SUSTAINED ACTION DOSAGE FORM

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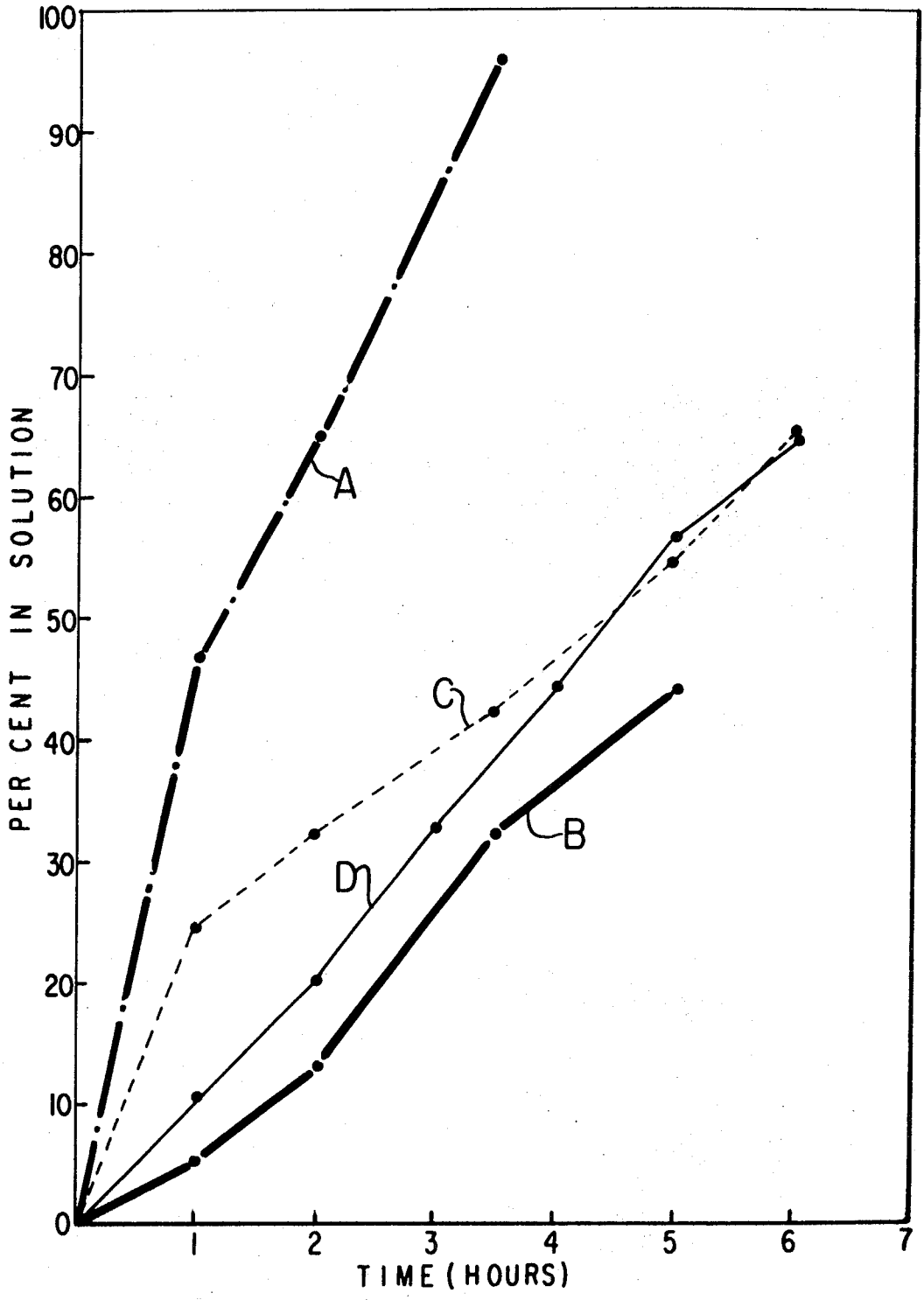

