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Controlled release compositions comprising gellan gum gels

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(54) Title: CONTROLLED RELEASE COMPOSITIONS COMPRISING GELLAN GUM GELS

(57) Abstract

The present invention is concerned with a controlled release gellan gum system comprising a biologically active ingredient dispersed therein.

CONTROLLED RELEASE COMPOSITIONS COMPRISING GELLAN GUM GELS

The present invention relates to a composition and method for the effective controlled timed release of various molecular weight biologically active molecules ranging from small molecular weight vitamins to large proteins to an intended recipient such as a human or animal in an therapeutically effective manner and amount employing gellan gum.

BACKGROUND OF THE INVENTION

Encapsulation of ingredients in gels, such as gellan gum, is known. For example, Japanese Patent No. 62125850 discloses encapsulation of ingredients, such as food, oils, medicines and the like, within beads of gellan gum. This published patent application reports that in an example, a salad oil emulsion was added as 0.5ml size drops to a 1% gellan gum solution. This publication reports that resulting beads had a 0.35mm thick skin and contained 0.3ml of oil in each sphere.

U.S. Patent No. 4,563,366 discloses a gelled food product which comprises a matrix containing at least one dispersed food ingredient which comprises vegetable, fruit, meat, fish, sugar, and/or milk.

GB Patent No. 2219803 discloses a gelling composition which comprises a blend of gellan, kappa-carrageenan and mannan. This gelling composition is said to be useful as a gelling matrix in food products such as pet foods and the like.

Japanese Patent No. 63267361 discloses a gel which is said to contain fragrances, microbicides, insecticides, and the like, in addition to a gelation agent selected from gellan gum, and its combination with carrageenan, gelatin, agar, locust bean, gum, xanthan gum, carboxymethyl cellulose and the like.

Most conventional tablets are hard to swallow, especially for children and the elderly. It is proposed that gellan gum gels, with their moist jelly-like easy to swallow texture, can present an attractive alternative for oral delivery. The gel structure could be swallowed by itself or suspended in a liquid formulation.

However, controlled release of biologically active molecules is desired in particular when the bioavailability of the biologically active molecule is required to be delivered in an effective manner over a long period of time (i.e. several hours) and/or with constant release rate, and/or independently of dosage strength.

OBJECTIVES OF THE INVENTION

It is an objective of the invention to provide a control release system. This and other objects are met in this invention which is described in detail hereinafter.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides a composition and a method whereby gellan gum gels can be used effectively to release biologically active molecules in an effective controlled release manner over time. A method is also provided for setting, adjusting and regulating the release characteristics for an intended recipient and user such as a human or an animal. A therapeutic effective amount of active ingredient is delivered to the recipient by this invention.

In one aspect the invention provides a method for providing a controlled rate of release for a therapeutically effective drug which comprises forming a solid composition of a low acyl gellan gum, at least one additional gelling or non-gelling polymer, and said therapeutically effective drug, wherein said low acyl gellan gum and said at least one additional gelling or non-gelling polymer provide said controlled rate of release for said therapeutically effective drug.

In another aspect the invention provides a solid composition comprising a low acyl gellan gum, at least one additional gelling or non-gelling polymer, and a therapeutically effective drug, wherein said low acyl gellan gum and said at least one additional gelling or non-gelling polymer provides a controlled rate of release for an effective amount of said therapeutically effective drug therein.

In another aspect the invention provides a method of treating a patient comprising administering a solid composition comprising a low acyl gellan gum, at least one additional gelling or non-gelling polymer, and a therapeutically effective drug, wherein said low acyl gellan gum and said at least one gelling or non-gelling polymer provide a controlled rate of release for an effective amount of said therapeutically effective drug therein.

DETAILED DESCRIPTION OF THE INVENTION

According to one embodiment of the present invention, a gellan gum is provided with an effective pore size range that can be easily modified to affect the release characteristics of a biologically active molecule to its intended recipient such as a human or an animal.

Accordingly, the present invention enables a "tunable" release of biologically active molecules to the intended target over, during and after a desired time.

Such tuning can be achieved in several ways including by varying gum concentration, the nature and concentration of gelling cations, and by incorporating other polymers in the gel network. A polymer of choice to be added to gellan gum gel is xanthan gum. Increasing the concentration of xanthan gum in the gel increases the viscosity in the gel and reduces its effective pore size. One skilled in the art will recognise that affecting the average effective pore size or the viscosity in the gel will affect the release characteristics of such system after reading this specification.

