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 (54) Title: SUSTAINED RELEASE FORMULATION CONTAINING THREE DIFFERENT TYPES OF POLYMERS

(57) **Abrégé/Abstract:**

Verapamil depot drug formulations include the pharmaceutical itself and a three component release rate controlling matrix composition. The three components of the matrix composition are (1) an alginate component, such as sodium alginate, (2) an enteric polymer component, such as methacrylic acid copolymer, and (3) a pH independent gelling polymer, such as hydroxypropyl methylcellulose or polyethyleneoxide. The drug release rate can be adjusted by changing the amount of one or more of these components of the composition.

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(21) International Application Number: PCT/US96/01711 (22) International Filing Date: 8 February 1996 (08.02.96) (30) Priority Data: 08/395,565 1 March 1995 (01.03.95) US (71) Applicant: HALLMARK PHARMACEUTICALS, INC. [US/US]; 5 Campus Drive, Somerset, NJ 08873 (US). (74) Agent: MARSH, James, H., Jr.; Staas & Halsey, Suite 500, 700 Eleventh Street, N.W., Washington, DC 20001 (US).	(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: SUSTAINED RELEASE FORMULATION CONTAINING THREE DIFFERENT TYPES OF POLYMERS (57) Abstract Verapamil depot drug formulations include the pharmaceutical itself and a three component release rate controlling matrix composition. The three components of the matrix composition are (1) an alginate component, such as sodium alginate, (2) an enteric polymer component, such as methacrylic acid copolymer, and (3) a pH independent gelling polymer, such as hydroxypropyl methylcellulose or polyethyleneoxide. The drug release rate can be adjusted by changing the amount of one or more of these components of the composition.		

**SUSTAINED RELEASE FORMULATION
CONTAINING THREE DIFFERENT TYPES OF POLYMERS**

Field of The Invention

5 The present invention is directed to formulations for
preparing sustained release drug forms useful for releasing
pharmaceuticals at controlled rates, generally in the stomachs
and/or gastrointestinal tracts of hosts. In particular the
invention relates to an improved depot drug form useful in
10 connection with preparing sustained release tablets.

Background of the Invention

A zero order release profile for a drug from its controlled
release dosage form sometimes is desirable in clinical use. The
technology used to formulate zero order release dosage forms is
15 well documented. The entrapment of a drug in a matrix is a common
approach to formulate sustained release tablets with a zero order
release profile.

It has been reported that depot drug formulations for
controlled release of pharmaceutical drugs may be prepared using
20 alginates alone (see U.S. patent no. 5,132,295), using combinations
of alginates and polyacrylates (see U.S. patent no. 5,230,901) and
using combinations of alginates and a pH independent hydrocarbon
gelling agent, such as, for example, hydroxypropylmethyl cellulose
(se U.S. patent no. 4,792,452). It is also known that the use of
25 alginates alone for this purpose often presents difficulties in

tableting, film coating and storage.

Adding polyacrylates to the alginate formulation overcomes these difficulties to some extent; however, tablets formed using alginates and polyacrylates often have a pH dependent dissolution profile. In a low pH environment, alginates and polyacrylates do not swell and/or dissolve properly. This leads to drug release by a diffusion mechanism through non-viscous capillaries resulting in a different dissolution rate than in a high pH environment. On the other hand, in a high pH environment, alginates swell and become soluble while polyacrylates may or may not do the same. This leads to drug release both by erosion and diffusion at a rate which is different than the low pH release rate.

In formulations which include an alginate and a pH independent gelling polymer such as, for example, hydroxypropylmethyl cellulose, such polymers hydrate at low pH levels to create a viscous gel layer for drug release. At high pH levels, however, tablets become smaller and smaller during drug release due to polymer erosion, and this leads to a reduction in surface area which may affect dissolution rate.

The novelty of the present invention is the provision of a sustained release formulation which reduces, and perhaps eliminates these problems completely. In particular the invention provides a controlled release drug formulation which includes an alginate compound, an enteric polymer, such as polyacrylate, and a gelling

polymer, such as, for example, hydroxypropylmethyl cellulose. Such a combination of ingredients facilitates manufacturing procedures and improves drug dissolution profile.

In the formulation in accordance with the present invention, the gelling
5 polymer provides excellent binding and controlled release characteristics
thereby facilitating the manufacturing processes. During dissolution,
hydroxypropyl methylcellulose hydrates to form a gel layer to control drug
release at low pH levels. At high pH levels, enteric polymer increases erosion
rate so as to maintain a constant dissolution rate regardless of tablet size. So
10 reduction in tablet size does not reduce release rate. Thus, the formulations of
the present invention provide improved drug release profiles compared with
the prior art formulations described above.