FIG. 1

SUSTAINED ACTION DOSAGE FORM

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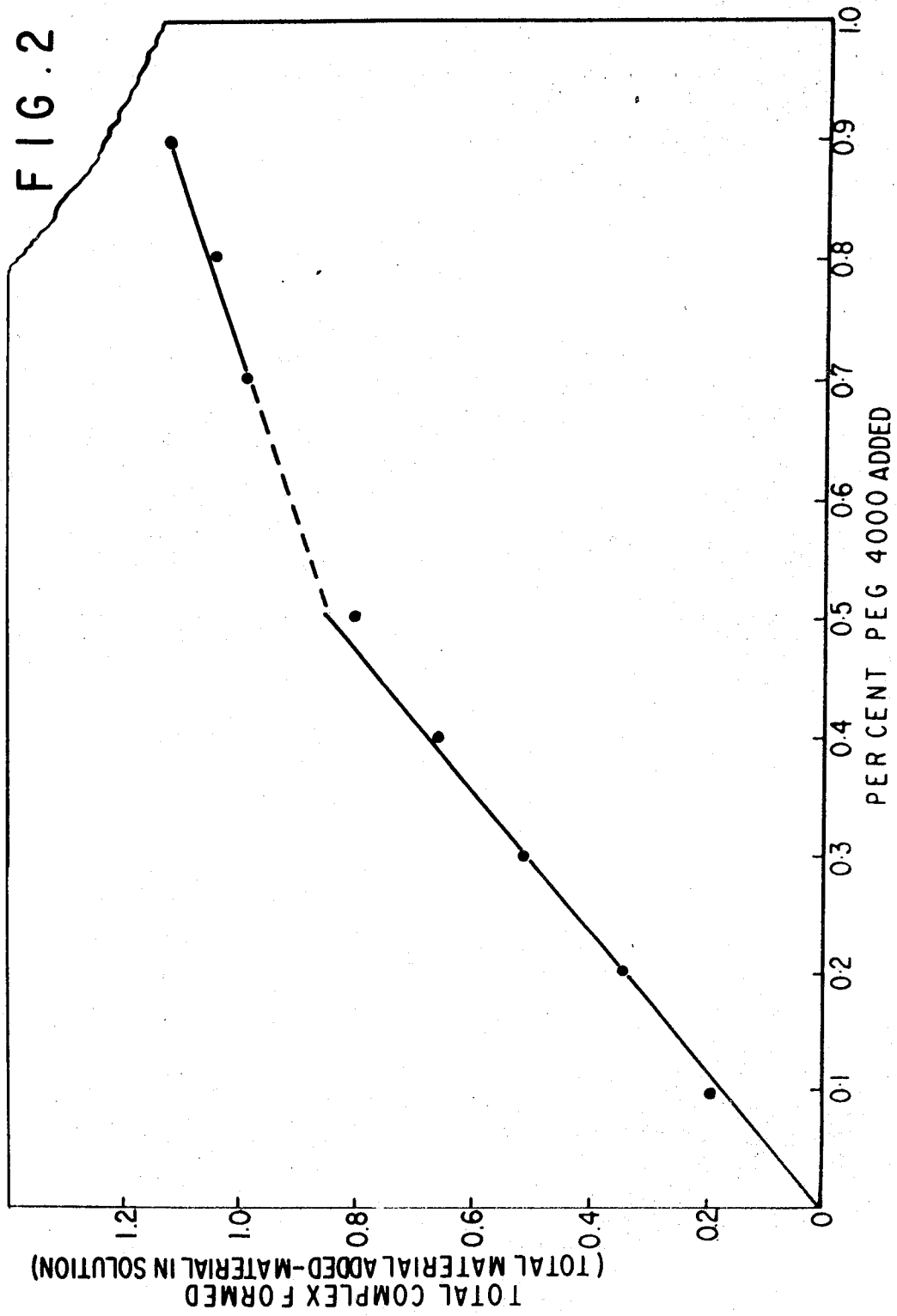
FIG. 2