A useful property of gellan gum for the present invention is its ability to gel with most cations, including counter ions of the biologically active molecule to be incorporated into the gel. Aptly, the gel phase employed in this invention comprises a gellan gum.

Gellan gum refers to and includes the extracellular polysaccharide obtained by the aerobic fermentation of the microorganism, *Sphingomonas elodea*, in a suitable nutrient medium. Various forms of gellan gum are known (e.g., native, deacylated, deacylated clarified, partially deacylated, and partially deacylated clarified) and may be employed as a gel in practicing this invention. Mixtures thereof may be employed.

It is preferred that the gellan gum employed in a gel of this invention comprises a "low acyl" gellan gum. As used herein, the term "low acyl" denotes a level of acylation of the gellan gum of about 0.3 to about 30% by weight although gellan gum with greater or lower acylation levels may be employed in practicing this invention if desired. Another way for tuning release characteristics from the gel would be to mix some native gellan gum (high acyl content) with its deacylated form.

Gellan Gum is a naturally occuring polysaccharide that is produced by inoculating a carefully formulated fermentation medium with the microorganism Sphingomonas elodea (ATTC 31461). Gellan gum is available in clarified form KELOGEL® for foods and industrial products and a clarified form GELRITE ® from Monsanto Company, St. Louis, Missouri, for microbiological media, plant tiessue culture and pharmaceutical applications. The gelling mechanism of Gellan Gum is based on cation inducted macromolecular chain reorganization. Gellan gum includes nonclarified, clarified, and partially clarified native, deacylated and partial deacylated forms as well as mixtures thereof and the like.

A process for the preparation of gels useful herein comprises admixing water with gellan gum to a concentration from about 0.1% to about 5% by weight to form a gum containing composition, with or without sequestrant, optionally with other polymers, and maintaining said gum composition at a temperature sufficiently warm to maintain full hydration of said gum such that gelation will occur upon subsequent cooling. A biologically-active ingredient may then be admixed with the warm solution along with optionally admixing solubilizing and suspending aids. Further optionally admixing therewith includes cations. Cooling the warm solution containing said biologically active ingredient to a temperature in the range sufficient to induce

gelation then follows. The biologically active ingredient is thus within the gelled gum.

It is preferred that the gellan gum be present in the gelled phase in an amount of about 0.1 to about 5% by weight, based on the weight of the gelling agent in water, for example, about 0.25 to about 2.5% by weight although greater or lesser amounts may be employed if desired.

The gelled phase may also optionally contain a preservative. A preferred preservative is n-propyl p-hydroxybenzoate and the like. The preservative is suitably employed in a minor amount, such as not greater than about 0.2% by weight of the gelled phase although greater or lesser amounts may be employed if desired.

Optionally, if desired, the gelled phase may further contain a biocide, typically present in an amount of about 0.05% to about 2.5% by weight based on the weight of the gelled phase although greater or lesser amounts may be employed if desired.

If desired, the gellan gum may typically be gelled by a suitable cation such as calcium, magnesium, mixtures thereof and the like. A particularly attractive method of inducing gelation is to use the counter ion of biologically active molecule(s) to be incorporated into the gel.

The form and texture of the gel will depend on the desired application. For example, to be used as an oral (intact) delivery system care should be taken to obtain a gel hard enough to be handled easily by hand without breaking or damage to the gel. If the gel needs to be mixed with food, a softer, easier to break gel structure maybe desirable. Such change of texture can easily be adjusted by the person skilled in the art by varying gum and cation concentration and other optional additives after reading this specification.

If one of skill in the art should desire to employ multivalent gelling cations, these illustrative cations could be suitably provided by salts such as calcium chloride, magnesium chloride, calcium sulphate, magnesium sulphate, mixtures thereof and the like. Other suitable cations may be employed if desired, including that of the biologically active molecule(s).

In an instance where monovalent gelling cations are employed in practicing this invention, it is preferred that the gelling solution remains substantially free of multivalent ions, such as calcium, magnesium or the like. One of skill in the art will appreciate that it is normal practice in the art to use multivalent ions to increase gel strength.

