iodide and 2,2,3,3,4,4,5,5-octafluoropentyl iodide, for instance. Such alkyl iodides are used in an amount of about 1–10 equivalents. Silver oxide, potassium carbonate, sodium carbonate or the like is used as a deacidifying agent and dimethylformamide, dimethylacetamide or the like is used as a solvent. The reaction is generally carried out at room temperature.

The halogenating agent to be used in the production of the compound (XIV) includes, among others, phosphorus oxychloride, phosphorus pentoxide and phosphorus tribromide and is used in an amount of 1 equivalent to a large excess. The reaction is carried out at a temperature of about 50°–150° C. The alcohol to be used for the conversion of compound (XIV) to compound (XIII) includes methanol and ethanol and further those alcohol derivaitves mentioned for use in process 1) and is used in an amount of 1 equivalent to a large excess, and the base includes those sodium alcoholates and potassium alcoholates which correspong to the respective alcohols as well as potassium t-butoxide, sodium hydride and so forth. An appropriate reaction temperature may be selected within the range of room temperature to the boiling point of the solvent used.

For direct bromination of the compound (XIII) with N-bromosuccinimide, the reaction is preferably carried out under light irradiation, and carbon tetrachloride, chloroform, tetrachloroethane or the like is used as a solvent.

The oxidizing agent to be used for the conversion of compound (XIII) to compound (XV) includes, among others, peracids such as meta-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid as well as hydrogen peroxide. Usable as solvents for the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, acetic acid and water, for instance, and these can be used either singly or in admixture. Said oxidizing agent is preferably used in an amount of about 1 equivalent to an excess relative to the compound (XIII), more preferably about 1–10 equivalents. The reaction is carried out at a temperature of about 0° C. (ice cooling) to around the boiling point of the solvent used generally for a period of about 0.1–24 hours, preferably for about 0.1–4 hours.

The conversion of compound (XV) to compound (XVI) is effected by heating (at about 80°–120° C.) the compound (XV) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid and so on. The reaction period is generally 0.1–10 hours.

The alkali to be used in the alkaline hydrolysis of compound (XVI) to compound (XVII) includes, among others, sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. Methanol, ethanol and water, for instance, may be mentioned as usable solvents. The reaction is generally carried out at a temperature of about 20°–60° C. for a period of about 0.1–2 hours.

For the production of compound (IV) from compound (XVII), a chlorinating agent such as thionyl chloride or an organic sulfonic or organic phosphoric acid chloride such as methanesulfonyl chloride, p-toluenesulfonyl chloride or diphenylphosphoryl chloride is used. When a chlorinating agent such as thionyl chloride is used, it is used in an amount of 1 equivalent to a large excess relative to the compound (XVII) and a solvent such as chloroform, dichloromethane or tetrachloroethane is used, and the reaction is generally carried out at a temperature of about 20°–80° C. for a period of about 0.1–2 hours. When an organic sulfonic or organic phosphoric acid chloride is used, it is used in an amount of 1 equivalent to a slight excess relative to the compound (XVII) and the reaction is generally carried out in the presence of a base. As usable bases, there may be mentioned organic bases such as triethylamine and tributylamine and inorganic bases such as sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The base is used in an amount of 1 equivalent to a slight excess. As usable solvents, there may be mentioned, for example, chloroform, dichloromethane, carbon tetrachloride and acetonitrile. An appropriate reaction temperature and an appropriate reaction can be selected within the ranges of about 0° C. (ice cooling) to

around the boiling point and several minutes to several hours, respectively.

The above-mentioned novel benzimidazole compounds have excellent gastric antisecretory activity, gastric mucosa-protecting activity and antiulcer activity but have low toxicity, so that they can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, human).

The basic inorganic salt of magnesium and that of calcium, which are to be used in accordance with the invention, are now described.

Said basic inorganic salt of magnesium includes, among others, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2$)] and aluminum magnesium hydroxide [$2.5MgO.Al_2O_3.xH_2O$] and said basic inorganic salt of calcium includes, among others, precipitated calcium carbonate and calcium hydroxide. It is only required of such basic inorganic magnesium and calcium salts to show basicity (pH of not less than 7) when they are in the form of a 1% aqueous solution or suspension.

Said basic inorganic magnesium and calcium salts may be used either singly or in combination of two or more species in an amount which may vary depending on the kinds thereof but generally lies within the range of about 0.3–20 parts by weight, preferably about 0.6–7 parts by weight, per part by weight of the benzimidazole compounds.

The composition of the invention may further contain such additives as vehicles (e.g. lactose, corn starch, light silicic anhydride, microcrystalline cellulose, sucrose), binders (e.g. α-form starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone), disintegrating agents (e.g. carboxymethylcellulose calcium, starch, low substituted hydroxypropylcellulose), surfactants [e.g. Tween 80 (Kao-Atlas), Pluronic F68 (Asahi Denka; polyoxyethylene-polyoxypropylene copolymer], antioxidants (e.g. L-cysteine, sodium sulfite, sodium ascorbate), lubricants (e.g. magnesium stearate, talc), etc.

The composition of the invention is prepared by homogeneously admixing the above benzimidazole compound, the basic inorganic salt of magnesium and/or basic inorganic salt of calcium, and the above additives.

The particle sizes of said benzimidazole compound and said inorganic salt are not especially critical in a condition that they can be homogeneously admixed. For example, preferable perticle size is about less than 100 μm, more preferable one is about less than 20 μm.

The moisture amount in the composition is preferably about 6–60%, more preferably about 20–40% as equibrium relative humidity (E.R.H). The method of admixing is optional if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, or the basic inorganic salt of magnesium and/or of calcium may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing.

Said mixture can be made up into dosage forms suited for oral administration, such as tablets, capsules, powders, granules and fine granules, by per se known means.

Tablets, granules and fine granules may be coated by a per se known method for the purpose of masking of the taste or providing them with enteric or sustained release property. Usable as coating agents are, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluornic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Röhm, West Germany; methacrylic acid-acrylic acid copolymer) and pigments such as titanium oxide and ferric oxide.

Tablets, granules, powders, fine granules and capsules can be produced by a conventional method (e.g. the method described in the 10th edition of the Japanese Pharmacopeia under General Rules for Preparations). Thus, for example, tablets are produced by adding the basic inorganic salt of magnesium and/or of calcium to a mixture of the benzimidazole compound, vehicle and disintegrant, mixing, adding a binder, granulating the mixture, adding a lubricant etc. and tableting the resultant granular composition. Granules are produced by extrusion in approximately the same manner as in the production of tablets or by coating nonpareils, which contain sucrose and corn starch, with a mixture of benzimidazole compound, a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and additives (e.g. sucrose, corn starch, crystalline cellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone) Capsules are produced by mere mixing and filling. The dosage forms thus obtained show excellent stability with slight changes in appearance and little decreases in content even after storage for a long period of time.

The pharmaceutical composition of the present invention as obtained in the above manner exhibits excellent gastric antisecretory, gastric mucosa-protecting and antiulcer activities and has low toxicity and therefore can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, pig, human).

The pharmaceutical composition of the invention can be orally administered for the treatment of digestive ulcers in mammals in admixture with pharmacologically acceptable carriers, vehicles, diluents and so forth and in the form of capsules, tablets, granules and some other dosage forms, as mentioned hereinabove. The dose as the benzimidazole compound lies within the range of about 0.01 mg to 30 mg/kg/day, preferably about 0.1 mg to 3 mg/kg/day.

The following reference examples and working examples as well as the experimental examples described later herein illustrate the present invention in more detail but are by no means limitative of the present invention.

REFERENCE EXAMPLE 1

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethylphosphoric acid triamide (2.07 g) was heated at 70°–80° C. with stirring for 4.5 days. Then, the insoluble matter was filtered off and the filtrate was concentrated. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract layer was dried over magnesium sulfate, then the solvent was distilled off, and the residue was

applied to a silica gel column (50 g). Elution with chloroform-methanol (10:1) and recrystallization from ethyl acetate-hexane gave 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles. Melting point 148°–149° C.

The following compounds (VII) were produced from the corresponding compounds (V) in the same manner as above.

Compounds (VII)

	R^3	R^5	R^4	Melting point (°C.)
	CH_3	H	OCH_2CF_3	131.0–131.5
Note 1	H	H	$OCH_2CH_2CH_3$	Oil
Note 2	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note 1:
NMR spectrum ($CDCl_3$) δ: 1.01 (3H, t, J = 7 Hz), 1.81 (2H, m), 2.50 (3H, s), 3.93 (2H, t, J = 7 Hz), 6.50–6.80 (2H, m), 8.10 (1H, d, J = 7 Hz)
Note 2:
NMR spectrum ($CDCl_3$) δ: 1.07 (3H, t, J = 7.5 Hz), 1.65–2.02 (2H, m), 2.21 (3H, s), 2.52 (3H, s), 3.99 (2H, t, J = 6 Hz), 6.68 (1H, d, J = 6 Hz), 8.15 (1H, d, J = 6 Hz)

REFERENCE EXAMPLE 2

Concentrated sulfuric acid (2 drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyridine-1-oxide (2.5 g) in acetic anhydride (8 ml) and the mixture was stirred at 110° C. for 2 hours and then concentrated. The residue was dissolved in methanol (30 ml), 2 N aqueous sodium hydroxide (20 ml) was added, and the mixture was stirred at room temperature for 2 hours. After concentration, water was added to the residue and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, the solvent was then distilled off, and the residue was applied to a silica gel (50 g) column. Elution with chloroform-methanol (10:1) and recrystallization from isopropyl ether gave 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyridine as a brown oil.

NMR spectrum ($CDCl_3$) δ: 2.07 (3H, s), 4.28 (1H, brs), 4.49 (2H, t, J=12 Hz), 4.67 (2H, s), 6.69 (1H, d, J=5 Hz), 8.34 (1H, d, J=5 Hz)

The following compounds (IX) were produced from the corresponding compounds (VII) in the same manner as mentioned above.

Compounds (IX)

	R^3	R^5	R^4	Melting point (°C.)
	CH_3	H	OCH_2CF_3	93.5–94.0
Note 1	H	H	$OCH_2CH_2CH_3$	Oil
Note 2	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note 1
NMR spectrum ($CDCl_3$) δ: 1.0 (3H, t, J = 7.5 Hz), 1.79 (2H, m), 3.92 (2H, t, J = 6 Hz), 4.51–4.90 (1H, brs), 4.68 (2H, s), 6.68 (1H, dd, J = 2 and 6 Hz), 8.30 (1H, d, J = 2 Hz), 8.28 (1H, d, J = 6 Hz)
Note 2
NMR spectrum ($CDCl_3$) δ: 1.03 (3H, t, J = 7.5 Hz), 1.82 (2H, m), 2.02 (3H, s), 3.95 (2H, t, J = 6 Hz), 4.62 (2H, s), 5.20 (1H, brd, s), 6.68 (1H, d, J = 6 Hz), 8.25 (1H, d, J = 6 Hz)

REFERENCE EXAMPLE 3

Thionyl chloride (0.2 ml) was added to a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyridine (350 mg) in chloroform (10 ml) and the mixture was refluxed for 30 minutes and then concentrated. The residue was dissolved in methanol (5 ml) and the solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml). The resultant mixture was refluxed for 30 minutes. The methanol was distilled off, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with dilute sodium hydroxide solution and dried over magnesium sulfate. The solvent was then distilled off, and the residue was applied to a silica gel (20 g) column. Elution with ethyl acetate-hexane (2:1) and recrystallization from ethyl acetate-hexane gave 370 mg of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]-methylthio]benzimidazole hemihydrate as colorless plates. Melting point 145°–146° C.

The following compounds (II) were produced by reacting the compound (III) with the corresponding compound (IV) in the same manner as mentioned above.

Compounds (II)

	R^1	R^2	R^3	R^5	R^4	Melting point (°C.)
	H	H	CH_3	H	OCH_2CF_3	149–150
	H	H	H	H	$OCH_2CH_2CH_3$	84–86
Note	H	H	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note
NMR spectrum ($CDCl_3$) δ: 0.95 (3H, t, J = 7.5 Hz), 1.84–1.92 (2H, m), 2.15 (3H, s), 3.80 (2H, t, J = 6 Hz), 4.42 (2H, s), 6.55 (1H, d, J = 6 Hz), 7.09 (2H, m), 7.50 (2H, m), 8.21 (1H, d, J = 6 Hz)

REFERENCE EXAMPLE 4

A solution of m-chloroperbenzoic acid (1.3 g) in chloroform (15 ml) was added dropwise to a solution of 2-[[3-methyl-4-(2,2,3,3,3-pentafuloropropoxy)-2-pyridyl]methylthio]-methylthio]benzimidazole 2.2 g) in chloroform (20 ml) with ice cooling over 30 minutes and, then, the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated. The concentrate was applied to a silica gel (50 g) column. Elution with ethyl acetate and recrystallization from acetone-isopropyl ether gave 1.78 g of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methyl-sulfinyl]benzimidazole [hereinafter sometimes referred to as compound (A)] as pale yellow prisms. Melting point 161°–163° C. (decomposition).

The following compounds (I) [hereinafter sometimes referred to as compound (B), compound (C) and compound (D), respectively] were produced in the same manner from the corresponding compounds (II).

Compounds (I)

	R^1	R^2	R^3	R^5	R^4	Melting point (°C.)
(B)	H	H	CH_3	H	OCH_2CF_3	178–182 (decomp.)
(C)	H	H	H	H	$OCH_2CH_2CH_3$	123–125 (decomp.)
(D)	H	H	CH_3	H	$OCH_2CH_2CH_3$	81–83

EXAMPLE 1

Of the components given below, the compound (A), magnesium hydroxide, L-cysteine, corn starch and lactose were mixed together, then microcrystalline cellulose, light silicic anhydride and magnesium stearate, each in half the intended amount, were added. After sufficient admixing, the mixture was compression-molded on a dry granulator (roller compactor; Freund, Japan. The compressed mass was ground in a mortar, the resultant granular mass was passed through a round sieve (16 mesh). The remaining portions of microcrystalline cellulose, light silicic anhydride and magnesium stearate were added to the sieved mass and, after admix-

ing, the whole mixture was made up into tablets each weighing 250 mg on a rotary tableting machine (Kikusui Seisakusho, Japan).