SUSTAINED ACTION DOSAGE FORM

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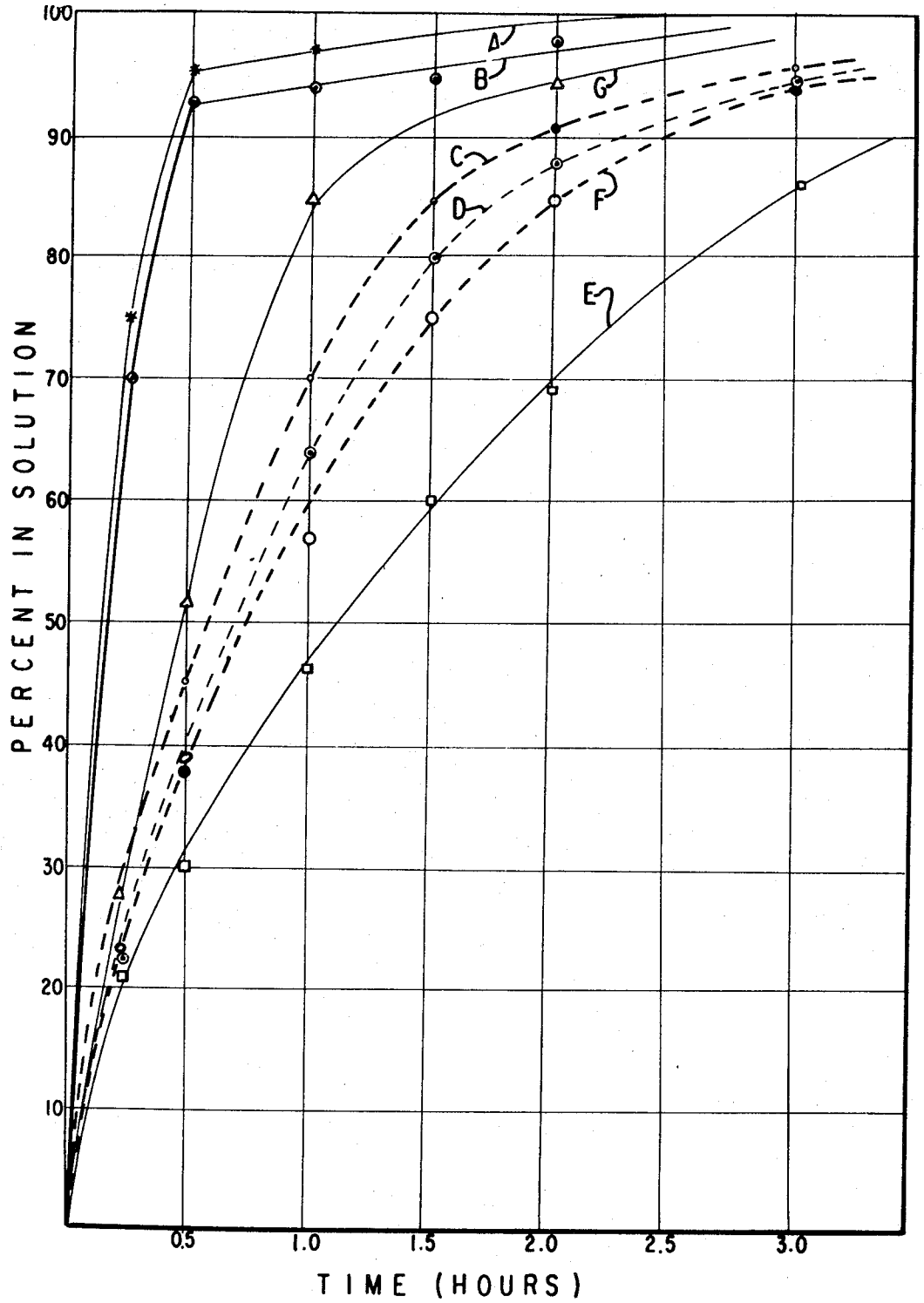

FIG. 3

United States Patent Office 3,634,584 Patented Jan. 11, 1972

3,634,584

SUSTAINED ACTION DOSAGE FORM

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Continuation-in-part of abandoned application Ser. No. 730,742, May 21, 1968. This application Feb. 13, 1969, Ser. No. 800,827

Int. Cl. A61j 3/10; A61k 27/12

U.S. Cl. 424—21 8 Claims

ABSTRACT OF THE DISCLOSURE

The invention is directed to a sustained-release dosage form utilizing a carboxy vinyl polymer and polyethylene glycol complex as a means of controlling the rate of release of a drug, substantially independent of pH.

This application is a continuation-in-part of application Ser. No. 730,742 filed May 21, 1968, now abandoned.

This invention relates to tableted therapeutic compositions with delayed release action including the ability to release a drug, or the active ingredient, gradually over relatively long periods of time, and to methods for preparing and using such compositions. More particularly, the invention relates to a sustained action dosage composition, containing a high molecular weight carboxy vinyl polymer and polyethylene glycol, and having a controlled rate of release of a contained drug, substantially independent of pH.