As hereinbefore described, an object of the present invention is to contain within a gel having effective release properties a biologically active ingredient for its subsequent controlled release from the gel. Aptly, the active ingredients comprise small molecules or larger proteins whose release characteristics may be different and can be tuned in different ways for effective release to a human or animal as has been discovered in this invention.

Examples of such biologically active molecules includes without limitation, for small species, ascorbic acid (vitamin C), sodium naproxen, sodium salicylate, ibuprofen and for larger proteins, insulin, myoglobin, bovine somatotropin, and albumin, mixtures thereof and the like. Those of skill in the art will recognize that other biologically active molecules may be employed equally well in practicing this invention and that examples provided herein are for illustration only and are not intended to be limiting in any way.

It can be appreciated from the above recitation that the range of biologically active ingredients having a wide range of molecular weights can be employed in practicing this invention according to the Examples and teachings herein without limitation.

Gelation is desirably achieved by addition of gelling cations, typically monovalent or divalent ions such as calcium, potassium or sodium. Such cations may be present in sufficient quantity in the biologically active ingredient such that no external source is needed. If added to warm solution, the mixture is allowed to cool and set to form a gel. If it is required for the solution to be kept at room temperature (i.e. for temperature sensitive or volatile biologically active molecules), the addition of a slow diffusing (dissolving) cation source is preferred.

EXAMPLES

Examples are provided by way of illustration and are not intended to limit the invention in any way.

Example for Gelled System

To 10 mL of dionized water brought to approximately 90 C was added 30 mg of GELRITE® gellan gum and stirred until fully hydrated to form a 0.3% solution. Then the solution was cooled down to 55°C and 100 mg (to obtain a dose of ca. 10 mg/mL) of Albumin dissolved in 1 mL water was added to the warm solution and stirred until properly dispersed. To this solution was added 0.5 mL of a warm concentrated solution of calcium chloride to reach 6 mM overall calcium concentration. Using a preset 2 mL pipet, warm aliquots were transferred into round shaped molds and left overnight to set upon cooling. Other formulations (with various gellan gum concentration and other actives were also prepared in a similar way and are summarized in Table 1 following.

Active Ingredient	GELRITE® Initial Concentration	Active Dose (per mL of Gel)	Overall Calcium Concentration
Albumin	0.3%	10 mg/mL	6 mM
Albumin	0.5%	10 mg/mL	6 mM
Albumin	0.75%	10 mg/mL	6 mM
Albumin	1.0%	10 mg/mL	6 mM
Albumin	0.3%	20 mg/mL	6 mM
Albumin	0.5%	20 mg/mL	6 mM
Albumin	0.75%	20 mg/mL	6 mM
Albumin	1.0%	20 mg/mL	6 mM
Myoglobin	0.5%	10 mg/mL	6 mM
Myoglobin	0.75%	10 mg/mL	6 mM
Insulin	0.5%	10 mg/mL	6 mM
Bovine Somatotropin	0.3%	10 mg/mL	6 mM
Bovine Somatotropin	0.5%	10 mg/mL	6 mM
Bovine Somatotropin	0.75%	10 mg/mL	6 mM
Bovine Somatotropin	1.0%	10 mg/mL	6 mM
Ascorbic Acid	0.5%	10 mg/mL	6 mM
Ascorbic Acid	0.75%	10 mg/mL	6 mM
Sodium Naproxen	0.5%	10 mg/mL	6 mM
Sodium Naproxen	0.75%	10 mg/mL	6 mM
Sodium	0.75%	100 mg/mL	No calcium

Naproxen			added
Ibuprofen	0.75%	75 mg/mL	No calcium added
Ibuprofen	0.75%	100 mg/mL	No calcium added
Ibuprofen	0.75%	125 mg/mL	No calcium added
Ibuprofen	0.75%	150 mg/mL	No calcium added
Sodium Salicylate	0.75%	150 mg/mL	No calcium added
Sodium Salicylate	0.75%	180 mg/mL	No calcium added
Sodium Salicylate	0.75%	210 mg/mL	No calcium added
Sodium Salicylate	0.75%	250 mg/mL	No calcium added

Release rates for the active ingredient were obtained using an automated dissolution apparatus with the basket attachments (USP I) at 50 rpm and 37°C with 1 liter of solvent. Release media were dionized water for the proteins, 0.1M phosphate buffer for sodium naproxen, simulated gastric fluid (SGF) for vitamin C and sodium salicylate, and simulated intestinal fluid (SIF) for Ibuprofen. Samples of the fluid were removed at timed intervals and compared to the appropriate standard solution on a UV spectrophotometer. Typical release curves are presented in Figures 1 to 9 attached.