Composition per tablet:	
Compound (A)	50 mg
Magnesium hydroxide	30 mg
L-Cysteine	20 mg
Corn starch	20 mg
Lactose	65.2 mg
Microcrystalline cellulose	60 mg
Light silicic anhydride	1.8 mg
Magnesium stearate	3.0 mg
Total	250.0 mg

EXAMPLE 2

Tablets were produced in the same manner as in Example 1 except that omeprazole (Note) was used instead of the compound (A).

Note: 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.

EXAMPLE 3

Of the components given below, the compound (B), precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose were mixed together, water was added, and the mixture was kneaded, then dried in vacuum at 40° C. for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this was added magnesium stearate and the resultant mixture was made up into tablets each weighing 200 mg on a rotary tableting machine (Kikusui Seisakusho, Japan).

Composition per tablet:	
Compound (B)	30 mg
Precipitated calcium carbonate	50 mg
Corn starch	40 mg
Lactose	73.4 mg
Hydroxypropylcellulose	6 mg
Magnesium stearate	0.6 mg
Water	(0.05 ml)
Total	200.0 mg

EXAMPLE 4

Tablets were produced in the same manner as in Example 3 except that timoprazole (Note) was used instead of the compound (B).

Note: 2-[(2-Pyridyl)methylsulfinyl]benzimidazole.

EXAMPLE 5

The ingredients given below were mixed well in the porportions given below, water was added, and the mixture was kneaded and granulated in an extruder granulator (Kikusui Seisakusho; screen size 1.0 mm ϕ). The granules were immediately converted to spherical form in a spheronizer (Fuji Powder's Marumerizer, Japan; 1,000 rpm). The spherical granules were then dried under vacuum at 40° C. for 16 hours and passed through round sieves to give 12- to 42-mesh granules.

Composition per 200 mg of granules	
Compound (B)	30 mg
Heavy magnesium carbonate	20 mg
Corn starch	80 mg
Microcrystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	26 mg
Water	(0.1 ml)
Total	200 mg

EXAMPLE 6

Granules were produced in the same manner as in Example 5 except that the compound (D) was used instead of the compound (B).

EXAMPLE 7

Enteric granules were produced by coating the granules obtained in Example 2 with an enteric coating composition specified below using a fluidized bed granulator (Okawara, Japan) under conditions such that the inlet air temperature was 50° C. and the granule temperature was 40°60 C. No. 1 hard capsules were filled with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine (Parke-Davis, U.S.A.).

Enteric coating composition:	
Eudragit L-30D	138 mg (solids 41.4 mg)
Talc	4.1 mg
Polyethylene glycol 6000	12.4 mg
Tween 80	2.1 mg
Water	276 µl
Composition of enteric granules:	
Granules of Example 5	200 mg
Enteric coat	60 mg
Total	260 mg
Composition per capsule:	
Enteric granules	260 mg
No. 1 hard capsule	76 mg
Total	336 mg

EXAMPLE 8

Of the components given below, the compound (B), magunesium carbonate, socrose, corn starch and crystalline cellulose were thoroughly mixed together to obtain dusting powder.

Nonpareils were put on a centrifugal fluidized coating-granulatar (CF-360 Freund, Japan) and then coated with the dusting powder as described above, while spraying hydroxypropylcellulose solution [4% (w/w)], to give spherical granules. The spherical granules were dried in vacuum at 40° C. for 16 hours and then passed through round sieves to give 12 to 32-mesh granules.

Composition per 190 mg of granules:	
Nonpareil	75 mg
Compound (B)	15 mg
Magnesium carbonate	15 mg
Sucrose	29 mg
Corn starch	27 mg
Crystalline cellulose	27 mg
Hydroxypropylcellulose [Hydroxypropoxy group content: 53.4–77.5%]	2 mg
Water	(0.05 ml)
Total	190 mg

EXAMPLE 9

Enteric granules were produced by coating the granules obtained in Example 8 with an enteric coatig composition specified below usig a fluidized bed granulator (Okawara, Japan) under conditions such that inlet air temperature was 50° C. and the granule temperature was 40° C. No. 2 hard capsules were filled with the enteric granules thus obtained in an amount of 240mg per capsule using a capsule filling machine (Parke-Davis, USA).

Enteric coating composition:	
Eudragit L-30D	104.7 mg (solids 31.4 mg)
Talc	9.6 mg
Polyethylene glycol 6000	3.2 mg
Tween 80	1.6 mg
Titanium oxide	4.2 mg
Water	(220 μl)
Composition of enteric granules:	
Granules of Example 8	190 mg
Enteric coat	50 mg
Total	240 mg
Composition per capsule:	
Enteric granules	240 mg
No. 2 hard capsule	65 mg
Total	305 mg

EXAMPLE 10

Composition 1:	
Compound (B)	450 g
Magnesium carbonate	450 g
Sucrose	450 g
Corn starch	450 g
Low substituted hydroxypropylcellulose [Hydroxypropoxy group content: 10.0–13.0% (w/w), average particle size: no more than 30 μm]	450 g
Composition 2:	
Sucrose	420 g
Corn starch	360 g
Low substituted hydroxypropylcellulose [Hydroxypropoxy group content: 10.0–13.0% (w/w), average particle size: no more than 30 μm]	360 g

Ingredients of the above composition 1 and composition 2 were thoroughly mixed together to obtain dusting powder 1 and dusting powder 2, respectively.

2250 g of nonpareils were put on a centrifugal fluidized coating granulatar (CF-360 Freund, Japan) and then coated with the dusting powder 1, then with the dusting powder 2, while spraying 60 g of hydroxypropylcellulose in water (2000 ml) to give spherical granules.

The spherical granules were dried in vacuum at 40° C. for 16 hours and then passed through round sieve to give 12 to 32 - mesh granules.

EXAMPLE 11

Enteric granules were produced by coating 3800 g of the granules obtained in Example 10 with an enteric coating composition specified below using a fluidized bed granulatar (Okawara, Japan) under conditions such that inlet air temperature was 50° C. and the granule temperature was 40° C. No. 2 hard capsules were filled with the enteric granules thus obtained in an amount of 240 mg per capsule using a filling machine (Parke-Davis), USA).

Enteric coating composition:	
Eudragit L30D-55	628 g
Talc	192 g
Polyethylene glycol 6000	64 g
Titanium oxide	64 g
Tween 80	32 g
Water	4400 ml
Composition per capsule:	
Enteric granules	240 mg
No. 2 hard capsule	65 mg

Experimental Example 1

Granules were produced by the method of Example 5 and, after storage at 50° C. and 75% RH for 1 week, were observed for changes in appearance. Granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate or that one of other additives specified below in Table 1.

TABLE 1

Additive	Changes in apperance after 1 week at 50° C. and 75% RH
The invention:	
Heavy magnesium carbonate	–
Magnesium oxide	–
Magnesium metasilicate aluminate	–
Synthetic hydrotalcite	–
Aluminum magnesium hydroxide	–
Magnesium silicate	–
Precipitated calcium carbonate	–
Magnesium hydroxide	–
Controls:	
Sodium carbonate	– (to yellow)
Potassium carbonate	– (to yellow)
Sodium hydrogen carbonate	– (to yellow)
Magnesium chloride	– – (to violet)
Magnesium sulfate	– – (to violet)
Calcium chloride	– – (to violet)
Aluminum silicate	– (to violet)
No additive (lactose)	– – (to violet)

Notes:
–: No changes in
–: Moderately
– –: Severely

As a result, no substantial changes in appearance were noted for the compositions supplemented with the additives of the invention.

Experimental Example 2

Granules were produced in the same manner as in Example 5 except that the compound (A), the compound (C), the compound (D), omeprazole or timoprazole was used instead of the compound (B). After storage at 50° C. and 75% RH for 1 week, they were observed for changes in appearance. As a control to each composition, granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate and stored under the same conditions.

Compound		Additive	Changes in appearance after 1 week at 50° C. and 75% RH
Compound (A)	Invention:	Heavy magnesium carbonate	–
	Control:	Lactose	+ +
Omeprazole	Invention:	Heavy magnesium carbonate	–
	Control:	Lactose	+ +
Timoprazole	Invention:	Heavy magnesium carbonate	–
	Control:	Lactose	+ +
Compound (C)	Invention:	Heavy magnesium carbonate	–
	Control:	Lactose	+ +
Compound (D)	Invention:	Heavy magnesium carbonate	–
	Control:	Lactose	+ +

Notes:
–: No change
+ +: Severely

As is evident from the above results, the pharmaceutical compositions of the invention were all stable whether the active ingredient was the compound (A), omeprazole, timoprazole, the compound (C) or the compound (D).

Experimental Example 3

Pharmaceutical conditions were produced in the same manner as in Example 3 and 5 except that different basic inorganic Mg or Ca salts were used or that lactose was used as a control, and Example 6. After strage at 50° C. and 75% RH for 1 week or at 40° C. for 6 months, the compositions were observed for changes in appearance and for active ingredient content (residual percentage).

TABLE 2

	Additive		Initial	50° C., 75% RH, 1 week	40° C., 6 months
	Tablets made by the procedure of Example 3				
Invention	Heavy magnesium carbonate	Appearance	White	No change	No change
		Content	100%	98.0%	99.5%
	Precipitated calcium carbonate	Appearance	White	No change	No change
		Content	100%	97.4%	96.5%
	Magnesium silicate	Appearance	White	No change	No change
		Content	100%	94.5%	95.0%
Control	No addition (lactose)	Appearance	Pale violet	Dark violet	Dark violet
		Content	100%	73.5%	82.1%
	Granudles made by the procedure of Example 5				
Invention	Heavy magnesium carbonate	Appearance	White	No change	No change
		Content	100%	98.2%	99.1%
	Precipitate calcium carbonate	Appearance	White	No change	No change
		Content	100%	97.2%	98.6%
	Magnesium oxide	Appearance	White	No change	No change
		Content	100%	99.4%	99.0%
Control	No addition (lactose)	Appearance	Pale violet	Dark violet	Dark violet
		Content	100%	84.2%	89.4%
	Capsules of Example 7				
Invention	Heavy magnesium carbonate	Appearance	White	No change	No change
		Content	100%	98.4%	99.1%

The above results clearly indicate that the compositions of the invention show no changes in appearance at all and are stable in terms of the active ingredient content.

What we claim is:

1. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of the anti-ulcer compound 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl]methylsulfinyl] benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3–20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

2. A pharmaceutical composition as claimed in claim 1, wherein the basic inorganic salt of magnesium is magnesium carbonate.

3. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of the anti-ulcer compound 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl] benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium

silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3–20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

* * * * *

EXHIBIT 2

PROPOSED CLAIM CONSTRUCTION OF THE DISPUTED TERMS OF CLAIMS 1 AND 2 OF U.S. PATENT NO. 5,045,321

Claim Language	Plaintiffs Proposed Construction	Defendants Proposed Construction
1. A pharmaceutical composition,	a medicinal drug product in a state suitable for administration to a patient	the mixture of lansoprazole with a basic inorganic salt of magnesium and/or calcium, which may contain any necessary additives that are used to make the tablet or granules but does not include any excipients used for coating the pharmaceutical composition
wherein the composition is made up into tablets or granules	term "granule" refers to a small pellet that is typically combined with other granules into a tablet or capsule	term "granules" means either an irregularly shaped or a spheroid shaped mass of particles made up of a pharmaceutical composition, which also may contain additives
and then coated by a coating agent,	"coated by a coating agent" refers to covering a tablet or granule with a pharmaceutically acceptable coating	"coated by a coating agent" means the tablets or granules containing the pharmaceutical composition are coated with a material that masks the taste or provides enteric or sustained release properties
which comprises an effective amount of the anti-ulcer compound 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl]methylsulfinyl] benzimidazole,	Ordinary meaning	Ordinary meaning
and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium	phrase "basic inorganic salt" is a proton acceptor salt containing an inorganic element	Ordinary meaning

hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide;		
the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight;	phrase "the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight" means that the ratio of basic inorganic salt to benzimidazole compound by weight in the pharmaceutical composition is between 0.3 and 20	phrase "the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3-20 parts by weight" means the weight of the basic inorganic salt that is in even contact with the benzimidazole falls between about 0.3 to 20 parts by weight
the benzimidazole compound being in contact with the basic inorganic salt evenly.	"the benzimidazole compound being in contact with the basic inorganic salt evenly" ("contact . .. evenly") means a mixture of the benzimidazole compound in contact with the basic (*i.e.*, alkaline) inorganic salt in a uniformly basic environment	"the benzimidazole compound being in contact with the basic inorganic salt evenly" means the benzimidazole compound and the inorganic salt are mixed homogenously together
2. A pharmaceutical composition as claimed in claim 1, wherein the basic inorganic salt of magnesium is magnesium carbonate.	Ordinary meaning	Ordinary meaning

EXHIBIT 3

REDACTED

EXHIBIT 4

MAIL ROOM MAY 21 1990 BOARD OF PATENT APPEALS & INTERFERENCES
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of

Tadashi MAKINO et al.

Serial No. 07/014,303 Group Art Unit: 125

Filed: February 13, 1987 Examiner: F. Waddell

For: *STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION*

RECEIVED 90 MAY 29 PM 2:22 GROUP 110

SECOND REPLY BRIEF

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

This is a Reply Brief to the Examiner's Answer on Remand (nominated as a "Supplemental Examiner's Answer") dated April 20, 1990. The appeal is maintained as to claims 16, 29 and 30.[1]

ORAL HEARING (RECONFIRMATION)

Appellants confirm their request for Oral Hearing (filed with the previous, March 16, 1990 Reply Brief.)

[1]The appeal is from the final rejection of claim 16 and the refusal to allow claims 29 and 30, entered via amendment after final rejection as per the remand from the Board. The appeal is expressly withdrawn as to claim 7.