Various processes and compositions have been proposed for delaying or prolonging the release of medicaments in oral form. One such composition is disclosed in U.S. Pat. 3,074,852 in which a solid medicinal component is combined with a carboxy vinyl polymer, such as Carbopol 934.

The slow release compositions of the prior art are pH dependent. That is, there is a delayed release of a drug in a medium having a pH from about pH 4 to about pH 11, but there is a rapid release of a drug in a medium of low pH where the polymeric material is not hydrated.

For example, sustained action formulations of oxazepam utilizing the prior art compositions demonstrate a pH-dependent drug release. In an acidic solvent (0.1 N HCl), representing gastric fluid, the polymer is not hydrated and consequently does not significantly retard the dissolution of the active component from the dosage unit. However, in a buffer solution (pH 7.5) representing the intestinal fluid, hydration of the polymer takes place with a resulting slowing of the release of the drug.

Because the acid content of the stomach varies considerably and the time interval during which a dosage composition remains in the stomach also varies, ideally, a sustained action system should be independent of pH so that the release of the drug would be independent of the foregoing factors.

It is an object of the present invention to provide a medicinal composition having delayed release characteristics which is substantially independent of pH.

It is another object of the present invention to provide a pharmaceutical composition which is capable of releasing drug immediately and then uniformly over long periods of time.

It is another object of this invention to provide a pharmaceutical composition in which the rate of release of drugs of different solubilities may be controlled.

Other objects and features of the invention will be apparent to those skilled in the art from reading the following description, taken in conjunction with the drawings in which:

FIG. 1 is a graph of the drug release characteristics of a typical pH-dependent drug release composition and of a composition of the present invention, both in an acidic medium and in an alkaline medium;

FIG. 2 is a graph of the phase solubility study of Carbopol 934 and polyethylene glycol having a molecular weight of about 4000; and

FIG. 3 is a graph of the drug release characteristics of drug-containing compositions at various ratios of carboxy vinyl polymer and polyethylene glycol.

It has been found that the rate of release of a drug from a therapeutic composition may be made substantially independent of pH where the composition includes a carboxy vinyl polymer and a polyethylene glycol. The drug preferably is utilizable in powdered form. The drug comprises about 1 to 90 percent by weight, preferably 5 to 20 percent by weight, of the tablet composition. The total of the carboxy vinyl polymer and polyethylene glycol preferably comprises about 10 to 60 percent by weight, preferably about 20 to 50 percent by weight, of the composition. The remainder of the composition may be a fast release drug, extenders, lubricants, flavoring agents, coloring agents and the like, as is well known in the art.

The carboxy vinyl polymer may be present in the amount of about 4 to 30 percent by weight, preferably about 10 to 30 percent. Advantageous results may be obtained when the carboxy vinyl polymer is present in the amount of about 15 to 25 percent by weight.

Similarly the polyethylene glycol may be present in the amount of about 4 to 30 percent by weight, preferably about 10 to 30 percent by weight. Advantageous results may be obtained where the polyethylene glycol is present in the amount of about 15 to 25 percent by weight.

It was discovered that the incorporation of a polyethylene glycol and a carboxy vinyl polymer in a therapeutic formulation resulted in a product demonstrating a significant decrease in the rate of drug release in an acidic medium, with substantially no effect on the rate of release in a pH 7.5 medium. Without wishing to be bound by a theory of operation, the probable mechanism by which this delayed release occurs in the acidic medium is through the formation of a molecular complex between the polyethylene glycol and the carboxy vinyl polymer. The complex, however, is apparently not stable in a basic medium, and in the latter environment the normal hydration of the carboxy vinyl polymer acts as a delaying-mechanism. By varying the ratio of complexable to free polymeric substances in the dosage form, the release of drugs of varying solubilities may be controlled.

The carboxy vinyl polymer is substantially insoluble in water and is the acid form of a polymer prepared as described in U.S. Pat. No. 2,798,053, granted July 2, 1957, selectively utilizing from about 0.75 to 2 percent by weight of polyalkenyl polyether, for example, polyallyl sucrose as the crosslinking material, the remainder being essentially acrylic acid or its equivalent and the polymerization being carried out in a hydrocarbon diluent with a free radical catalyst, for example, benzoyl peroxide. The carboxy vinyl polymers employed in this invention are more specifically described in U.S. Pat. No. 2,909,462, of particular interest being the preparation produced in acid form. A particularly effective embodiment of the high molecular weight carboxy vinyl polymer is a water-soluble polymer of acrylic acid crosslinked with 1% of a polyallyl ether of sucrose having an average of about 5.8 allyl groups for each molecule of sucrose (Carbopol 934) (formerly known as "Good-rite K-934").