Figure 1: Release of various actives from 0.5% GELRITE gels (6 mM Ca). In all cases, active dose: 10 mg/mL. Average of 3 different gels for each curve.

Figure 2: Effect of GELRITE (GR) concentration on the release of Na-Naproxen (active dose: 10 mg/mL) from gels (6 mM Ca). USP 50 RPM, 37°C in 0.1M phosphate buffer. Average of 3 gels for each curve.

Figure 3: Effect of GELRITE (GR) concentration on the release of Myoglobin (active dose: 10 mg/mL) from gels (6 mM Ca). USP 50 RPM, 37°C in deionised water. Average of 3 gels for each curve.

Figure 4: Effect of GELRITE (GR) concentration on the release of Albumin (active dose: 10 mg/mL) from gels (6 mM Ca). USP 50 RPM, 37°C in deionized water. Average of 3 gels for each curve.

Figure 5: Effect of active dose on the release of Albumin from 0.5% (6 mM Ca) GELRITE gels. USP 50 RPM, 37°C in deionized water. Average of 3 gels for each curve.

Figure 6: Effect of active dose on the release of Vitamin C from 0.5% (6 mM Ca) GELRITE gels. USP 50 RPM, 37°C in simulated gastric fluid (pH 1.2). Average of 3 gels for each curve.

Figure 7: Effect of active dose on the release of Ibuprofen from 0.75% (No calcium added) GELRITE gels. USP 50 RPM, 37°C in simulated intestinal fluid (pH 6.8). Average of 3 gels for each curve.

Figure 8: Effect of active dose on the release of sodium salicylate from 0.75% (No calcium added) GELRITE gels. USP 50 RPM, 37°C in simulated gastric fluid (pH 1.2). Average of 3 gels for each curve.

Figure 9: Effect of release medium / solubility on the release characteristics of small molecular weight active ingredients from 0.75% (No calcium added) GELRITE gels. USP 50 RPM, 37°C in simulated gastric fluid (pH 1.2) for Vitamin C and sodium salicylate, in simulated intestinal fluid (pH 6.8) for sodium Naproxen, and in phosphate buffer for Ibuprofen. Active dose is 150 mg/mL in all cases except for Vitamin C which is 100 mg/mL. Average of 3 gels for each curve.

As seen in Figure 1, there is a profound difference in release characteristics between small molecules (i.e. Vitamin C and Naproxen) and larger proteins (i.e. myoglobin and albumin). For small molecules t_{50} (the time needed to release 50% of the drug from the gel) is less than 1.5 hours (ca. 30 minutes for vitamin C). For larger proteins t_{50} is more than 5 hours. It also appears that the larger the protein the slower the release rate. Therefore such gels can be used to release biologically active molecules at different rates according to their molecular weight.

For small molecules such as ascorbic acid and sodium naproxen, gum concentration has little effect on the release characteristics. This is depicted in Figure 2. In this case, one can see that increasing gum concentration in the gel from 0.5% to 0.75% (a 50% increase) has no significant effect on the release curves. However, for larger proteins, the gel network has a pronounced effect on the release characteristics. Hence an effective way of tuning release characteristics of proteins and the like would be to change gum concentration in the composition.

In Figure 3, one can see that the same increase in gum concentration (i.e. from 0.5% to 0.75%) has a profound effect on the release of myoglobin from the gels. Similarly, as shown in Figure 4, the release of albumin from the gels is significantly affected when gum concentration is increased from 0.5% to 1.0%. Therefore, for a given protein, the higher the gum concentration the smaller the release rate. Without being bound by theory it is believed that this can be explained in terms of gel effective pore size which decreases as gum concentration increases and can be used as a way of tailoring proteins release characteristics.

Those skilled in the art will recognize that blending gellan gum with another gelling or non gelling polymer would be another way of changing the effective pore size in the gel and therefore would also affect release characteristics. Concentration can also be employed. Preferred polymeric additives to Gelrite gels would be, but are not limited to, xanthan gum and native gellan gum (high acyl content).

The effect of active loading in gels is shown in Figures 5-8. For small loadings, up to ca. 30 mg/mL, release curves of both large (see Figure 5) and small (see Figure 6) molecules are affected. The higher the active concentration the faster the release. On the other hand, for higher loadings, above ca.