The following comments are directed to the detailed comments concerning appellants' arguments newly presented at pages 7-9 of the April 20, 1990 Examiner's Answer on Remand.[2]

A mosaic combination of four (4) primary references and two (2) secondary references is spun together to make a rejection of the claims on the basis of obviousness under 35 USC § 103. The answer to the overall combination and specific comments as to two of the four primary references are found in the Appeal and first Reply Briefs, and will not be repeated here. The fact that the Examiner has essentially *ignored* key points in the Appeal and Reply Briefs, *including the absence of any "prior art" status under 35 USC §§ 102, 103 for one of the references* essential to this mosaic combination, cannot be overlooked.

NOHARA

The Examiner's Answer on Remand does not address the fact that Example 4 of the Nohara et al. '333 reference is *not* available as prior art against the applicants' invention, despite the fact that the Examiner relies on this disclosure as prior art.[3]

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[2]The remaining issues discussed in the Examiner's Answer on Remand have been treated in appellants' previous submissions, which will not be repeated.

[3]The previous submissions explain in detail why this portion of the reference is not available as prior art, yet the Examiner's Answer on Remand simply *ignores* this fact, without comment.

Not only is this reference not "prior art" under 35 USC §§ 102/103, it is also misconstrued in the Examiner's Answer on Remand, which states that "[t]he material of example 4 of the 4,689,333 [patent] are excipients and/or diluents." In fact, basic inorganic salts are not included among the list of carriers, excipients, disintegrators, lubricants and binders found at column 7, lines 8-13.[4] Needing to find a missing link in the prior art to reconstruct the claimed invention even in hindsight, the Examiner's Answer on Remand has *not* found such a link and reaches the bold, naked conclusion that the necessary teaching is present, when it manifestly is not.

The Examiner's Answer on Remand has effectively relied on hindsight to interpret the general disclosure of the reference as referring to mixtures of active ingredient with basic salt. Thus, even assuming, arguendo, the prior art status of Nohara, Nohara does not teach that which the Examiner's Answer on Remand says it does.

---

[4]Moreover, the specific examples listed in this section of the '333 reference are not supported in the original July 1985 disclosure. Compare column 7, lines 8-13 of the '333 reference with column 6, lines 53-60 of parent patent 4,628,098.

RAINER

The Examiner's Answer on Remand fails to contradict appellants' assertion that the Rainer et al. reference does not disclose or suggest any mixing of antacids with the picoline derivatives discovered by Rainer et al., much less mixing sufficient to establish even contact. The Examiner's Answer on Remand also fails to point to any other evidence of record remedying this deficiency. The generalizations contained in the Examiner's Answer on Remand are no substitute for evidence demonstrating any motivation for mixing antacids with the Rainer et al. picoline derivatives. The present record fails to establish any reason why the antacids would have to be mixed at all with the picoline derivatives in Rainer et al., much less any reason for continuing the mixing to the extent that even contact is obtained.

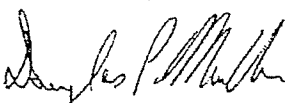
Similarly, the Examiner's Answer on Remand provides no evidence to support the generalized criticism of the Declaration that "routine mixing in the art is not seen to be less than five (5) minutes" at page 8 of the Examiner's Answer on Remand.

THE SECONDARY REFERENCES

With respect to the secondary references, the Examiner's Answer on Remand fails to point out any reasons why stabilizers found to be effective for the isocarbostyril compounds of the secondary references would be expected to be effective for the vastly different compounds of the present claims and the primary references. The generalization at page 9 of the Examiner's Answer on Remand that "it is obvious to employ the basic inorganic salts to stabilize any old pharmaceutical" clearly reflects an improper hindsight analysis.

Wherefore, in view of the foregoing Remarks and particularly the failure of the Examiner's Answer on Remand to address key issues essential to his rejection, reversal is requested.

Respectfully submitted,



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EXHIBIT 5

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EXHIBIT 6

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EXHIBIT 7

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was *even* worse, (e) [Archaic.] *emphasizing identity*: namely; particularly; as, one there was, *even* John.
2. in a smooth manner; showing regularity; evenly; as, the soldiers marched *even*. [Obs.]
3. in an even manner. [Obs.]
even if; though; despite the fact that.

ē-vēne′, *v.i.* to happen. [Obs.]

ē′ven-ēr, *n.* 1. one who or that which evens.
2. an equalizer in the form of a lever to govern the power applied: commonly applied to a doubletree.
3. in weaving, an appliance to spread the yarn on the beam.

ē′ven-fall, *n.* the first part of the evening; twilight. [Poet.]

ē′ven-hand, *n.* equality of rank. [Obs.]

ē′ven-hand″ed, *a.* impartial; equitable; just.

ē′ven-hand″ed-ly, *adv.* in an evenhanded manner.

ē′ven-hand″ed-ness, *n.* the state of being evenhanded.

ē′ven-ing, *n.* [ME. *evening*; AS. *æfnung*, evening, from *æfen*, even, eve.]
1. the last part of the day; close of the day and early part of night; period between sunset or the last meal of the day and bedtime.
2. in some parts of the South, in rural areas, and in parts of England, the period from noon through sunset and twilight.
3. a part of the night spent in a specified way; as, a musical *evening*.
4. the decline or latter part of anything; as, the *evening* of power; the *evening* of life.

ē′ven-ing, *a.* in, for, or of the evening.

ē′ven-ing dress (or **clōthes**), formal clothes worn on formal occasions in the evening and at night.

ē′ven-ing flow′ēr, in botany, any plant of the genus *Hesperantha*, common to South Africa, characterized by fragrant flowers which open in the evening.

ē′ven-ing gown, a woman's evening dress, usually long and décolleté.

ē′ven-ing grōs′bēak, a night-singing bird, *Coccothraustes vespertina*, common in North America.

ē′ven-ing prāyer (prār), same as *evensong*.

ē′ven-ing prim′rōse, an erect, biennial herb, *Œnothera biennis*, having yellow or white flowers opening in the evening.

ē′ven-ing stär, a bright planet, usually Venus, that can be seen in the western sky soon after sunset: also called *Vesper*, *Hesperus*.

ē′ven-ly, *adv.* [ME. *evenly*, *evenliche*; AS. *efenlice*, evenly.]
1. with an even, level, or smooth surface; without roughness, elevations, or depressions; as, things *evenly* spread.
2. equally; uniformly; as, *evenly* balanced.
3. in a level position; horizontally.
4. impartially; without bias.

ē′ven-mind″ed, *a.* characterized by evenness of temper or equanimity.

ē′ven-ness, *n.* [ME. *evennes*; AS. *efennys*, evenness, equality, from *efen*, even.] the state or quality of being even.

ē′ven-song, *n.* 1. a song or hymn to be sung in the evening.
2. in the Church of England, a form of worship to be said or sung in the evening; evening prayer.
3. in the Roman Catholic Church, vespers.
4. evening. [Archaic.]

ē-vent′, *n.* [L. *eventus*, *eventum*, an event, occurrence, from *evenire*, to happen; *e-*, out, and *venire*, to come.]
1. that which comes, arrives, or happens, especially an incident of importance; as, the course of *events*.
2. a consequence, a result; an outcome.
3 any one of a series of contests or items in a program; as, the automobile race is the next *event*.
Syn.—incident, occurrence, issue, result, consequence.

ē-vent′, *v.i.* to happen. [Obs.]

ē′ven-tem′pēred (-pērd), *a.* not quickly angered or excited; placid; calm.

ē-ven′tēr-āte, *v.t.*, to rip open; to disembowel. [Obs.]

ē-vent′ful, *a.* 1. full of outstanding events or incidents; as, an *eventful* period of history.
2. having an important outcome; momentous; as, an *eventful* conversation.
Syn.—important, critical, stirring, notable.

ē′ven-tīde, *n.* evening. [Archaic or Poet.]

ē-ven′ti-lāte, *v.t.* 1. to winnow; to fan. [Obs.]
2. to discuss. [Obs.]

ē-ven-ti-lā′tion, *n.* 1. the act of fanning; ventilation. [Obs.]
2. discussion. [Obs.]

ē-vent′less, *a.* lacking events or excitement; monotonous; uninteresting.

Ēv-en-tog′nā-thī, *n.pl.* [L., from Gr. *eu-*, well, *entos*, within, and *gnathos*, the jaw.] a group of teleost fishes found in fresh water, including the carps, chubs, etc.

ēv-en-tog′nā-thous, *a.* of or pertaining to the *Eventognathi*.

ē-ven-trā′tion, *n.* [L. *e-*, out, from, and *venter* (*-tris*), the belly.] in pathology, (a) evisceration; (b) the escape or protrusion of part of the viscera through a rupture in the abdominal wall.

ē-ven′tū-al, *a.* [L. *eventus*, an event.]
1. coming or happening as a consequence or result of anything; final; ultimate; as, *eventual* victory.
2. contingent; depending on future events or conditions.

ē-ven-tū-al′i-ty, *n.*; *pl.* **ē-ven-tū-al′i-ties**, 1. a possible event, outcome, or condition; contingency; as, we must be ready for any *eventualities*.
2. in phrenology, the faculty of remembering the sequence of occurrences or events.

ē-ven′tū-al-ly, *adv.* in the end; finally; ultimately.

ē-ven′tū-āte, *v.i.*; eventuated, *pl.*, *pp.*; eventuating, *ppr.* [L. *eventus*, event, and *-ate*.] to happen in the end; to result (often with *in*).

ē-ven-tū-ā′tion, *n.* the act or condition of eventuating.

ev′ēr, *adv.* [ME. *ever*, *evere*; AS. *æfre*, ever.]
1. at any time; at any period or point of time; as, have you *ever* seen the city of Paris, or shall you *ever* see it?
2. at all times; always; continually; as, *ever* fair.
3. repeatedly.
4. at all; by any chance; in any case; as, if it *ever* starts, we can go.
Ever is also used colloquially as an intensifier; as, was she *ever* tired!
ever and anon; at one time and another; now and then. [Archaic.]
ever so; extremely; very; as, *ever so* good. [Colloq.]
for ever and a day; forever.
or ever; before; as, *or ever* the silver cord be loosed. [Archaic.]

ev″ēr-dūr′ing, *a.* enduring forever; everlasting.

ev′ēr-glāde, *n.* a region of low, spongy land, usually flooded with water and covered with tall grass; swampland.

ev′ēr-green, *a.* having green leaves throughout the year; as, the pine is an *evergreen* tree: opposed to *deciduous*.

ev′ēr-green, *n.* 1 a plant that retains its leaves through all the seasons, as the conifers, holly, etc.
2. [*pl.*] the twigs and branches of any evergreen species, used for ornamentation.


EVERGREEN TREE

ev′ēr-ich, *a.* every. [Obs.]

ev″ēr-ich-ōn′, *pron.* every one. [Obs.]

ev-ēr-lāst′ing, *a.* 1. lasting forever; eternal; immortal.
2. perpetual; continuing indefinitely or during the present state of things; durable; as, the *everlasting* hills.
3. going on too long; seeming never to stop; tiresome; as, *everlasting* disputes.

ev-ēr-lāst′ing, *n.* 1. eternity.
2. any of various plants, from the permanence of the color and form of their dry flowers, as cudweeds, immortelles, etc.
3. a stout, ribbed woolen cloth; lasting.
the Everlasting; God.

ev-ēr-lāst′ing-ly, *adv.* 1. in an everlasting manner.
2. very; excessively. [Colloq.]

ev-ēr-lāst′ing-ness, *n.* the state of being everlasting.

ev-ēr-liv′ing, *a.* living without end; eternal.

ev-ēr-mōre′, *adv.* always; eternally; at all times; as, happy *evermore*: used also as a substantive, as, for *evermore*.

Ē-vēr′ni-á, *n.* [L., from Gr. *euernēs*, sprouting well; *eu-*, well, and *ernos*, a sprout.] a small genus of lichens.

ē-vērse′, *v.t.* to overthrow or subvert. [Obs.]

ē-vēr′si-ble, *a.* that can be everted.

ē-vēr′sion, *n.* [L. *eversio* (*-onis*), an overthrowing, from *eversus*, pp. of *evertere*, to overthrow.]
1. an overthrowing; destruction. [Obs.]
2. a turning or rolling backward or inside out.
eversion of the eyelids; ectropion, a condition in which the eyelids are turned outward, so as to expose the red internal tunic.

ē-vēr′sive, *a.* designed or tending to evert; subversive. [Obs.]

ē-vērt′, *v.t.* [L. *evertere*, to overthrow; *e-*, out, from, and *vertere*, to turn.]
1. to overturn; to overthrow. [Obs.]
2. to cause to turn inside out.

ē-vēr′tē-brăl, *a.* [L. *e-* priv., and *vertebra*, vertebra.] not vertebral in origin or character, as the anterior portion of the skull.

Ē-vēr′tē-brā′tà, *n.pl.* same as *invertebrata*.

ē-vēr′tē-brāte, *a* and *n.* same as *invertebrate*.

ē-vēr′tŏr, *n.* a muscle that everts a part, especially the foot.

ev′ēr-y, *a.* [ME. *every*, *everi*; AS. *æfre ælc*.]
1. all, as of the items or individuals constituting an aggregate, considered separately; each, taken as part of an aggregate.
2. all possible; as, he was given *every* chance to do the job.
3. each interval of (a specified number or time); as, he arrives *every* three days.
every bit; in all points; fully; quite; as, that is *every bit* as good.
every each; every one. [Obs.]
every now and then; from time to time; now and then.
every other; each alternate; as, *every other* Saturday was a holiday.

ev′ēr-y, *pron.* each; everyone. [Obs.]

ev′ēr-y-bod″y, *n.* every person; everyone.

ev′ēr-y-dāy, *a.* 1 daily; as, one's *everyday* routine.
2. suitable for every ordinary day; as, *everyday* shoes.
3. usual; common; as, an *everyday* occurrence.

ev′ēr-y-one (-wun), *pron.* everybody; every person.

ev′ēr-y one, 1. everyone.
2. every person or thing.

ev′ēr-y-thing, *n.* 1. every thing; all things; all; as, *everything* in human life is interesting.
2. all things pertinent.
3. that which is of the greatest value or importance; as, a good reputation is *everything* to a woman.

ev′ēr-y-when, *adv.* at every point in time; always.

ev′ēr-y-where (-hwār), *adv.* [ME. *everihwar*, everywhere, *ever*, *evere*, ever, and *ihwar*, everywhere, from AS. *gehwær*, everywhere.] in every place; in all places.

ev′ēr-y-where″ness, *n.* omnipresence. [Rare.]

ev′ēr-y-whith″ēr, *adv.* in or to every place or direction. [Rare.]