The polyethylene glycol employed in the present invention may have a molecular weight from about 1,000 to 20,000, preferably 4,000 to 6,000. The limiting factors are melting point at the lower molecular weights and solu-

bility at the higher molecular weights, the determining factors being the dose form, storage conditions, and the like. Advantageous results have been obtained with polyethylene glycol having a molecular weight of about 4,000, hereafter sometimes referred to as "PEG 4000."

The use of the invention to control the release of drugs from tablets containing a carboxy vinyl polymer-polyethylene glycol mixture has been demonstrated with a substantially insoluble drug, oxazepam, and with quinine salt, a readily soluble drug. Oxazepam is the generic name for 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepine-2-one. The dosage and mode of administration of oxazepam and quinine are well known, see for instance, Physicians Desk Reference, 22nd edition, 1967, p. 124 etc. It is to be understood that the invention is applicable to other drugs as well.

EXAMPLE I

The following example illustrates the effect on the dissolution rate of a relatively insoluble compound.

Part 1

Tablets were prepared from the following control formula which does not contain polyethylene glycol.

FORMULA A

Ingredient	Milligrams	Weight percent
Oxazepam	30	9.7
Carbopol 934 (2.5% Carbosil)	62	20.0
Lactose	211	68.1
Magnesium stearate	7	2.2
Total	310	100.0

The ingredients were weighed, screened, and blended, then densified by compacting in a tableting machine.

Dissolution tests on the tablets were performed using a low agitation procedure. In such a procedure one tablet is placed in a two liter, round bottom flask containing 1750 milliliters of a solvent, and agitated. Agitation is accomplished by rotating a 7.5 centimeter Teflon paddle located 2.5 centimeters from the bottom of the flask at 50 revolutions per minute.

One group of Formula A tablets were placed in one-tenth normal hydrochloric acid (0.1 N HCl). The pH of 0.1 N HCl is about 1.5. The amount of oxazepam in solution at various time intervals was recorded. A second group of Formula A tablets was placed in 0.2 molar solution of disodium phosphate and monosodium phosphate buffered to a pH of 7.5. Samples were withdrawn at the times indicated by the dots in FIG. 1, either 1, 2, 3, 3½, 4, 5 or 6 hours. The samples were filtered and assayed for drug content. The results are shown in FIG. 1 where the percent of drug in solution is recorded.

Part 2

Tablets were prepared as in Part 1 in which the delayed release portion had the following formula which includes polyethylene glycol.

FORMULA B

Ingredient	Milligrams	Weight percent
Oxazepam	30	7.8
Carbopol 934 (2.5% Carbosil)	93	24.2
PEG 4000	75	19.5
Lactose	180	46.7
Magnesium stearate	7	1.8

Following the procedure of Part 1, one group of Formula B tablets was placed in 0.1 N HCl and another group of Formula B tablets was placed in a phosphate solution buffered to a pH of 7.5. The amount of oxazepam in solution was determined at various time intervals as indicated by the dots in FIG. 1. The results are shown in FIG. 1.

Curve A in FIG. 1 shows the amount of oxazepam from Formula A in solution in a pH 1.5 medium at various times after immersion.

Curve B in FIG. 1 shows the amount of oxazepam from Formula A in solution in a pH 7.5 medium at various times after immersion.

Curve C in FIG. 1 shows the amount of oxazepam from Formula B in solution in a pH 1.5 medium at various times after immersion.

Curve D in FIG. 1 shows the amount of oxazepam from Formula B in solution in a pH 7.5 medium at various times after immersion.

As may be seen from a comparison of curves A and B with curves C and D, the oxazepam in tablets containing both Carbopol 934 and PEG 4000 was released at a rate substantially independent of pH. The oxazepam in tablets without PEG 4000 was released more quickly in a pH 1.5 solution than in a pH 7.5 solution. The oxazepam in tablets containing both Carbopol 934 and PEG 4000 was released at a rate that was substantially independent of pH. Also, there is a substantially lower release rate in an acidic medium such as gastric juices, so that the oxazepam will not be totally released in the stomach, but will continue to be released in the intestines and at a substantially uniform rate.