According to an aspect of the present invention, there is provided a
tablet for sustained release of a drug, comprising a drug; an alginate
15 compound; an enteric polymer; and a pH independent gelling polymer.

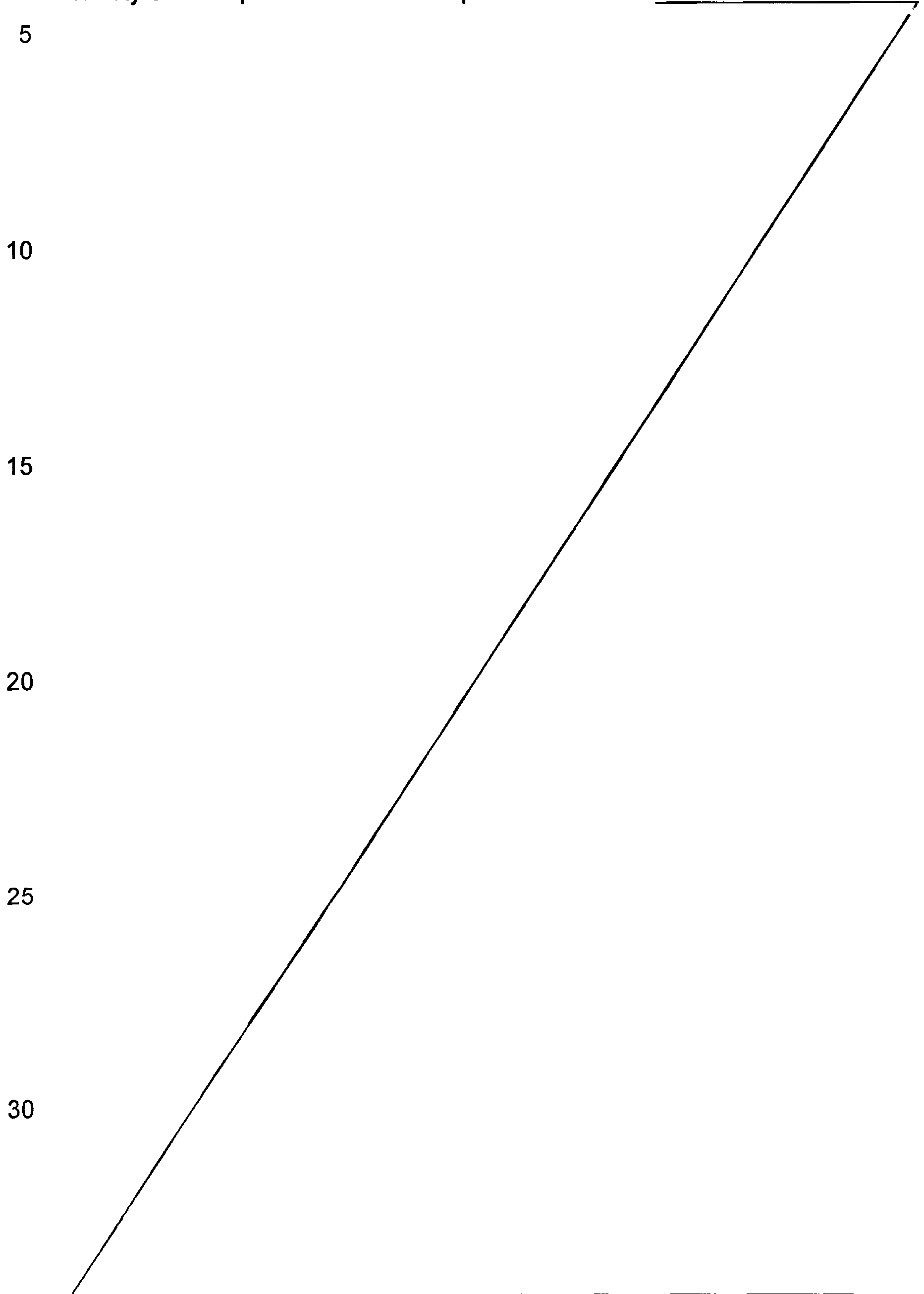
According to another aspect of the invention, a tablet for sustained
release of a drug comprising an effective amount of a drug to be released
over a period of time; an alginate component; an amount of an enteric
polymer effective at high pH levels to improve release rate due to tablet size
20 change in the dissolution process; and an amount of a pH independent gelling
polymer effective, to promote binding and controlled release in the tablet.

According to a further aspect of the invention, a controlled release
formulation for use in forming a depot drug form in conjunction with a
pharmaceutical compound comprising an alginate component, an amount of
25 an enteric polymer effective at high pH levels to improve dissolution rate due
to tablet size change in the dissolution process, and an amount of a pH
independent gelling polymer effective to promote binding and controlled
release in the tablet.