ē-ves′ti-gāte, *v.t.* to investigate. [Obs.]

ev′et, *n.* [AS. *efete*, a newt.] an eft; a newt.

ē-vī′brāte, *v.i.* to vibrate. [Obs.]

ē-vict′, *v.t.*; evicted, *pt.*, *pp.*; evicting, *ppr.* [L. *evictus*, pp. of *evincere*, to overcome, prevail; *e-*, from, and *vincere*, to conquer.]
1. to put (a tenant) out by a judicial process or course of legal proceedings; to expel from lands or tenements by law.
2. in law, formerly, to recover (property) through court judgment or superior claim.
3. to convince; to prove. [Obs.]
4. to expel by force.

ē-vic′tion, *n.* [LL. *evictio* (*-onis*), from L. *evictus*, pp. of *evincere*, to evict.]
1. the act of evicting or the condition of being evicted.
2. proof; conclusive evidence. [Obs.]

ev′i-dence, *n.* [ME. *evidence*; OFr. *evidence*, evidence; L. *evidentia*, clearness, from *evidens* (*-entis*), clear, evident; *e-*, from, and *videre*, to see.]
1. the condition of being evident.
2. something that makes another thing evident; indication; sign.
3. something that tends to prove; ground for belief.
4. in law, (a) something legally presented before a court, as a statement of a witness, an object, etc., which bears on or establishes the point in question: distinguished from *testimony* and *proof*; (b) a person who presents testimony; witness; as, state's *evidence*.
in evidence; plain; visible; conspicuous; as, his nose was very much *in evidence*.
king's or *queen's evidence*; in English law, state's evidence.

EXHIBIT 8

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EXHIBIT 9

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15

Sustained- and Controlled-Release Drug Delivery Systems

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I. INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained- or controlled-release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained- or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.

If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for the duration of treatment, whether it be for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors, or to localization to cells or to specific areas of the body.

It is obvious that this imaginary delivery system will have changing requirements for different disease states and different drugs. Thus, we wish to deliver the therapeutic agent to a specific site, for a specific time. In other words, the objective is to achieve both spatial and temporal placement of drug. Currently, it is possible to only partially achieve both of these goals, with most drug delivery systems.

In this chapter, we present the theory involved in developing sustained- and controlled-release delivery systems and applications of these systems as therapeutic devices. Although suspensions, emulsions, and compressed tablets may demonstrate sustaining effects within the body, compared with solution forms of the drug, they are not considered to be sustaining and

are not discussed in this chapter. These systems classically release drug for a relatively short period, and their release rates are strongly influenced by environmental conditions.

II. TERMINOLOGY

In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Although descriptive terms such as "timed release" and "prolonged release" gives excellent manufacturer identification, they can be confusing to health care practitioners. For purposes of this chapter, sustained release and controlled release will represent separate delivery processes. *Sustained release* constitutes any dosage form that provides medication over an extended time. *Controlled release*, however, denotes that the system is able to provide some actual therapeutic control, whether this be of a temporal nature, spatial nature, or both. In other words, the system attempts to control drug concentrations in the target issue. This correctly suggests that there are sustained-release systems that cannot be considered controlled-delivery systems.

In general, the goal of a sustained-release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain *zero-order* release from the dosage form. Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration-dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat-action tablets are an alternative method of sustained release in which multiple doses of a drug are contained within a dosage form, and each dose is released at a periodic interval. Delayed-release systems, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun. Enteric-coated tablets are an example of this type of dosage form.

Controlled-release, although resulting in a zero-order delivery system, may also incorporate methods to promote localization of the drug at an active site. In some cases, a controlled-release system will not be sustaining, but will be concerned strictly with localization of the drug. *Site-specific* systems and *targeted-delivery* systems are the descriptive terms used to denote this type of delivery control.

The ideal of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, enterohepatic recycling, sweat, fecal, and so on. Since, for most drugs, these elimination processes are first-order, it can be said that at a certain blood level, the drug will have a specific rate of elimination. The idea is to delivery drug at this exact rate for an extended period. This is represented mathematically as

$$\text{Rate in} = \text{rate out} = k_{elim} \times C_d \times V_d$$

where C_d is the desired drug level, V_d is the volume of distribution, and k_{elim} the rate constant for drug elimination from the body. Often such exacting delivery rates prove to be difficult to achieve by administration routes other than intravenous infusion. Noninvasive routes (e.g., oral) are obviously preferred.

Figure 1 shows comparative blood level profiles obtained from administration of conventional, controlled-, and sustained-release dosage forms. The conventional tablet or capsule provides only a single and transient burst of drug. A pharmacological effect is seen as long as the amount of drug is within the therapeutic range. Problems occur when the peak concentration is above or below this range, especially for drugs with narrow therapeutic windows. The slow first-order release obtained by a sustained-release preparation is generally achieved by slowing the release of drug from a dosage form. In some cases, this is accomplished by a continuous release process; however, systems that release small bursts of drug over a prolonged period can mimic the continuous-release system.

III. ORAL SYSTEMS

Historically, the oral route of administration has been used the most for both conventional and novel drug delivery systems. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. The types of sustained- and controlled-release systems employed for oral administration include virtually every currently known theoretical mechanism for such application. This is because there is more flexibility in dosage design, since constraints, such as sterility and potential damage at the site of administration, are minimized. Because of this, it is convenient to discuss the different types of dosage forms by using those developed for oral administration as initial examples.

With most orally administered drugs, targeting is not a primary concern, and it is usually intended for drugs to permeate to the general circulation and perfuse to other body tissues (the obvious exception being medications intended for local gastrointestinal tissue treatment). For this reason, most systems employed are of the sustained-release variety. It is assumed that increasing concentration at the absorption site will increase the rate of absorption and, therefore, increase circulating blood levels which, in turn, promotes greater concentrations of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through the biological milieu, and absorption through an epithelial membrane to

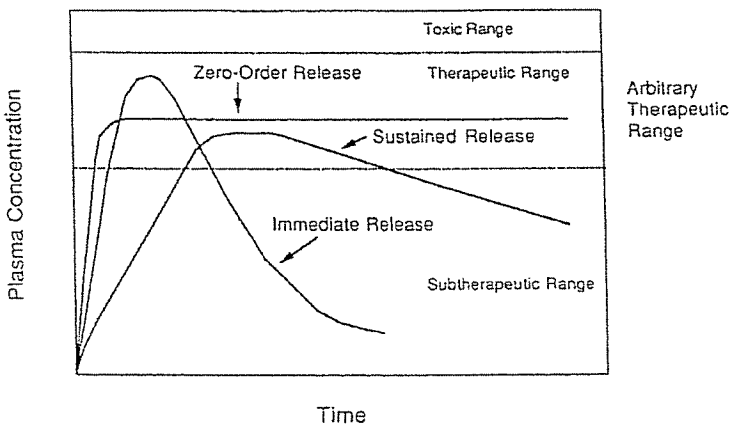


Fig. 1 Drug level versus time profile showing differences between zero-order controlled release, slow first-order sustained release, and release from a conventional tablet or capsule.

the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such systems.

A. Biological Factors Influencing Oral Sustained-Release Dosage Form Design

Biological Half-Life

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion, and all other processes that permanently remove drug from the bloodstream.

Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency. However, this is limited, in that drugs with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 hr, such as furosemide or levodopa [1], are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hr, are also generally not used in sustaining forms, since their effect is already sustained. Digoxin, warfarin, and phenytoin are some examples [1]. Furthermore, the transit time of most dosage forms in the gastrointestinal (GI) tract (i.e., mouth to ileocecal junction) is 8–12 hr, making it difficult to increase the absorptive phase of administration beyond this time frame. Occasionally, absorption from the colon may allow continued drug delivery for up to 24 hr.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained-release product. Since the purpose of forming a sustained-release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs and devices in the absorptive areas of the GI tract is about 8–12 hr, the maximum half-life for absorption should be approximately 3–4 hr; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17–0.23 hr^{-1} to give 80–95% over this time period [3]. The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining systems.

The foregoing calculations assume that absorption for the therapeutic agent occurs at a relatively uniform rate over the entire length of the small intestine. For many compounds, this is not true. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorption. Absorption of ferrous sulfate, for example, is maximal in the upper jejunum and duodenum, and sustained-release mechanisms that do not release drug before passing out of this region are not beneficial [5].

One method to provide sustaining mechanisms of delivery for compounds such as these has been to try to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that coadministration of food results in a sustaining effect [6]. Although administration of food can create highly variable effects, there have been methods devised to

circumvent this problem. One such attempt is to formulate low-density pellets, capsules [7], or tablets [8]. These float on top of the gastric juice, delaying their transfer out of the stomach [9]. The increase in gastric retention results in higher blood levels for *p*-aminobenzoic acid, a drug with a limited GI absorption range [10], however, drugs that have widespread absorption in the intestinal system would likely not benefit from an increase in emptying time [11].

Another approach is that of bioadhesive materials. The principle is to administer a device with adhesive polymers having an affinity for the gastric surface, most probably the mucin coat [12]. Bioadhesives have demonstrated utility in the mouth, eye, and vagina, with a number of commercially available products. To date, use of bioadhesives in oral drug delivery is a theoretical possibility, but no promising leads have been published.

An alternative to GI retention for drugs with poor absorption characteristics, is to use chemical penetration enhancers. Membrane modification through chemical enhancers has been very well demonstrated for a variety of tissues in the body, including the gastrointestinal tract. Concern about this approach is the potential toxicity that may arise when protective membranes are altered. Although there are numerous safety studies for oral products containing surfactants, which are known penetration enhancers, there has not been a definitive safety study in humans using an agent that is specifically present in the formulations as a penetration enhancer.

Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite. For example, aloprenolol was more extensively metabolized in the intestinal wall when given as a sustained-release preparation [13]. High concentrations of dopa-decarboxylase in the intestinal wall will result in a similar effect for levodopa [14]. If levodopa is formulated in a dosage form with a drug compound that can inhibit the dopa-decarboxylase enzyme, the amount of levodopa available for absorption increases and can sustain its therapeutic effects. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

B. Physicochemical Factors Influencing Oral Sustained-Release Dosage Form Design

Dose Size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5–1.0 g is considered maximal for a conventional dosage form [15]. This also holds for sustained-release dosage forms. Those compounds that require a large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amounts of a drug with a narrow therapeutic range.

Ionization, pK_a, and Aqueous Solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pK_a of the compound and the absorptive environment. It would seem, untuitively, that presenting the drug in an uncharged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to an uncharged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. Considering

that these dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release processes must be defined. For many compounds, the site of maximum absorption will also be the area in which the drug is the least soluble. As an example, consider a drug for which the highest solubility is in the stomach and is uncharged in the intestine. For conventional dosage forms, the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For dissolution- or diffusion-sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release.

Compounds with very low solubility (less than 0.01 mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. Examples of drugs that are limited in absorption by their dissolution rate are digoxin [16], griseofulvin [17], and salicylamide [18]. The lower limit for the solubility of a drug to be formulated in a sustained-release system has been reported to be 0.1 mg/ml [19], so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in a sustained delivery system. Diffusional systems will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

Partition Coefficient

When a drug is administered to the GI tract it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. *Partition coefficient* is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore, these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells. Phenothiazines are representative of this type of compound [20]. Compounds with very low partition coefficients will have difficulty penetrating membranes, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

Stability

Orally administered drugs can be subject to both acid–base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in the solid state; therefore, this is the preferred composition of delivery for problem cases. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drug is delivered in the small intestine and, hence, is subject to degradation. Propantheline [21] and probanthine [22] are representative examples of such drugs.

C. Oral Sustained- and Controlled-Release Products

Because of their relative ease of production and cost, compared with other methods of sustained or controlled delivery, dissolution and diffusion-controlled systems have classically been of

primary importance in oral delivery of medication. Dissolution systems have been some of the oldest and most successful oral systems in early attempts to market sustaining products.

D. Dissolution-Controlled Systems

It seems inherently obvious that a drug with a slow dissolution rate will demonstrate sustaining properties, since the release of drug will be limited by the rate of dissolution. This being true, sustained-release preparations of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier. Representative products using dissolution-controlled systems are listed in Tables 1 and 2.

Dissolution-controlled systems can be made to be sustaining in several different ways. By alternating layers of drug with rate-controlling coats, as shown in Fig. 2, a pulsed delivery can be achieved. If the outer layer is a quickly releasing bolus of drug, initial levels of drug in the body can be quickly established with pulsed intervals following. Although this is not a true controlled-release system, the biological effects can be similar. An alternative method is to administer the drug as a group of beads that have coatings of different thicknesses. This is also shown in Fig. 3. Since the beads have different coating thicknesses, their release will occur in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at later times will be achieved from those with thicker coatings. This is the principle of the Spansule capsule marketed by SmithKline Beecham.

This dissolution process can be considered to be diffusion-layer controlled. This is best explained by considering the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film as the rate-determining step. This dissolution process at steady state is described by the Noyes–Whitney equation:

$$\frac{dC}{dt} = k_D A(C_s - C) = \frac{D}{h} A(C_s - C) \tag{1}$$

where

dC/dt = dissolution rate
k_D = dissolution rate constant
D = diffusion coefficient
C_s = saturation solubility of the solid
C = concentration of solute in the bulk solution

It can be seen that the dissolution rate constant k_D is equivalent to the diffusion coefficient divided by the thickness of the diffusion layer (D/h).