Other tablets having sustained release characteristics may be prepared by the foregoing procedure but substituting other active ingredients for oxazepam. Such active ingredients include:

amphetamine sulfate
acetyl salicylic acid
aminophylline
antazoline hydrochloride
alkaloids of belladonna
ampicillin
ascorbic acid
atropine sulfate
aureomycin
bethanecholchloride
caffeine
codeine sulfate
colchicine
cortisone
dextroamphetamine sulfate
digitoxin
dihydrostreptomycin
dienestrol
diethyl carbamazine citrate
diethylpropion
doxylamine succinate
d-methorphan hydrobromide
erythrityltetranitrate
ephedrine sulfate
erogonovine maleate
ethisterone
hexocyclium methylsulfate
isoniazid
morphine sulfate
meprobamate
mercurophylline
methyltestosterone
methamphetamine hydrochloride
neostigmine bromide
nicotinic acid
nicotinamide
N-acetyl-p-aminophenol
pentobarbital
pyrilamine maleate
pilocarpine hydrochloride
progestrone
prednisone
propylthiouracil
piperazine tartrate
phenobarbital sodium

promazine hydrochloride
potassium phenoxymethyl penicillin
pheniramine maleate
piperazine tartrate
quinidine sulfate
quinine sulfate
reserpine
sodium penicillin
sodium salicylate
sulfadiazine
sulfanilamide
tolbutamide
tolazoline hydrochloride

and their pharmaceutically active acid-addition salts.

EXAMPLE 2

The following example illustrates the slow release of a readily water soluble compound.

Twenty tablets were prepared according to each of the following formulas where amounts are stated in grams.

Ingredient	A	B	C	D	E	F	G
Quinine hydrochloride	0.050	0.050	0.050	0.050	0.050	0.050	0.050
Carbopol 934	0.050	0.050	0.050	0.050	0.050	0.050	0.050
Carbowax 4000	None	0.010	0.040	0.050	0.075	0.100	0.190
Tricalcium phosphate	0.390	0.380	0.350	0.340	0.315	0.290	0.200
Magnesium stearate	0.010	0.010	0.010	0.010	0.010	0.010	0.010
Total	0.500	0.500	0.500	0.500	0.500	0.500	0.500

The tricalcium phosphate acts as a diluent and the magnesium stearate as a lubricant.

The ingredients were weighed, screened, and blended, then densified by compacting in a tableting machine. The tablets were crushed and screened as necessary to obtain granules. The granules were compacted in a tableting machine to form tablets for testing.

Dissolution tests on tablets of each formula were performed in a Stoll-Gershberg (U.S.P.) apparatus as follows. Two tablets were placed in a beaker in a basket without discs, in 500 milliliters of 0.1 N hydrochloric acid. The basket was oscillated and samples withdrawn, with filtration, at intervals of 15 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes and 180 minutes after tablet addition to the solution. Each withdrawn sample was diluted with aqueous solution and assayed spectrophotometrically for drug content. The results are shown in FIG. 3.

The results show that with no polyethylene glycol present there was substantially no retardation of the dissolution of the quinine hydrochloride in the pH 1.5 medium. Formulations B, C, D and E with progressively increasing quantities of PEG showed a stepwise decrease in the dissolution of the quinine hydrochloride reaching the slowest rate of dissolution in sample E. In sample E the PEG content was 15% by weight and the ratio of Carbopol 934 to PEG was 1:1.5.

Formulations F and G with further progressively increasing concentrations of PEG showed a stepwise increase in the dissolution rate of the quinine hydrochloride from the minimum rate reached with Formula E. This is believed to be due to the presence of an excess of PEG in the presence of the Carbopol-PEG complex which functioned as a retarding mechanism. The excess PEG acted as a solubilizing agent to increase the dissolution of the quinine hydrochloride.

It may be inferred from the foregoing data that the rate of dissolution of an active ingredient may be readily controlled by varying the PEG content and the ratio of Carbopol to PEG in the system.

From the foregoing data it is apparent that the use of varying relative amounts of the carboxy vinyl polymer and polyethylene glycol will permit the formulation of a sustained action system giving a desired release rate of a drug, substantially independent of pH.