Detailed Description of the Preferred Embodiments

30 The present invention provides sustained release tablets formulated
with a mixture of a pharmaceutical composition, an alginate, an enteric
polymer and a pH independent gelling polymer from which the pharmaceutical
composition may be released at a controlled rate. In a particularly preferred

form of the invention, the formulation may be used to provide a depot drug form for controlled release of a verapamil containing pharmaceutical composition. However, the formulation, is also useful in connection with a variety of other pharmaceutical compositions and the



invention should not be considered as being limited by the exact composition and/or nature of the pharmaceutical composition which is released under controlled conditions therefrom.

5 In a preferred form, the formulation of the invention may contain 1) an alginate component in the form of a water soluble salt of an alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises, and preferably from about 100 to about 6,000 centipoises, in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer; 2) An enteric polymer
10 composition component, such as a cellulose derivative or a methacrylic acid copolymer (preferably [®]Eudragit L/S); and 3) a pH independent gelling polymer component, such as a cellulose derivative or polyethyleneoxide, having a viscosity within the range of from about 10 to about 100,000 centipoises, and preferably
15 from about 50 to about 15,000 centipoises in a 2% by weight water solution at 20° C.

The overall tablet formulation should include the alginate component in an amount so as to establish a weight ratio of alginate:active drug of from about 0.5:1 to about 3:1, and
20 preferably from about 0.7:1 to 1.5:1, in the formulation. Furthermore, the overall tablet formulation should also include the enteric polymer, such as polyacrylate composition component in an amount so as to establish a weight ratio of enteric polymer:active drug of from about 0.1:1 to about 2:1, and preferably from about

0.2:1 to 1:1, in the formulation. Still further to the overall tablet formulation should also include the pH independent gelling polymer component in an amount so as to establish a weight ratio of gelling polymer:active drug of from about 0.03:1 to about 2:1, and preferably from about 0.1:1 to 1:1, in the formulation.

Suitable enteric polyacrylate materials are fully described, for example, in U.S. letters patent no. 5,230,901. In this regard, the term polyacrylate is used herein to encompass the polyacrylates, the polymethacrylates and the copolymers of acrylic and methacrylic acid disclosed in the '901 patents. These materials are also described in, for example, Houben-Weyl, Methoden der organischen Chemie, Thieme-Verlag, Stutt, 12961. Products which are commercially available under the name Eudragit® are particularly suitable. Other suitable enteric polymers include, for example, cellulose derivatives such as, cellulose acetate phthalate, cellulose phthalate hydroxypropylmethyl ether, polyvinyl acetate phthalate, etc.

Other ingredients which may be optionally included in the formulation of the invention include 1) one or more binders such as, for example, povidone (polyvinylpyrrolidone), modified starch, low viscosity hydroxypropylmethyl cellulose, etc.; 2) one or more fillers such as, for example, microcrystalline cellulose, lactose, starch, calcium sulfate, etc.; 3) one or more lubricants such as,

for example, magnesium stearate, stearic acid, etc.; 4) one or more coating film formers such as, for example, Opadry (a hydroxypropylmethyl cellulose based coating system); and 5) one or more colorants such as, for example, FD&C green dye. The binder materials may be present in an amount up to about 10% by weight of the entire formulation and the lubricant materials may be present in an amount within the range of from about 0.1% to about 5.0% by weight of the entire formulation.

In the specific examples set forth below, three specific embodiments of the invention are exemplified. These embodiments have been designated A, B and C.

SPECIFIC EXAMPLES OF THE PREFERRED EMBODIMENTS

	<u>COMPONENT</u>	<u>AMOUNT OF COMPONENT IN EACH EMBODIMENT</u>		
		<u>A</u>	<u>B</u>	<u>C</u>
15	1. VERAPAMIL HCL	240 MG	120 MG	240 MG
	2. SODIUM ALGINATE	250 MG	80 MG	200 MG
20	3. HYDROXYPROPYLMETHYL CELLULOSE	50 MG	15 MG	--
	4. POLYETHYLENEOXIDE	--	--	60 MG
25	5. METHACRYLIC ACID COPOLYMER (®Eudragit L/S)	120 MG	30 MG	100 MG
30	6. POVIDONE	50 MG	25 MG	40 MG
	7. MICROCRYSTALLINE CELLULOSE	60 MG	80 MG	80 MG
35	8. MAGNESIUM STEARATE	5 MG	2 MG	5 MG

Items 1 through 7 listed above are mixed in a mixer such as a high shear granulator or planetary mixer to obtain homogeneity. The mix is then granulated in water or other suitable granulation fluids and dried in a dryer. The dried granular mass is then milled and then item 8 (a lubricant) is added during milling. The lubricated granular mass is then compressed into tablets using a tablet press. The foregoing steps are conventional steps used in the tablet forming industry.