Equation (1) predicts that the rate of release can be constant only if the following parameters are constant: (a) surface area, (b) diffusion coefficient, (c) diffusion layer thickness, and (d) concentration difference. These parameters, however, are not easily maintained constant, especially surface area. For spherical particles, the change in surface area can be related to the weight of the particle; that is, under the assumption of sink conditions, Eq. (1) can be rewritten as the cube-root dissolution equation:

$$W_0^{1/3} - W^{1/3} = k_D t \tag{2}$$

where k_D is the cube-root dissolution rate constant, W_0 and W are the initial weight and the weight of the amount remaining at time t, respectively.

Table 1 Encapsulated Dissolution Products

Product	Active ingredient(s)	Manufacturer
Ornade Spansules	Phenylpropanolamine hydrochloride, chlorpheniramine maleate	Smith Kline Beecham
Thorazine Spansules	Chlorpromazine hydrochloride	Smith Kline Beecham
Contac 12-Hour capsules	Phenylpropanolamine hydrochloride, chlorpheniramine maleate, atropine sulfate, scopolamine hydrobromide, hyoscyamine sulfate	Smith Kline Consumer Products
Artane Sequels	Trihexyphenidyl hydrochloride	Lederle
Diamox Sequels	Acetazolamide	Lederle
Nicobid Temples	Nicotinic acid	Rorer
Pentritol Temples	Pentaerythritol tetranitrate	Rorer
Chlor-Trimeton Repetabs	Chlorpheniramine maleate	Schering
Demazin Repetabs	Chlorpheniramine maleate, phenylephrine hydrochloride	Schering
Polaramine Repetabs	Dexchlorpheniramine maleate	Schering

E. Diffusional Systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices. These will be considered separately.

Reservoir Devices

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of

Table 2 Matrix Dissolution Products

Product (tablets)	Active ingredient(s)	Manufacturer
Dimetane Extentabs	Brompheniramine maleate	Robins
Dimetapp Extentabs	Brompheniramine maleate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride	Robins
Donnatal Extentabs	Phenobarbital, hyoscyamine sulfate, atropine sulfate, scopolamine hydrobromide	Robins
Quinidex Extentabs	Quinidine sulfate	Robins
Mestinon Timespans	Pyridostigmine bromide	ICN
Tenuate Dospan	Diethylpropion hydrochloride	Merrel
Disophrol Chronotabs	Dexbrompheniramine maleate, pseudoepherine sulfate	Schering

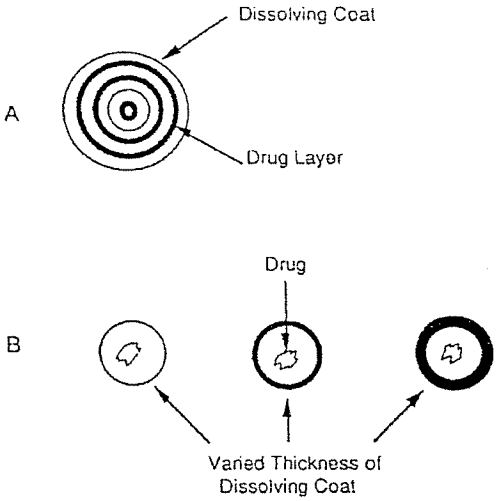


Fig. 2 Two types of dissolution-controlled, pulsed delivery systems: (A) single bead-type device with alternating drug and rate-controlling layers; (B) beads containing drug with differing thickness of dissolving coats.

release of drug from the system. A schematic description of this process is given in Fig. 4, and characteristics of the system are listed in Table 3.

The process of diffusion is generally described by a series of equations that were first detailed by Fick [23]. The first of these states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane. The equation is given as

$$J = -D\frac{dC}{dX} \tag{3}$$

where the flux J, given in units of amount/area–time, D is the diffusion coefficient of the drug in the membrane in units of area/time. This is a reflection of the drug molecule's ability to diffuse through the solvent and is dependent on such factors as molecular size and charge.

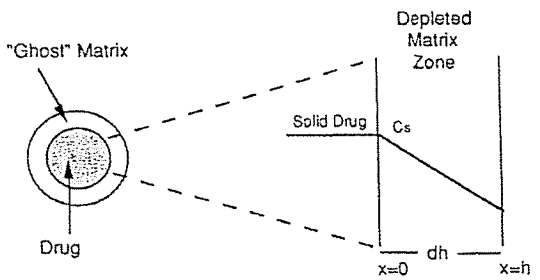


Fig. 3 Schematic representation of a matrix release system. C_s is the saturation concentration of drug controlling the concentration gradient over the distance h, of the remaining ghost matrix.

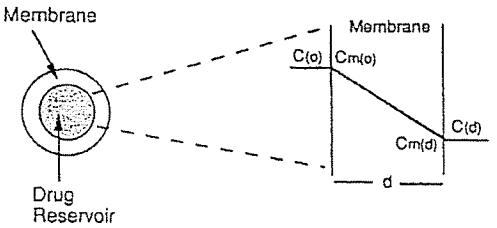


Fig. 4 Schematic representation of a reservoir diffusional device. $C_{m(0)}$ and $C_{m(d)}$ represent concentrations of drug at inside surfaces of the membrane and $C_{(0)}$ and $C_{(d)}$ represent concentrations in the adjacent regions. (From Ref. 29.)

This coefficient may be dependent on concentration [24]; hence, its designation as a coefficient and not a constant, although for the purpose of designing a pharmaceutical system it is usually considered a constant [25]. dC/dX represents the rate of change in concentration C relative to a distance X in the membrane.

It is useful to make the assumption that a drug on either side of the membrane is in equilibrium with its respective membrane surface. There is, then, an equilibrium between the membrane surfaces and their bathing solutions as shown in Fig. 4. This being so, the concentration just inside the membrane surface can be related to the concentration in the adjacent region by the following expressions:

$$K = \frac{C_{m(0)}}{C_{(d)}} \quad \text{at } x = 0 \tag{4}$$

$$K = \frac{C_{m(d)}}{C_{(d)}} \quad \text{at } x = d \tag{5}$$

where K is the partition coefficient. This coefficient denotes the ratio of drug concentration in the membrane to that in the bathing medium at equilibrium. In general, a hydrophilic molecule will partition favorably to the medium, whereas a hydrophobic compound will preferentially partition to the polymer. C_m is the concentration of drug on the inside surface of the membrane, $C_{m(d)}$ the concentration on the outside surface, and d the thickness of the diffusion layer, the diffusional path length.

Assuming that D and K are constant, Eq. (3) can be integrated and simplified to give

$$J = \frac{DK\Delta C}{d} \tag{6}$$

Table 3 Characteristics of Reservoir Diffusional Systems

Description	Drug core surrounded by polymer membrane that controls release rate
Advantages	Zero-order delivery is possible
	Release rate variable with polymer type
Disadvantages	System must be physically removed from implant sites
	Difficult to deliver high-molecular-weight compounds
	Generally increased cost per dosage unit
	Potential toxicity if system fails

Where ΔC is the concentration difference across the membrane. The other variables are as defined previously. Drug release will vary, depending on the geometry of the system. The simplest system to consider is that of a slab, where drug release is from only one surface, as shown in Fig. 5. In this case, Eq. (6) can be written as

$$\frac{dM_t}{dt} = \frac{ADK\Delta C}{d} \tag{7}$$

where M_t is the mass of drug released after time t, dM_t/dt the steady-state release rate at time t, and A the surface area of the device. Equations of a similar form can be written for other geometries, such as spheres or cylinders [26].

Since the left side of Eq. (7) represents the release rate of the system, a true controlled-release system with a zero-order release rate can be possibly only if all of the variables on the right side of Eq. (7) remain constant. A constant effective area of diffusion, diffusional path length, concentration difference, and diffusion coefficient are required to obtain a release rate that is constant. These systems often fail to deliver at a constant rate, since it is especially difficult to maintain all these parameters constant. The use of a solid drug core reservoir results in a constant effective concentration, that of the solubility of the drug. Often, however, the polymer may be affected by the bathing medium. Swelling or contraction of the polymer membrane causes a change in the diffusional path length of the diffusion coefficient of the drug through the barrier. For example, if the polymer swells, the diffusion path length will increase. The ability of the drug to diffuse through the membrane, however, will increase. This is because the diffusion coefficient of the drug in the bathing medium, which has perfused the polymer during swelling, will be greater than in the unswelled polymer.

Although the partition coefficient is expected to remain constant, its magnitude is important. Since this coefficient represents the concentration of drug in the membrane relative to that in the core, an excessively high partition coefficient will allow quick depletion of the core and an ineffective delivery system. For effective diffusional systems, the partition coefficient should be less than unity. If the value of this coefficient is greater than 1, the surrounding polymer does not represent a barrier, and drug release becomes first-order.

Although diffusional systems can provide constant release at steady state, they will demonstrate initial release rates, which may be faster or slower. This depends on the device [27]. For reservoir devices, a system that is used relatively soon after construction will demonstrate a large time in release, since it will take time for the drug to diffuse from the reservoir to the membrane surface. On the other hand, systems that are stored will demonstrate a burst effect, since, on standing, the membrane becomes saturated with available drug. The magnitude of these effects is dependent on the diffusing distance (i.e., the membrane thickness). Figure 6 gives examples of this phenomenon. This plot shows the approach to steady-state release for

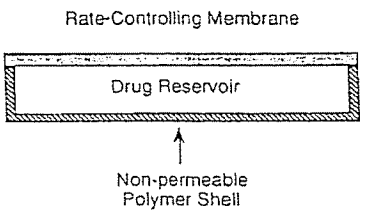


Fig. 5 Diagrammatic representation of the slab configuration of a reservoir diffusional system.

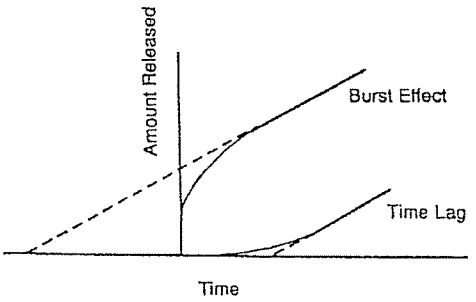


Fig. 6 Plot showing the approach to steady state for a reservoir device that has been stored for an extended period (the burst effect curve) and for a device that has been freshly made (the lag time curve). (From Ref. 29.)

a typical reservoir device that has been stored (burst effect), and for a device that has been freshly made (time lag).

Reservoir diffusional systems have several advantages over conventional dosage forms. They can offer zero-order release of drug, the kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions. The inherent disadvantages are that, unless the polymer used is soluble, the system must somehow be removed from the body after the drug has been released. This is an important dosage form consideration with implantable systems. A silicone elastomer reservoir has been used to orally deliver iodine, through the water supply, to large populations suffering from deficiency [28]. For a system such as this, the nonerodible device poses no significant problem; however, the appearance of the drug-depleted matrix in the stool can often alarm a naive patient.

Another important point to consider is that, in general, the amount of drug contained in the reservoir is far greater than the usual dose needed, since the dosage form is designed to sustain delivery over many dosing intervals. Any error in production or any accidental damage to the dosage form that would directly expose the reservoir core could expose the patient to a potentially toxic dose of drug. This becomes important when designing these dosage forms for drugs with narrow therapeutic ranges or high toxicity. Table 4 gives a representative listing of available products employing reservoir diffusion systems.

Matrix Devices

A matrix device, as the name implies, consists of drug dispersed homogeneously throughout a polymer matrix as represented in Fig. 7. In the model, drug in the outside layer exposed to

Table 4 Reservoir Diffusional Products

Product	Active ingredient(s)	Manufacturer
Duotrate	Pentaerythritol tetranitrate	Jones
Nico-400	Nicotinic acid	Jones
Nitro-Bid	Nitroglycerin	Marion
Cerespan	Papaverine hydrochloride	Rhône-Poulenc Rorer
Nitrospan	Nitroglycerin	Rorer
Measurin	Acetylsalicylic acid	Sterling Winthrop

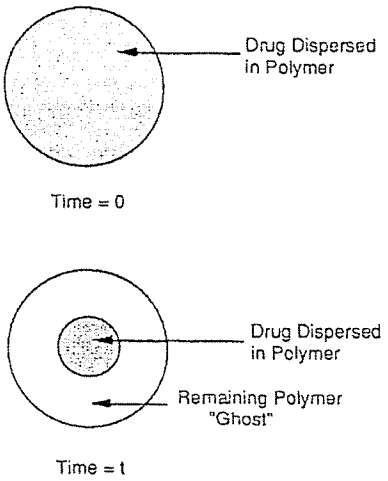


Fig. 7 Matrix diffusional system before drug release (time = 0) and after partial drug release (time = t).

the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. Obviously, for this system to be diffusion-controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions [29,30]: (a) a pseudo-steady state is maintained during drug release, (b) the diameter of the drug particles is less than the average distance of drug diffusion through the matrix, (c) the bathing solution provides sink conditions at all times, (d) the diffusion coefficient of drug in the matrix remains constant (i.e., no change occurs in the characteristics of the polymer matrix).

The next equations, which describe the rate of release of drugs dispersed in an inert matrix system, have been derived by Higuchi [29]. The following equation can be written based on Fig. 3:

$$\frac{dM}{dh} = C_0\, dh - \frac{C_s}{2} \tag{8}$$

where

dM = change in the amount of drug released per unit area
dh = change in the thickness of the zone of matrix that has been depleted of drug
C_0 = total amount of drug in a unit volume of the matrix
C_s = saturated concentration of the drug within the matrix.