Figure 6 shows that for Ibuprofen, almost identical release curves are obtained when increasing loading from 75 mg/mL to 150 mg/mL (an increase of a factor 2). Similarly for sodium salicylate, an increase from 150 mg/mL to 250 mg/mL has little effect on release characteristics. This is depicted in Figure 8 and such property can be used to obtain oral dosage forms with release characteristics independent of the dosage strength, this can be attractive to design similar systems for both children and adults.

Another important parameter to take into account is the solubility of the drug in the release medium. Typical examples for small molecules are shown in Figure 9. When the active molecule is very soluble in the release medium, fast release may occur. This is the case for vitamin C in SGF and Ibuprofen in phosphate buffer. However when solubility of the active is reduced, such as Naproxen in SIF or sodium salicylate in SGF, a significant lowering in release rate is observed. The most significantly affected active ingredient is sodium salicylate, which probably turns into less soluble salicylic acid in the SGF low pH environment.

Different drugs require different release profiles. For example, if it may be desired for a pain killer or headache medicine to be released rather quickly while blood pressure regulators or anthihistaminics might require extended release profiles. It is an object of the invention to show that release profiles from gellan gum gels is drug dependent and should be used in a case-by-case basis.

For a given drug, it might be of interest to obtain different release rates from a similar formulation. It is an object of this invention to show that for a specific cases (proteins or large molecules) an increase of gellan gum concentration in the gels reduces release rates.

It might be desirable to obtain the same release characteristics from formulation containing different level of actives. For example, an adult may require the delivery of 500mg of a given drug over a period of five hours while a child would require only 250mg over the same period of time. This is an object of this invention to show that in some cases (small soluble drugs with high loading) release rates are independent of drug loading.

However, in some cases, it might be of interest to have a loading-dependent release rate from a given formulation. This is another object of this invention to show that in specific cases, for example high molecular weight proteins at low loading, release rates are dependent of loading.

Examples of other freestanding gel compositions containing vitamins, analgesics, antihistamines, decongestants, antitussives that were successfully prepared are summarized in Table 2 following.

TABLE 2

Active Name	Active Dose (mg/mL)	Gelrite® Concentration (%)	Comments
Na-Naproxen	125	1.0	Clear gels, no calcium added
Na-Salicylate	100	0.5	Clear gels, no calcium added
Acetaminophen	100	0.75	White opaque gels, 6mM Ca^{++} added
Pseudoephedrine HCl	30	0.75	Clear Gels, 6mM Ca^{++} added (weaker gels without Ca^{++})
Phenylpropanolamine	12.5	0.75	Clear Gels, 6mM

HCl			Ca^{++} added (weaker gels without Ca^{++})
Chloropherinamine	2	0.75	Clear Gels, 6mM Ca^{++} added
Bromopheniramine	2	0.75	Clear Gels, 6mM Ca^{++} added
Dextromethorphan	5	0.75	Clear Gels, 6mM Ca^{++} added
Diphenydramine HCl	12.5	0.75	Clear Gels, 6mM Ca^{++} added (weaker gels without Ca^{++})

Thus, it is apparent that there has been provided, in accordance with the instant invention, a process that fully satisfies the objects and advantages set forth herein above. While the invention has been described with respect to various specific examples and embodiments thereof, it is understood that the invention is not limited thereto and many alternatives, modifications and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications and variation as fall within the spirit and broad scope of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for providing a controlled rate of release for a therapeutically effective drug which comprises forming a solid composition of a low acyl gellan gum, at least one additional gelling or non-gelling polymer, and said therapeutically effective drug, wherein said low acyl gellan gum and said at least one additional gelling or non-gelling polymer provide said controlled rate of release for said therapeutically effective drug.

2. The method of claim 1 wherein said at least one additional gelling or non-gelling polymer is selected from a group consisting of xanthan gum; native gellan gum; or high acyl gellan gum.

3. The method of claim 1 further comprising a cation.

4. The method of claim 3 wherein said cation is selected from a group consisting of monovalent cation; divalent cation; counter cation of said therapeutically effective drug; or mixtures thereof.

5. The method of claim 1 further comprising adjusting said controlled rate of release by changing pore size, viscosity, or both.