If desirable, an immediate-release portion of a drug may be included in one of several ways, such as in a separate layer of a double-layer tablet, or in the coating of a coated tablet.

EXAMPLE 3

The following example illustrates the preparation of a two-layered tablet embodiment of a composition of this invention.

Layer 1.—Sustained action portion

	Mg.
Oxazepam	30
Carbopol 934	75
Avicel (monocrystalline cellulose)	150
Carbowax 4000 (PEG 4000)	75
Lactose, monohydrate, USP	162
Magnesium stearate USP	8
Total	500

Layer 2.—Fast release portion

Oxazepam	15
Methylcellulose (400 cps.)	30
Amberlite IRPEA	3
FDA Yellow No. 5 lake	1.9
Magnesium stearate USP	1.5
Lactose, monohydrate, USP	138.6
Total	190.0

The total tablet weight was 690 mg.

Preparation of layer 1

All of the ingredients were mixed and screened then slugged on a tableting machine. The slugs were comminuted to produce granules of predetermined size. The granules were the compressed as a first layer in a double-layer, tableting machine.

Preparation of layer 2

All of the ingredients were mixed and screened then slugged on a tableting machine. The slugs were reduced in particle size and the resulting granules were recompressed as the second layer of the above tablets in a double-layer, tableting machine.

The dissolution rate of the drug contained in layer 1 is substantially similar to that shown in curve D of FIG. 1, when tested by the procedure of Example 1.

EXAMPLE 4

The following example illustrates the preparation of a tablet by a wet granulation method.

The sustained release layer of the tablet was prepared with:

	Mg.
Oxazepam	30
PEG 4000	75
Carbopol 934	75
Avicel	150
Lactose hydrous USP powder	162
Magnesium stearate USP	8
Total weight	500

All of the solid ingredients except magnesium stearate were wet granulated by mixing with ethyl ether, placed in trays and dried in an atmospheric oven at 135 degrees F. The dried mixture was passed through a number 12 (U.S. Standard sieve series) wire screen, and magnesium stearate was added through a number 30 screen. The ingredients were mixed thoroughly and pressed on a tablet press.

The fast release layer had the same formula as the fast release layer of Example 3 and was prepared by dry granulation as in Example 3. A two-layer tablet was formed as described in Example 3.

The dissolution of the active ingredient from the sustained release layer portion was shown to be substantially the same in a pH 7.4 phosphate buffer as that shown in curve D of FIG. 1.

Tablets may also be prepared following the above procedure but substituting absolute ethyl alcohol for ethyl ether in the granulating solution or by substituting PEG 6000, PEG 10,000, or PEG 20,000 for the PEG 4.000.

EXAMPLE 5

Sustained release tablets are prepared by the procedure of Example 4, but substituting the following formula per tablet:

	Mg.
Mephentermine sulfate powder	150
Carpobol 934	150
PEG 6000	150
Powdered sucrose	40
Talc	10
Total	500

EXAMPLE 6

Sustained release tablets are prepared by the procedure of Example 1, but substituting the following formula per tablet:

	Mg.
Promazine hydrochloride powder	25
Carbopol 934	125
PEG 20,000	125
Calcium stearate USP	11
Kaolin	214
Total	500

EXAMPLE 7

Sustained release tablets are prepared by the procedure of Example 1, but substituting the following formula per tablet:

	Mg.
6 - (1 - aminocyclohexanecarboxamido)-3,3-dimethyl 7 - oxo - 4 - thio - 1-azabicyclo[3.2.0]heptane-2-carboxylic acid	300
Carbopol 934	130
Carbowax 4000 (PEG 4000)	130
Lactose	75
Magnesium stearate	15
Total	650

EXAMPLE 8

Sustained release tablets are prepared by the procedure of Example 1, but substituting the following formula per tablet:

	Mg.
Crystalline acetylsalicylic acid (40 mesh USP)	300
Carbopol 934	75
PEG 20,000	75
White mineral oil	10
Dry starch	40
Total	500

EXAMPLE 9

Sustained release tablets are prepared by the procedure of Example 1, but substituting the following formula per tablet:

	Mg.
Potassium phenoxymethyl penicillin	250
Carbopol 934	75
PEG 4000	75
Sodium benzoate	10
Lactose (milk sugar)	90
Total	500

A process for making the sustained action pharmaceutical tablets comprises intimately mixing a powdered drug

with a carboxy vinyl polymer of acrylic acid copolymerized with about 0.75 to 2 percent of polyalkenyl polyether, and polyethylene glycol having a molecular weight of about 1,000 to 20,000 in which the drug comprises about 1 to 90 percent by weight of the mixture, and the carboxy vinyl polymer together with the polyethylene glycol comprises about 10 to 60 percent by weight of the composition, the latter being present in a ratio of about 1:0.5 to 1:3.8 to each other, and then compressing the intimately mixed ingredients to form tablets for oral medication.