From diffusion theory,

$$dM = \frac{D_m C_s}{h}\, dt \tag{9}$$

where D_m is the diffusion coefficient in the matrix. Equating Eqs. (8) and (9), integrating, and solving for h gives

$$M = [C_s D_m (2C_0 - C_s)t]^{1/2} \tag{10}$$

When the amount of drug is in excess of the saturation concentration, that is, $C_0 >> C_s$

$$M = (2C_s D_m C_0 t)^{1/2} \tag{11}$$

which indicates that the amount of drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

$$M = \left[D_s C_s \frac{p}{T} (2C_0 - pC_s)t \right]^{1/2} \tag{12}$$

where

p = porosity of the matrix
T = tortuosity
C_s = solubility of the drug in the release medium
D_s = diffusion coefficient in the release medium

This system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly.

For purposes of data treatment, Eq. (11) or (12) can be reduced to

$$M = kt^{1/2} \tag{13}$$

where k is a constant, so that a plot of amount of drug released versus the square root of time will be linear, if the release of drug from the matrix is diffusion-controlled. If this is the case, then, by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying the following parameters [31–35]: (a) initial concentration of drug in the matrix, (b) porosity, (c) tortuosity, (d) polymer system forming the matrix, and (e) solubility of the drug.

Matrix systems offer several advantages. They are, in general, easy to make and can be made to release high-molecular-weight compounds. Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although, occasionally, cracking of the matrix material can cause unwanted release. The primary disadvantages of this system are that the remaining matrix "ghost" must be removed after the drug has been released. Also, the release rates generated are not zero-order, since the rate varies with the square root of time. A substantial sustained effect, however, can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order. The characteristics of the system are summarized in Table 5, and a representative listing of available products is given in Table 6.

Table 5 Characteristics of Matrix Diffusion Systems

Description	Homogeneous dispersion of solid drug in a polymer mix
Advantages	Easier to produce than reservoir devices
	Can deliver high-molecular-weight compounds
Disadvantages	Cannot obtain zero-order release
	Removal of remaining matrix is necessary for implanted systems

Table 6 Matrix Diffusional Products

Product (tablets)	Active ingredient(s)	Manufacturer
Desoxyn-Gradumet	Methamphetamine hydrochloride	Abbott
Fero-Gradumet	Ferrous sulfate	Abbott
Tral Filmtab	Hexocyclium methylsulfate	Abbott
PBZ-SR	Tripelennamine	Geigy
Procan SR	Procainamide hydrochloride	Parke-Davis
Choledyl SA	Oxtriphylline	Parke-Davis

F. Bioerodible and Combination Diffusion and Dissolution Systems

Strictly speaking, therapeutic systems will never be dependent on dissolution only or diffusion only. However, in the foregoing systems, the predominant mechanism allows easy mathematical description. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion-controlled. Bioerodible devices, however, constitute a group of systems for which mathematical descriptions of release characteristics can be quite complex. Characteristics of this type of system are listed in Table 7. A typical system is shown in Fig. 8. The mechanism of release from simple erodible slabs, cylinders, and spheres has been described [36]. A simple expression describing release from all three of these erodible devices is

$$\frac{M_t}{M} = 1 - \left(1 - \frac{k_0 t}{C_0 a}\right)^n \tag{14}$$

where $n = 3$ for a sphere, $n = 2$ for a cylinder, and $n = 1$ for a slab. The radius of a sphere, or cylinder, or the half-height of a slab is represented by a. M_t is the mass of a drug release at time t and M is the mass released at infinite time. As a further complication, these systems can combine diffusion and dissolution of both the matrix material and the drug. Drug not only can diffuse out of the dosage form, as with some previously described matrix systems, but the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that, as the polymer dissolves, the diffusional path length for the drug may change. This usually results in a moving-boundary diffusion system. Zero-order release can occur only if surface erosion occurs and surface area does not change with time. The inherent advantage of such a system is that the bioerodible property of the matrix does not result in a ghost matrix. The disadvantages of these matrix systems are that release kinetics are often hard to control, since many factors affecting both the drug and the polymer must be considered.

Table 7 Characteristics of Bioerodible Matrix Systems

Description	A homogeneous dispersion of drug in an erodible matrix
Advantages	All the advantages of matrix dissolution system
	Removal from implant sites is not necessary
Disadvantages	Difficult to control kinetics owing to multiple processes of release
	Potential toxicity of degraded polymer must be considered

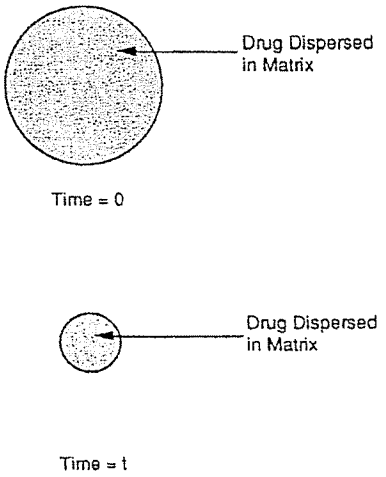


Fig. 8 Representation of a bioerodible matrix system. Drug is dispersed in the matrix before release at time = 0. At time = t, partial release by drug diffusion or matrix erosion has occurred.

Another method for the preparation of bioerodible systems is to attach the drug directly to the polymer by a chemical bond [37]. Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. This makes control of the rate of release somewhat easier. Another advantage of the system is the ability to achieve very high drug loading, since the amount of drug placed in the system is limited only by the available sites on the carrier.

A third type, which in this case utilizes a combination of diffusion and dissolution, is that of a swelling-controlled matrix [38]. Here the drug is dissolved in the polymer, but instead of an insoluble or eroding polymer, as in previous systems, swelling of the polymer occurs. This allows entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate, drug solubility, and the amount of soluble fraction in the matrix [39]. This system usually minimizes burst effects, since polymer swelling must occur before drug release.

G. Osmotically Controlled Systems

In these systems, osmotic pressure provides the driving force to generate controlled release of drug. Consider a semipermeable membrane that is permeable to water, but not to drug. A tablet containing a core of drug surrounded by such a membrane is shown in Fig. 9. When this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference. The rate of flow, dV/dt, of water into the device can be represented as

$$\frac{dV}{dt} = \frac{Ak}{h(\Delta\Pi - \Delta P)} \tag{15}$$

where

k = membrane permeability
A = area of the membrane

h = membrane thickness
$\Delta\Pi$ = osmotic pressure difference
ΔP = hydrostatic pressure difference

These systems generally appear in two different forms, as depicted in Fig. 9. The first contains the drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference. The second system contains the drug in solution in an impermeable membrane within the device. The electrolyte surrounds the bag. Both systems have single or multiple holes bored through the membrane to allow drug release. In the first example, high osmotic pressure can be relieved only by pumping solution, containing drug, out of the hole. Similarly, in the second example, the high osmotic pressure causes compression of the inner membrane, and drug is pumped out through the hole.

In the system with the bag, or if the hole is large enough in either system, the hydrostatic difference becomes negligible, and Eq. (15) becomes

$$\frac{dV}{dt} = \frac{Ak}{h(\Delta\Pi)} \tag{16}$$

indicating that the flow rate of water into the tablet is governed by permeability, area, and thickness of the membrane. The rate of drug leaving the orifice, dM/dt, is equivalent to the

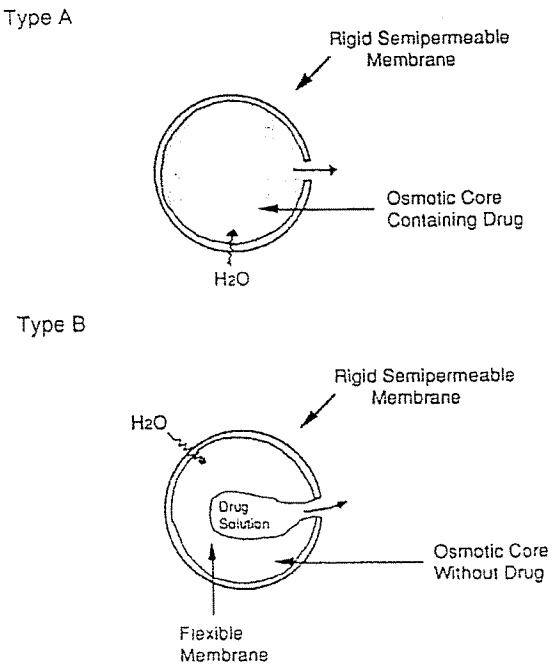


Fig. 9 Diagrammatic representation of two types of osmotically controlled systems. Type A contains an osmotic core with drug. Type B contains the drug solution in a flexible bag, with the osmotic core surrounding.

flow rate of incoming water multiplied by the solution concentration of drug, C_s, within the device:

$$\frac{dM}{dt} = \frac{dV}{dt} C_s \tag{17}$$

Osmotic systems have application in pharmacological studies, implantation therapies, and oral drug delivery.

In systems with solid drug dispersed with electrolyte, the size or number of bored hole(s) are the rate-limiting factors for release of drug. Quality control of the manufacture of these systems must be exceptional, since any variation in boring of the hole, accomplished with a laser drill, can have a substantial effect on release characteristics. Most of the orally administered osmotic systems are of this variety. A variation on this theme is an osmotic system of similar design without a hole. The building osmotic pressure causes the tablet to burst, causing all the drug to be rapidly released [40]. This design is useful for drugs that are difficult to formulate in tablet or capsule form.

These osmotic systems are advantageous in that they can deliver large volumes, and some are refillable. Most important, the release of drug is in theory independent of the drug's properties [41,42]. This allows one dosage form design to be used for almost any drug. Disadvantages are that the systems are relatively expensive and, for certain applications, require implantation. For drugs that are unstable in solution, these systems may be inappropriate because the drug remains in solution form for extended periods before release. System characteristics are summarized in Table 8.

H. Ion-Exchange Systems

Ion-exchange systems generally use resins composed of water-insoluble cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$$\text{Resin}^+\text{–drug}^- + X^- \rightarrow \text{resin}^+\text{–}X^- + \text{drug}^-$$

conversely,

$$\text{Resin}^-\text{–drug}^+ + Y^+ \rightarrow \text{resin}^-\text{–}Y^- + \text{drug}^+$$

where X^- and Y^+ are ions in the GI tract. The free drug then diffuses out of the resin. The drug–resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column, or by prolonged contact in solution.

Table 8 Characteristics of Osmotically Controlled Devices

Description	Drug surrounded by semipermeable membrane and release governed by osmotic pressure
Advantages	Zero-order release is obtainable
	Reformulation is not required for different drugs
	Release of drug independent of the environment of the system
Disadvantages	Systems can be much more expensive than conventional counterparts
	Quality control is more extensive than most conventional tablets

The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusional path length, and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin.

This system is advantageous for drugs that are highly susceptible to degradation by enzymatic processes, since it offers a protective mechanism by temporarily altering the substrate. This approach to sustained release, however, has the limitation that the release rate is proportional to the concentration of the ions present in the area of administration. Although the ionic concentration of the GI tract remains rather constant with limits [15], the release rate of drug can be affected by variability in diet, water intake, and individual intestinal content. A representative listing of ion-exchange products is given in Table 9.

An improvement in this system is to coat the ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethylcellulose or waxes [43]. These systems rely on the polymer coat to govern the rate of drug availability.

IV. TARGETED DELIVERY SYSTEMS

Targeted systems represent the next level in "state-of-the-art" controlled drug delivery systems. These systems address the problem of spatial placement of therapeutic compounds. Since the site of drug action is the target of these systems, oral administration is generally not used as a method of delivery.

A. Liposomes

Liposomes have been, and continue to be, of considerable interest in drug delivery systems. A schematic diagram of their production is shown in Fig. 10. Liposomes are normally composed of phospholipids that spontaneously form multilamellar, concentric, bilayer vesicles, with layers of aqueous media separating the lipid layers. These systems, commonly referred to as multilamellar vesicles (MLVs), have diameters in the range of 1–5 μm. Sonication of MLVs results in the production of small unilamellar vesicles (SUVs), with diameters in the range 0.02–0.08 μm. These vesicles are a single, lipid outer layer, with an aqueous inner core. Large unilamellar vesicles (LUVs) can also be made by evaporation under reduced pressure, resulting in liposomes with a diameter of 0.1–1 μm. Further extrusion of LUVs through a membrane filter will also result in SUVs.

To use liposomes as delivery systems, drug is added during the formation process. Hydrophilic compounds usually reside in the aqueous portion of the vesicle, whereas hydrophobic species tend to remain in the lipid proteins. The physical characteristics and stability of liposomal preparations depend on pH, ionic strength, the presence of divalent cations, and the nature of the phospholipids and additives used [44–46].

In general, these vesicle systems demonstrate low permeability to ionic and polar substances, but this varies greatly with liposome composition. Those made with positively charged phos-

Table 9 Ion-Exchange Products

Product	Active ingredient(s)	Manufacturer
Biphetamine capsules	Amphetamine, dextroamphetamine	Fisons
Tussionex suspension	Hydrocodone, chlorpheniramine	Fisons
Ionamin capsules	Phenteramine	Pennwalt
Delsym solution	Dextromethorphan hydrobromide	McNeil

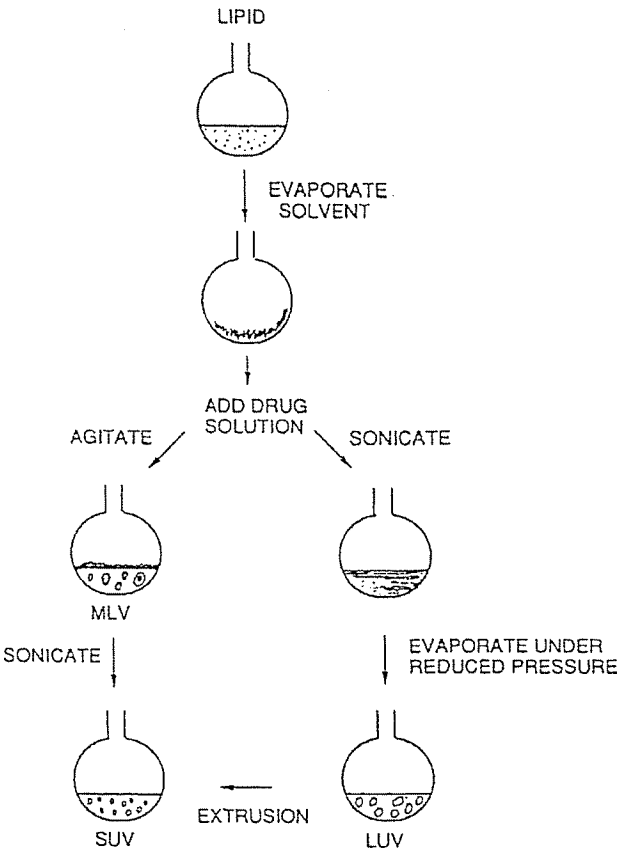


Fig. 10 Schematic representation of a procedure for the production of liposomes.

pholipids are impermeable to cations, whereas negatively charged liposomes are permeable to cations, and both types are readily permeated by anions [47]. The degree of saturation or the length of the phospholipid fatty acid chain will also greatly affect the solute permeability of the liposomes [48]. An increase in temperature can also alter permeability [49], by causing the lipids to undergo a phase transition to a less-ordered, more fluid configuration. Again, the transition is characteristic for differing types of lipids. This has been employed in a unique-targeting approach, by creating an environment of local hyperthermia, the liposomes are encouraged to release their encapsulated cargo in that specified area, for example, a capillary bed [50,51].