6. The method of claim 5 wherein changing said pore size, viscosity or both is achieved by changing at least one of concentration of low acyl gellan gum; nature and concentration of said gelling cation; nature and concentration of said at least one additional gelling or non-gelling polymer; or mixtures thereof.

7. A solid composition comprising a low acyl gellan gum, at least one additional gelling or non-gelling polymer, and a therapeutically effective drug, wherein said low acyl gellan gum and said at least one additional gelling or non-gelling polymer provides a controlled rate of release for an effective amount of said therapeutically effective drug therein.

8. The composition of claim 7 wherein said at least one additional gelling or non-gelling polymer is selected from a group consisting of xanthan gum; native gellan gum; or high acyl gellan gum.

9. The composition of claim 7 further comprising a cation.

10. The composition of claim 9 wherein said cation is selected from a group consisting of monovalent cation; divalent cation; counter cation of said therapeutically effective drug; or mixtures thereof.

11. The composition of claim 7 further comprising adjusting said controlled rate of release by changing pore size, viscosity, or both.

12. The composition of claim 11 wherein changing said pore size, viscosity or both is achieved by changing at least one of concentration of said low acyl gellan gum; nature and concentration of said gelling cation; nature and concentration of said at least one additional gelling or non-gelling polymer; or mixtures thereof.

13. A method of treating a patient comprising administering a solid composition comprising a low acyl gellan gum, at least one additional gelling or non-gelling polymer, and a therapeutically effective drug, wherein said low acyl gellan gum and said at least one gelling or non-gelling polymer provide a controlled rate of release for an effective amount of said therapeutically effective drug therein.

14. The method of claim 13 wherein said at least one additional polymer is selected from a group consisting of xanthan gum; native gellan gum; or high acyl gellan gum.

15. The method of claim 13 further comprising a cation.

16. The method of claim 15 wherein said cation is selected from a group consisting of monovalent cation; divalent cation; counter cation or said therapeutically effective drug; or mixtures thereof.

17. The method of claim 13 further comprising adjusting said controlled rate of release by changing pore size, viscosity, or both.

18. The method of claim 17 wherein changing said pore size, viscosity or both is achieved by changing at least one of concentration of said low acyl gellan gum; nature and concentration of said gelling cation; nature and concentration of said at least one additional gelling or non-gelling polymer; or mixtures thereof.

19. A method according to any one of claims 1 to 6 and 13 to 18 substantially as hereinbefore described with particular reference to the examples.

20. A composition according to any one of claims 7 to 12 substantially as hereinbefore described with particular reference to the examples.

Dated this twentieth day of December 2001

MONSANTO COMPANY
Patent Attorneys for the Applicant:

F B RICE & CO

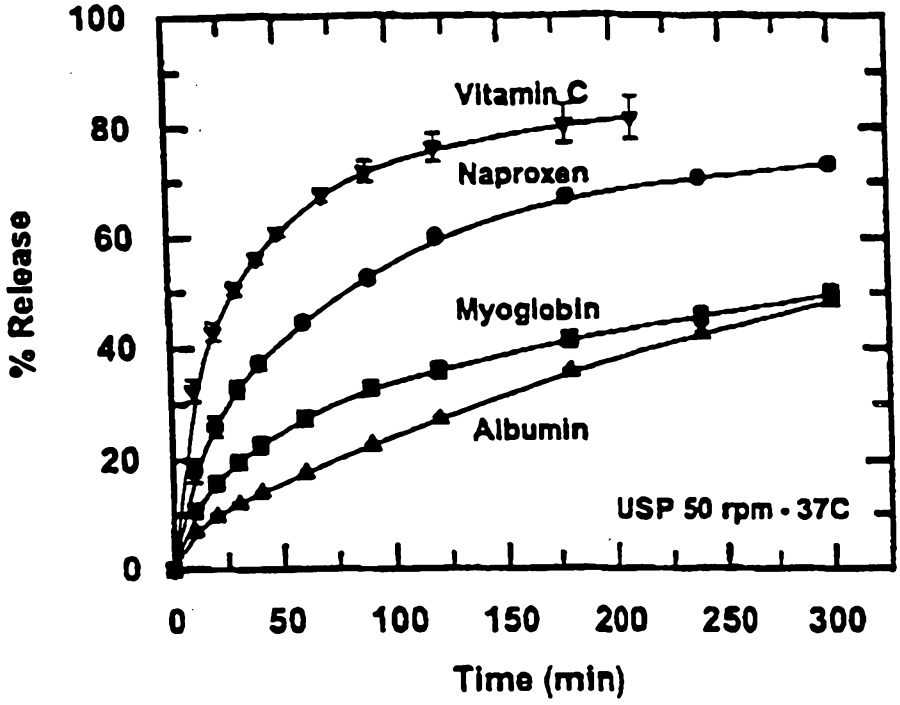

Figure 1: Release of various actives from 0.5% GELRITE gels (6 mM Ca). In all cases, active dose: 10 mg/mL. Average of 3 different gels for each curve.