In the preferred embodiments set forth above, the formulations of the invention have particular utility in the preparation of sustained release tables of verapamil. However, the invention is not limited to use in connection with this drug only. Tables containing other drugs requiring sustained release are well within the intended scope of the invention. For example, it is contemplated that the sustained release formulations of the invention have utility in connection with drugs such as propafenone, barucainide, nesapidil, gallopamil and biperiden. Other suitable pharmaceutical drugs which may require sustained release and which therefore are within the scope of the present invention are listed in U.S. patent no. 4,792,542 to Howard et al.

CLAIMS:

1. A tablet for sustained release of a drug comprising a drug; an alginate compound; an enteric polymer; and a pH independent gelling polymer.
2. A tablet as set forth in claim 1, wherein said gelling polymer comprises hydroxypropylmethyl cellulose.
3. A tablet as set forth in claim 1, wherein said enteric polymer comprises a methacrylic acid copolymer.
4. A tablet as set forth in claim 1, wherein said enteric polymer comprises a cellulose derivative.
5. A tablet as set forth in any one of claims 1 to 4, where said alginate component is a water soluble salt of alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer.
6. A tablet as set forth in claim 5, where said alginate component is a water soluble salt of alginic acid having a viscosity within the range of from about 100 to about 6,000 centipoises in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer.
7. A tablet as set forth in claim 1, wherein said pH independent gelling polymer component is a cellulose derivative.
8. A tablet as set forth in claim 1, wherein said pH independent gelling polymer component is polyethyleneoxide.
9. A tablet as set forth in claim 1, wherein said pH independent gelling polymer component has a viscosity within the range of from about 10 to about 100,000 centipoises in a 2% by weight water solution at 20° C.
10. A tablet as set forth in claim 9, wherein said pH independent gelling polymer component has a viscosity within the range of from about 50 to about 15,000 centipoises in a 2% by weight water solution at 20° C.

11. A tablet as set forth in claim 1 comprising an amount of said alginate component ranging from 0.5:1 to 3:1 based on the ratio of the said alginate to said drug; an amount of said enteric polymer ranging from 0.1:1 to 2:1 based on the ratio of the said enteric polymer to said drug; and an amount of said pH independent gelling polymer ranging from 0.03:1 to 2:1 based on the ratio of said pH independent gelling polymer to said drug.

12. A tablet as set forth in claim 11 wherein said alginate component is a water soluble salt of an alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer and said pH independent gelling polymer component has a viscosity within the range of from about 10 to about 100,000 centipoises in a 2% by weight water solution at 20° C.

13. A tablet as set forth in claim 12 comprising 240 parts by weight verapamil as said drug, 250 parts by weight sodium alginate as said alginate component, 50 parts by weight hydroxypropylmethyl cellulose as said gelling polymer, 30 parts by weight methacrylic acid copolymer as said enteric polyacrylate, further comprising 50 parts by weight polyvinylpyrrolidone, 60 parts by weight microcrystalline cellulose, and 5 parts by weight magnesium stearate.

14. A tablet as set forth in claim 11 comprising 120 parts by weight verapamil as said drug, 80 parts by weight sodium alginate as said alginate component, 15 parts by weight hydroxypropylmethyl cellulose as said gelling polymer, 120 parts by weight methacrylic acid copolymer as said enteric polyacrylate, further comprising 25 parts by weight polyvinylpyrrolidone, 80 parts by weight microcrystalline cellulose, and 2 parts by weight magnesium stearate.

15. A tablet as set forth in claim 13 comprising 240 parts by weight verapamil as said drug, 200 parts by weight sodium alginate as said alginate component, 60 parts by weight polyethyleneoxide as said gelling polymer, 100 parts by weight methacrylic acid copolymer as said enteric polyacrylate,

further comprising 40 parts by weight polyvinylpyrrolidone, 80 parts by weight microcrystalline cellulose, and 5 parts by weight magnesium stearate.

16. A tablet as set forth in claim 11 wherein said drug is verapamil.

17. A tablet as set forth in claim 11 wherein said amount of said alginate component ranges from 0.7:1 to 1:1.

18. A tablet as set forth in claim 11 wherein said amount of said enteric polymer ranges from 0.2:1 to 1:1.

19. A tablet as set forth in claim 11 wherein said amount of said gelling polymer ranges from 0.1:1 to 1:1.