Some proteins, such as those found in serum, are able to deform, penetrate the bilayer, or remove lipid components, resulting in changes in liposome permeability [52]. Many additives, such as cholesterol, are able to inhibit this effect, stabilizing the membrane structure of the vesicle and limiting cargo leakage [53]. This is achieved by allowing closer lipid packing [54]. The fact that impurities, such as cholesterol or free fatty acids [55], can dramatically change the permeability and surface charge of liposomes points to the necessity for strict controls on the quality and purity of lipids used in liposomal preparation.

Liposomes that remain impermeable to their contents cannot release these compounds without interaction with cells. This cellular interaction occurs by three different mechanism (Fig. 11) [56]. Of these, fusion and adsorption usually involve drug leakage, whereas effective drug delivery results from endocytosis.

1. *Fusion of the liposome with the cell membrane.* For this, the lipid portion of the vesicle becomes part of the cell wall.
2. *Adsorption to the cell wall.* For this, transfer of liposome content must be by diffusion through the lipids of the liposome and the cell membrane.
3. *Endocytosis of the vesicle by the cell.* The entire liposomal contents are made available to the cell.

The advantageous effects of liposomal carrier systems include protection of compounds from metabolism or degradation, as well as enhanced cellular uptake. Liposome-mediated delivery of cytotoxic drugs to cells in culture has resulted in improved potency [57,58]. Prolonged release of encapsulated cargo has also been demonstrated [59,60]. More recently, liposomes with extended circulation half-lives and dose-independent pharmacokinetics (Stealth liposomes) [61], have shown promise in delivery of drugs that are normally very rapidly degraded.

Liposomes, however, also have inherent disadvantages in the areas of stability and uniformity of production. Once a system has demonstrated merit for treatment of a particular disease state, the following must be determined before a formulation is acceptable for marketing and human use: (a) lipid purity and stability; (b) drug stability and leakage from the vesicles; (c) lipid–drug cargo interaction; and (d) control of vesicle size and drug-loading efficiency for large-batch production.

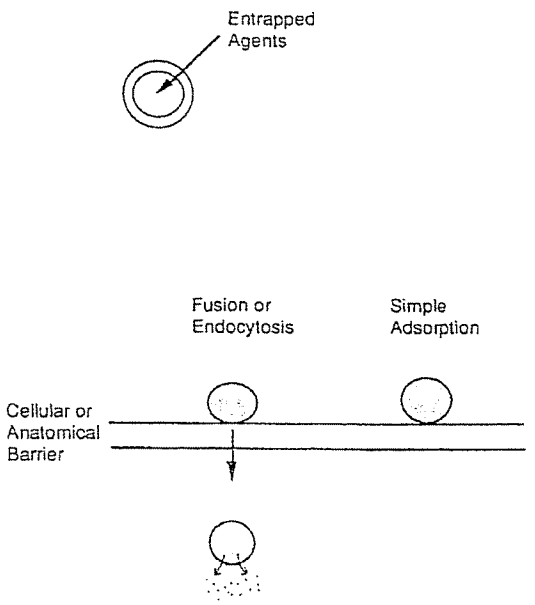


Fig. 11 Schematic representation of liposome interactions at a membrane surface.

B. Prodrugs

A *prodrug* is a compound resulting from chemical modification of a biologically active compound that will liberate the active form in vivo by enzymatic or hydrolytic cleavage. The primary purpose in forming a prodrug is to modify the physicochemical properties of the drug, usually to alter the membrane permeability of the parent compound. This change in physicochemical properties of the drug influences the ultimate localization of the drug. There are various reasons for formulating a prodrug system. If the parent compound is insoluble, this can be modified [62]. If it is easily degraded, modification can protect the parent compound from enzymatic or hydrolytic attack. Modifications can also reduce side effects, such as GI irritation [63]. Several drugs are now marketed in the form of a prodrug; for example, sulindac, a nonsteroidal anti-inflammatory agent, and numerous angiotension-converting enzyme (ACE) inhibitors. The necessary conversion of prodrug to parent can occur by a variety of reactions, the most common being hydrolytic cleavage [64]. The prodrug ester forms of a hydroxyl or carboxyl group of the parent compound can be readily cleaved by blood esterase. Other activation processes may include biochemical reduction or oxidation. However the conversion occurs, to achieve sustained drug action, the rate of conversion from prodrug to active compound should not be too high [65]. Site-specific, controlled delivery is achieved by the antiviral prodrug acyclovir, being converted to active form by a virus-specific enzyme [66]. Sustained release of steroid prodrugs, especially progestagens and progestagen–estrogen combinations, have seen a substantial amount of clinical experience, both as a means of birth control and as symptomatic menopausal treatment [67].

The concept of the double prodrug (proprodrugs), may allow more controlled delivery of various prodrug compounds [68]. For example, if a prodrug that shows site-specific activation, but has poor transport properties or stability problems, it could be converted to a proprodrug that transported better or is more stable (Fig. 12). Prodrug systems have been taken even further by including as prodrugs, polymer prodrugs, in which a drug is covalently linked to a polymer backbone. This type of system could encompass a staggering number of possibilities. Encouraging results have been shown with mitomycin [69,70], for example.

The most serious disadvantage to the prodrug approach to controlled–sustained delivery is that extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and, therefore, requires extensive and costly studies to determine safety and efficacy.

C. Nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm. They can be used as drug carriers, with the drug encapsulated, dissolved, adsorbed, or covalently attached

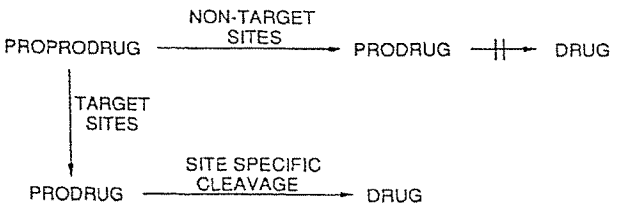


Fig. 12 Illustration of prodrug and proprodrug concept.

[71,72]. The small size of the nanoparticles permits administration by intravenous injection, and also permits their passage through capillaries that remove larger particles. They are usually taken up by the liver, spleen, and lungs [73,74].

Preparation of nanoparticles can be by a variety of different ways. The most important and frequently used is emulsion polymerization; others include interfacial polymerization, solvent evaporation, and desolvation of natural proteins. The materials used to prepare nanoparticles are also numerous, but most commonly they are polymers such as polyalkylcyanoacrylate, polymethylmethacrylate, polybutylcyanoacrylate, or from albumin or gelatin. Distribution patterns of the particles in the body can vary depending on their size, composition, and surface charge [75–77]. In particular, nanoparticles of polycyanoacrylate have been found to accumulate in certain tumors [78,79].

There are several possible ways that the drug cargo can be incorporated into nanoparticles. They may be bound by polymerization of the nanoparticles in the presence of drug solution, or by absorption of the drug onto prepolymerized nanoparticles. The drug will be dispersed in the particle's polymer matrix [80], or adsorbed to the surface, depending on its affinity to the polymer. Drugs used for nanoparticle delivery have been, for the most part, cytotoxic agents; dactinomycin (actinomycin D) [81], 5-fluorouracil [82,83], doxorubicin [84,85], and methotrexate [86]. But also for delivery of bioactive peptides and proteins, for example, growth hormone-releasing factor [87,88].

Nanoparticles show great promise as devices for the controlled release of drugs, provided that the choice of material for nanoparticle formation is made with the appropriated considerations of the drug cargo, administration route, and the desired site of action.

D. Resealed Erythrocytes

When red blood cells are placed in hypotonic media, they swell, which causes rupturing of the membrane and formation of pores. These pores allow free exchange of intra- and extracellular components. Readjustment of the solution tonicity to isotonic allows resealing of the membrane. This technique usually allows encapsulation of up to 25% of the drug or enzyme in solution [89]. In addition to this method, called the preswell dilution technique, there are other ways to form drug-loaded erythrocytes. In the dialysis technique, the red blood cells are placed in dialysis tubes that are immersed in a hypotonic medium. This results in retention of cytoplasmic components when the cells are resealed. Another method involves subjecting the cells to an intense electric field, causing pores to form, which again, can be resealed after drug uptake.

The potential advantages of loaded red blood cells as delivery systems are [90]:

1. They are biodegradable and nonimmunogenic.
2. They can be modified to change their resident circulation time, depending on their surface (cells with little membrane damage can circulate for prolonged periods).
3. Entrapped drug is shielded from immunological detection and external enzymatic degradation.
4. The system is relatively independent of the physicochemical properties of the drug (i.e., it does not require chemical modifications).

In general, normally aging erythrocytes and slightly damaged cells are sequestered in the spleen, whereas those heavily damaged or modified are removed from circulation by the liver [91]. This, along with a short storage life of about 2 weeks [92], constitutes the major drawbacks of using resealed erythrocytes as drug carriers.

E. Antibody-Targeted Systems

An alternative drug delivery system makes use of macromolecular attachment for delivery using immunoglobulins as the macromolecule. The obvious advantage of this system is that it can be targeted to the site of the antibody specificity. Although this usually does not provide much of a sustaining mechanism, the problem of spatial placement is addressed. The advantage in this is that far less drug is used, and side effects can be reduced substantially.

Drugs are linked, covalently or noncovalently, to the antibody [93], or placed in vesicles such as liposomes or microspheres, and the antibody used to target the liposome [94,95] (Fig. 13). Covalent attachment is generally not very efficient and also diminishes the antigen-binding capacity [96,97]. There are only a few functional groups available per antibody that can be used for chemical coupling without affecting the antibody's binding activity. If conjugation is done through an intermediate carrier molecule, one can increase the drug/antibody ratio [98,99]. Such intermediates have included dextran or poly-L-glutamic acid [100–102].

There are many drugs that have been conjugated to antibodies or their fragments, a few are daunomycin [103], cyclosporine [104], platinum [105], chlorambucil [106], and vindesine [107]. When choosing a drug for this type of delivery, one must consider many things [108], such as whether the drug is active extra- or intracellularly, if it must be cleaved from the antibody to be active, and the strength and method of coupling.

Immunoliposomes—liposomes loaded with drug cargo that have been surface-conjugated to antibodies, or antibody fragments—have also been investigated by a number of researchers. Linkage of antibody to a liposome can be covalent or noncovalent. Spacers are used for covalent binding, or the antibody is modified by attaching an "anchor" group [109] for noncovalent coupling. The anchor group, which is hydrophobic, inserts into the bilayer of the liposome, "anchoring" the antibody to the vesicle. Numerous antibody–liposome combinations have been looked at, delivering both drugs [110–112], and genetic material [113–115].

The obvious advantage to antibody-targeted systems is that through the use of monoclonal antibodies, which recognize only the tumor antigen, side effects of cytotoxic chemicals on the rest of the body could be greatly reduced. These systems represent a novel and currently high-interest research area of drug delivery. Their potential value in the delivery of compounds to directed targets has generated considerable interest.

V. DENTAL SYSTEMS

Controlled and sustained drug delivery has recently begun to make an impression in the area of treatment of dental diseases. Many researchers have demonstrated that controlled delivery of antimicrobial agents, such as chlorhexidine [118–120], ofloxacin [121–123], and metroni-

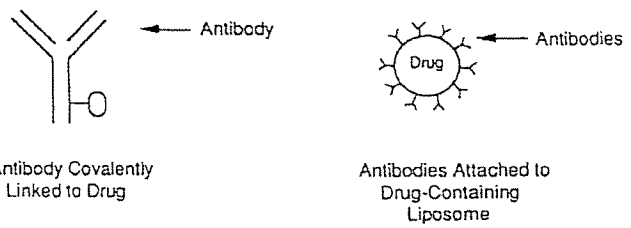


Fig. 13 Diagrammatic representation of two types of antibody-targeted systems. Drug is either covalently linked directly to the antibody, or is contained in liposomes that are targeted by attached antibodies.

dazole [124] can effectively treat and prevent periodontitis. The incidence of dental caries and formation of plaque can also be reduced by controlled delivery of fluoride [125,126]. Delivery systems used are film-forming solutions [119,120], polymeric inserts [122], implants, and patches. Since dental disease are usually chronic, sustained release of therapeutic agents in the oral cavity would obviously be desirable.

VI. OCULAR SYSTEMS

The eye is unique in its therapeutic challenges. An efficient mechanism, that of tears and tear drainage, which quickly eliminates drug solution, makes topical delivery to the eye somewhat different from most other areas of the body [127]. Usually less than 10% of a topically applied dose is absorbed into the eye, leaving the rest of the dose to potentially absorb into the bloodstream [128], resulting in unwanted side effects. The goal of most controlled delivery systems is to maintain the drug in the precorneal area and allow its diffusion across the cornea. Suspensions and ointments, although able to provide some sustaining effect, do not offer the amount of control desired [129,130]. Polymeric matrices can often significantly reduce drainage [131], but other newer methods of controlled drug delivery can also be used.