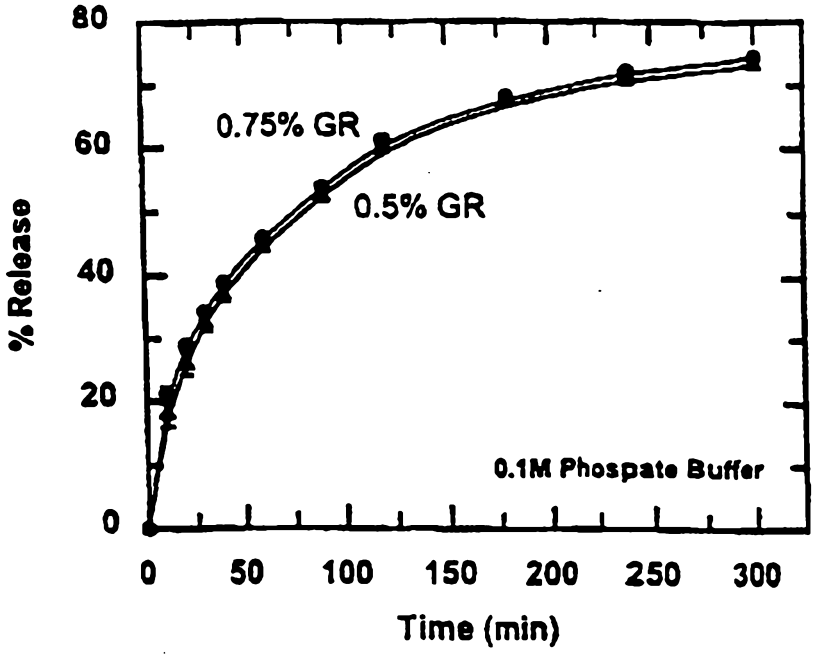

Figure 2: Effect of GELRITE (GR) concentration on the release of Na-Naproxen (active dose: 10 mg/mL) from gels (6 mM Ca). USP 50 RPM, 37°C in 0.1M phosphate buffer. Average of 3 gels for each curve.

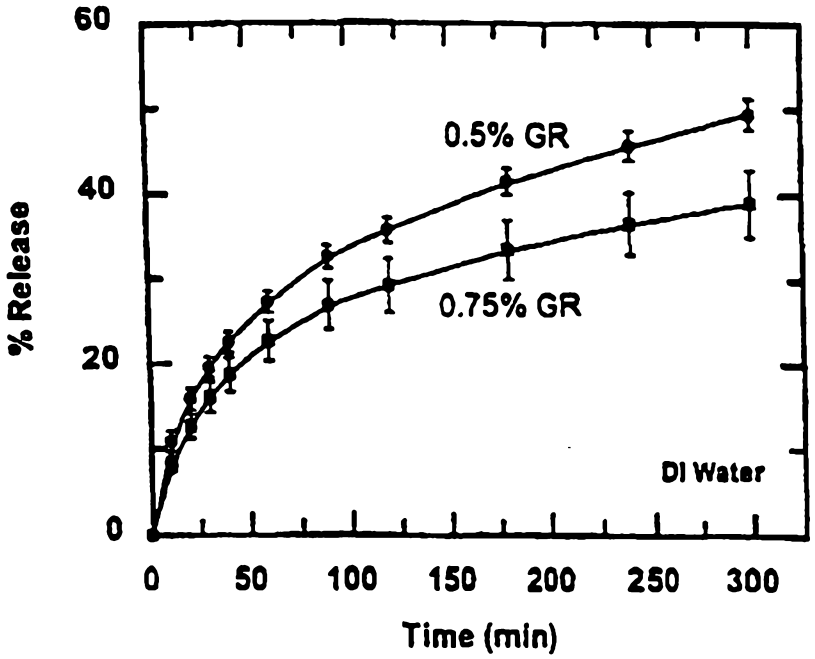

Figure 3: Effect of GELRITE (GR) concentration on the release of Myoglobin (active dose: 10 mg/mL) from gels (6 mM Ca). USP 50 RPM, 37°C in deionised water. Average of 3 gels for each curve.