The existence of a carboxy vinyl polymer-polyethylene glycol complex may be demonstrated as follows. A solution of polyethylene glycol is added to a solution of carboxy vinyl polymer at various pHs. A precipitate forms below about pH 4. No precipitate forms when the pH is about 4 or higher. The results indicate the formation of an insoluble complex below about pH 4, but not above about pH 4.

FIG. 2 is a graph of a phase solubility study of Carbopol 934 and PEG 4000. In carrying out the study known amounts of various concentrations by weight of PEG 4000 were added to known amounts of an aqueous solution of 0.5 percent by weight of Carbopol 934. The amount of PEG 4000 remaining in solution was determined and subtracted from the total PEG 4000 added to determine the amount of PEG 4000 in the complex. The slope of the curve of FIG. 2 indicates that the interaction is about 1:1.5 on a weight basis of the two polymers Carbopol 934 and PEG 4000. The ratio may vary through a range of 1:0.5 to 1:3.0.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

What is claimed is:

1. A tablet consisting essentially of

(A) A powdered, orally effective drug in an amount sufficient to give a pharmacologic response upon ingestion and absorption, said drug being intimately mixed with

(B) A substantially acid carboxy vinyl polymer of acrylic acid cross-linked with about 0.75 to about 2 percent by weight of a polyalkenyl polyether, and

(C) Polyethylene glycol having a molecular weight of about 1,000 to 20,000 in which said drug comprises about 1 to 90 percent by weight of the mixture, and said carboxy vinyl polymer together with said polyethylene glycol comprise about 10 to 60 percent by weight of the composition, the latter being present in a ratio of about 1:0.5 to 1:3.0 to each other,

said admixture then having been subjected to sufficient pressure to form a medicinal tablet; the rate of dissolution of (A) being readily controlled and substantially independent of pH by varying the content of (C) and the ratio of (B) to (C), the release of (A) of varying solubilities being further controllable by varying the ratio of complexable to free polymeric substance of (B) and (C), said tablet, on oral administration adapted to provide an insoluble molecular complex, unstable in basic media occurring between (C) and (B), in acidic media below about pH 4, said molecular complex functioning as the retarding mechanism.

2. A tablet composition as defined in claim **1** in the form of a double layer or coated tablet which further comprises a ready release portion of the same drug or a different drug included in a separate layer of the double layer tablet, or in the coating of a coated tablet.

3. A tablet composition as defined in claim **1** in which said carboxy vinyl polymer is present in the amount of 10 to 30 percent by weight and said polyethylene glycol is present in the amount of 5 to 30 percent by weight.

4. A tablet as defined in claim 1 in which said drug is selected from the class consisting of oxazepam and quinine salt.

5. A tablet as defined in claim 1 in which the ratio of carboxy vinyl polymer to polyethylene glycol is about 1:0.8 to 1:3.0.

6. A tablet composition as defined in claim 1 in which the components include:

	Milligrams
Oxazepam	15–60
Carboxy vinyl polymer	20–150
Polyethylene glycol	20–150
Extenders, lubricants, flavoring and the like	5–450

7. A tablet composition as defined in claim 1 in which the components are as follows:

	Milligrams
Quinine salt	15–60
Carboxy vinyl polymer	20–150
Polyethylene glycol	20–150
Extenders, lubricants, flavoring and the like	5–450

8. A tablet composition as defined in claim 1 in which the components are as follows:

	Percent by wt.
6 - (1 - aminocyclohexanecarboxamido)-3,3-dimethyl - 7 - oxo - 4 - thio-1-azabicyclo [3.2.0] heptane-2-carboxylic acid	5–20
Carboxy vinyl polymer	15–25
Polyethylene glycol	15–25
Diluents, lubricants, flavoring and the like	5–65

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424—19, 22