The application of ocular therapy generally includes glaucoma, artificial tears, and anticancer drugs for intraocular malignancies. The sustained release of artificial tears has been achieved by a hydroxypropylcellulose polymer insert [132]. However, the best-known application of diffusional therapy in the eye, Ocusert-Pilo, the device shown in Fig. 14, is a relatively simple structure with two rate-controlling membranes surrounding the drug reservoir containing pilocarpine. Thus, a thin, flexible lamellar ellipse is created and serves as a model reservoir device. The unit is placed in the eye and resides in the lower cul-de-sac, just below the cornea. Since the device itself remains in the eye, the drug is released into the tear film.

The advantages of such a device are that it can control intraocular pressure for up to a week [133]. Control is achieved with less drug and fewer side effects, since the release of drug is zero-order. The system is more convenient, since application is weekly, as opposed to the four times a day dosing for pilocarpine solutions. This greatly improves patient compliance and assures round-the-clock medication, which is of great importance for glaucoma treatment. The main disadvantage of the system is that it is often difficult to retain in the eye, and can be of some discomfort.

Another method of delivery of drug to the anterior segment of the eye, which has proved successful, is that of prodrug administration [134]. Since the corneal surface presents an effective lipoidal barrier, especially to hydrophilic compounds, it seems reasonable that a prodrug that is more lipophilic than the parent drug will be more successful in penetrating this barrier.

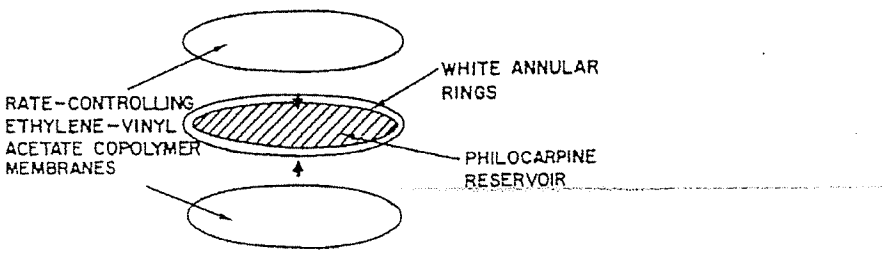


Fig. 14 Schematic diagram of the Ocusert intraocular device for release of pilocarpine.

One drug that has been formulated in this manner is dipivalyl epinephrine (Dividephrine), a dipivalyl ester of epinephrine. Epinephrine itself is poorly absorbed owing to its polar characteristics and is highly metabolized. The prodrug form is approximately ten times as effective at crossing the cornea and produces substantially higher aqueous humor levels [134,135]. For another prodrug, phenylephrine pivalate, there is some possibility that the prodrug itself is therapeutically active [136,137]. Many other drugs have been derivatized for prodrug ocular delivery: timolol [138,139], nadolol [140], pilocarpine [141,142], prostaglandin $F_{2\alpha}$ [143,144], terbutaline [145], acyclovir [146], vidarabine [147], and idoxuridine [148,149].

New sustained-release technologies are gaining in ocular delivery, as in other routes. Liposomes as drug carriers have achieved enhanced ocular delivery of certain drugs [150]; antibiotics [151–153], and peptides [154]. Biodegradable matrix drug delivery to the anterior segment has also been studied [155,156]. Prolonged delivery of pilocarpine can be achieved with a polymeric dispersion [157]. Implantation of polymers containing endotoxin for neovascularization [158], gancyclovir [159], 5-flurouracil [160], and injections of doxorubicin (Adriamycin) [161] have also resulted in sustained delivery. However, topical ocular delivery is preferred considerably over implants and injections.

VII. TRANSDERMAL SYSTEMS

The transdermal route of drug administration offers several advantages over other methods of delivery. For some cases, oral delivery may be contraindicated, or the drug may be poorly absorbed. This would also include situations for which the drug undergoes a substantial first-pass effect [162], and systemic therapy is desired.

The skin, although presenting a barrier to most drug absorption, provides a very large surface area for diffusion. Below the barrier of the stratum corneum is an extensive network of capillaries. Since the venous return from these capillary beds does not flow directly to the liver, compounds are not exposed to these enzymes during absorption [162]. A most notable example of such a drug is nitroglycerin, which as been administered both sublingually and transdermally to avoid first-pass metabolism. Other drugs that have seen success in controlled transdermal delivery are testosterone [163], fentanyl [164,165], bupranolol [166], and clonidine.

Transdermal controlled-release systems can be used to deliver drugs with short biological half-lives and can maintain plasma levels of very potent drugs within a narrow therapeutic range for prolonged periods. Should problems occur with the system, or a change in the status of the patient require modification of therapy, the system is readily accessible and easily removed.

One of the primary disadvantages to this method of delivery is that drugs requiring high blood levels to achieve an effect are difficult to load into a transdermal system owing to the large amount of material required. These systems would naturally be contraindicated if the drug or vehicle caused irritation to the skin. Also, various factors affecting the skin, such as age, physical condition, and device location, can change the reliability of the system's ability to deliver medication in a controlled manner. In other words, both the drug and the nature of the skin can affect the system design.

Current controlled transdermal-release systems can be classified into four types, as follows, with a representative product and manufacturer.

1. Membrane permeation-controlled system in which the drug permeation is controlled by a polymeric membrane.
   Transderm-Scop (scopolamine; Ciba-Geigy)

2. Adhesive dispersion-type system is similar to the foregoing but lacks the polymer membrane, instead the drug is dispersed into an adhesive polymer.
   Deponit (nitroglycerin; Wyeth)
3. Matrix diffusion-controlled system in which the drug is homogeneously dispersed in a hydrophilic polymer, diffusion from the matrix controls release rate.
   Nitrodur (nitroglycerin; Key)
4. Microreservoir dissolution-controlled system in which microscopic spheres of drug reservoir are dispersed in a polymer matrix.
   Nitrodisc (nitroglycerin; Searle)

Most marketed systems are of the polymeric membrane-controlled type, representative of these is Transderm-Scop. This product, shown in Fig. 15, is designed to deliver scopolamine over a period of days, without the side effects commonly encountered when the drug is administered orally [167]. The system consists of a reservoir containing the drug dispersed in a separate phase within a highly permeable matrix. This is laminated between the rate-controlling microporous membrane and an external backing that is impermeable to drug and moisture. The pores of the rate-controlling membrane are filled with a fluid that is highly permeable to scopolamine. This allows delivery of the drug to be controlled by diffusion through the device and skin. Control is achieved because, at equilibrium, the membrane is rate-limiting for drug permeation. To initiate an immediate effect, a priming dose is contained in a gel on the membrane side of the device.

Another drug that is popular for controlled transdermal release is nitroglycerin. Conventionally, this drug is administered sublingually, although the duration of action by this route is quite short. This is acceptable for acute anginal attacks, but not for prophylactic treatment. Oral administration has the disadvantage that large fractions of the dose are lost to first-pass metabolism in the liver. Topical ointments have long been used for prophylactic treatment of angina, but their duration is only 4–8 hr and, in addition, are not aesthetically acceptable. The transdermal nitroglycerin devices employ a variety of systems to provide 24-hr delivery.

VIII. VAGINAL AND UTERINE SYSTEMS

Sustained- and controlled-release devices for drug delivery in the vaginal and uterine areas are most often for the delivery of contraceptive steroid hormones. The advantages in administration by this route—prolonged release, minimal systemic side effects, and an increase in bioavailability—allow for less total drug than with an oral dose. First-pass metabolism that inactivates many steroid hormones can be avoided [168,169].

One such application is the medicated vaginal ring [170]. Therapeutic levels of medroxyprogesterone have been achieved at a total dose that was one-sixth the required oral dose [171]. Ring delivery devices have several problems that have limited their use; vaginal wall erosion and ring expulsion, to name a few. Microcapsules have also recently been useful for vaginal and cervical delivery [172]. Local progesterone release from this dosage form can alter cervical mucus to interfere with sperm migration [173]. Other steroids have also attained sustained delivery by an intracervical system [174]. The sustained release of progesterone from various polymers given vaginally have also been found useful in cervical ripening and induction of labor [175–177].

A more common contraceptive device is the intrauterine device (IUD). The first intrauterine devices used were of the undedicated type. These have received increased attention since the use of polyethylene plastics and silicone rubbers [178–180]. These materials had the ability to resume their shape following distortion. Because they are unmedicated, these IUDs cannot

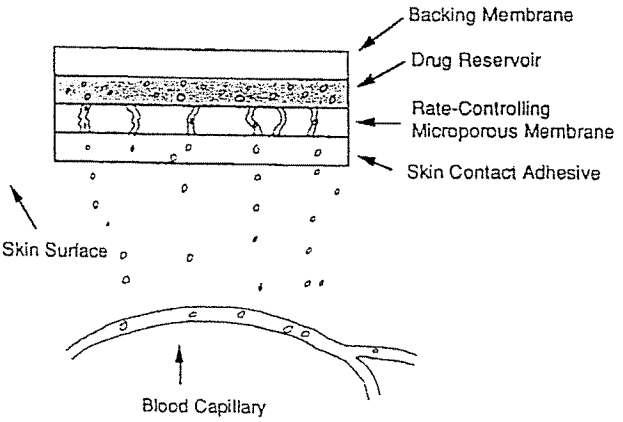


Fig. 15 Schematic diagram of a transdermal device for the delivery of scopolamine.

be classified as sustained-release products. It is believed their mechanism of action is due to local endometrial responses, both cellular and cytosecretory [181]. Initial investigations of these devices led to the conclusions that the larger the device, the more effective it was in preventing pregnancy. Large devices, however, increased the possibility of uterine cramps, bleeding, and expulsion of the device.

Efforts to improve IUDs have led to the use of medicated devices. Two types of agents are generally used, contraceptive metals and steroid hormones. The metal device is exemplified by the CU-7, a polypropylene plastic device in the shape of the number 7. Copper is released by a combination of ionization and chelation from a copper wire wrapped around the vertical limb. This system is effective for up to 40 months.

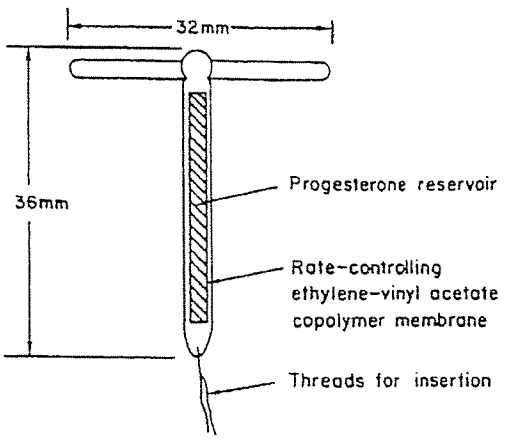


Fig. 16 Schematic diagram of the Progestasert intrauterine device for the release of progesterone.

The hormone-releasing devices have a closer resemblance to standard methods of sustained release because they involve the release of a steroid compound by diffusion [182,183]. The Progestasert, a reservoir system, is diagrammed in Fig. 16. Progesterone, the active ingredient, is dispersed in the inner reservoir, surrounded by an ethylene/vinyl acetate copolymer membrane. The release of progesterone from this system is maintained almost constant for 1 year. The effects of release are local, with none of the systematic side effects observed with orally administered contraceptives [184–191].

IX. INJECTIONS AND IMPLANTS

One of the most obvious ways to provide sustained-release medication is to place the drug in a delivery system and inject or implant the system into the body tissue. The concept of these delivery methods is not new, but the technology applied is contemporary. Administration of these systems often requires surgical implantation or specialized injection devices. The fact that these systems are in constant contact with exposed tissue components places certain requirements on the systems and their polymer composition.

In general, the materials used must be biocompatible; that is the polymers themselves must not cause irritation at the implantation site, or promote infection or sterile abscess. The most common polymers used are hydrogels, silicones, and biodegradable materials [192]. Hydrogels have the advantageous property of being able to retain large amounts of water within their structure without dissolving [193]. This high aqueous content makes them very compatible with living tissues, but disadvantageously, allows low-molecular-weight substances to diffuse out quickly. Cross-linking agents can be used to reduce this diffusional loss and to provide structural rigidity, but this can increase the frictional irritation of the hydrogel with its surrounding tissue.

Subcutaneous implantation is currently one of the most utilized routes to investigate the potential of sustained-delivery systems. This is because favorable absorption sites are available, and removal of the device can be accomplished at any time. Surgery is often required, and in itself can be considered a disadvantage, as well as the fact that once implanted, the delivery rate of the drug is usually fixed until the device is removed. The development of implants has a long history, starting initially with investigations on implanted silicone devices. The most notable new implantable product is Norplant, a contraceptive device releasing levonorgestrel for up to 5 years [194]. This product is implanted subdermally and requires only a local anesthetic. A variety of other drugs have also been used, including thyroid hormones, steroids, cardiovascular agents [195–198], insulin [199], and nerve growth factor [200].

Sustained-release injections, subcutaneous and intramuscular, have been investigated in a variety of different formulations [201,202]. Injections of degradable microspheres have efficiently prolonged delivery of numerous drugs [203–206], even antigenic substances and vaccines to produce immunity [207,208].

Some implantation devices have extended well beyond the classic diffusional systems and have included not only bioerodible devices, but implantable therapeutic systems that can be activated. There are devices activated by change in osmotic pressure to deliver insulin [209], morphine release trigger by vapor pressure [210], and pellets activated by magnetism to release their encapsulated drug load [211]. Such external control of an embedded device would eliminate many of the disadvantages of most implanted delivery systems.

X. CONCLUSIONS

The space limitations of a written work such as this do not permit a complete discourse on all of the sustained and controlled mechanisms available for possible drug delivery. Such a chapter

would be quite expansive, so that instead, an attempt has been made to cover as much as possible the major and currently marketed types. Current research in this area involves many more novel systems, many of which have strong therapeutic potential. The future of this area is limited only by the imagination of those who chose to become involved in this field.

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