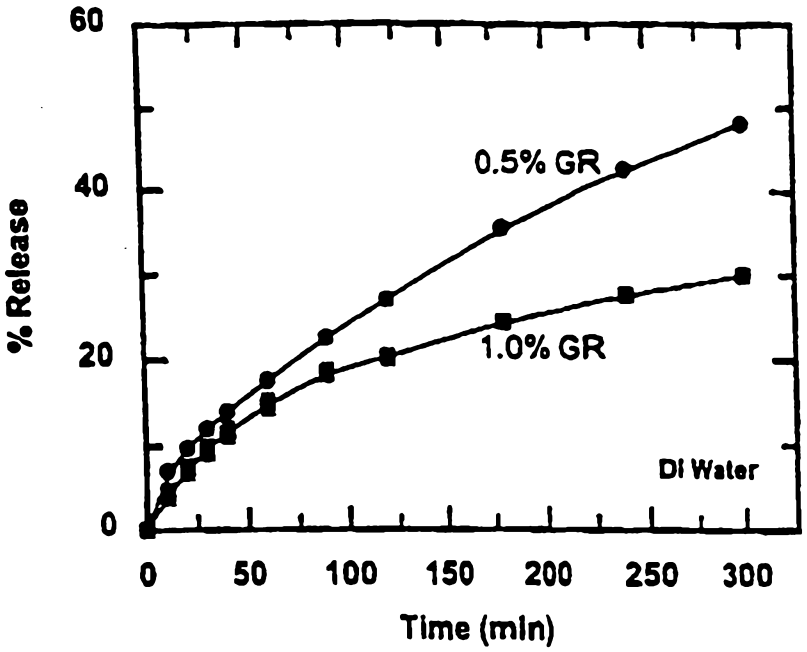

Figure 4: Effect of GELRITE (GR) concentration on the release of Albumin (active dose: 10 mg/mL) from gels (6 mM Ca). USP 50 RPM, 37°C in deionised water. Average of 3 gels for each curve.

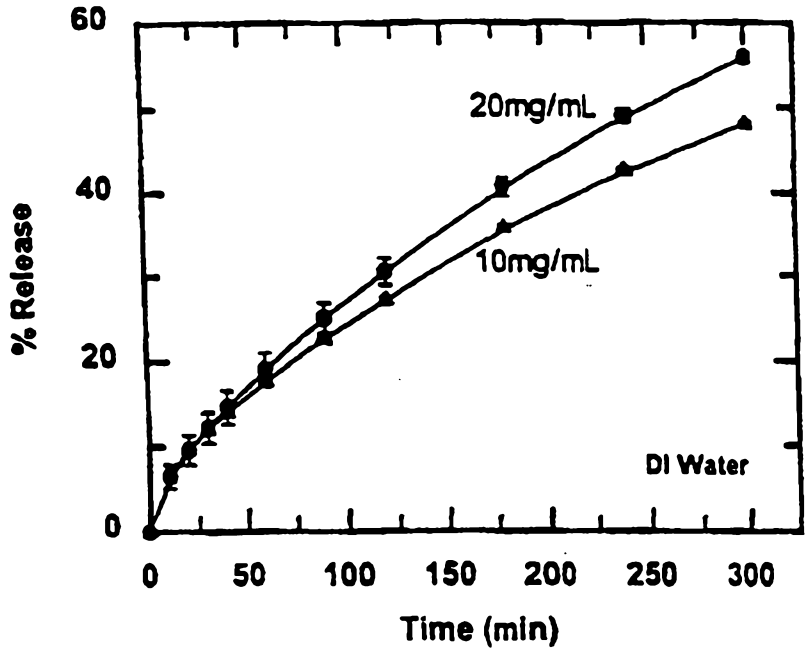

Figure 5: Effect of active dose on the release of Albumin from 0.5% (6 mM Ca) GELRITE gels. USP 50 RPM, 37°C in deionised water. Average of 3 gels for each curve.

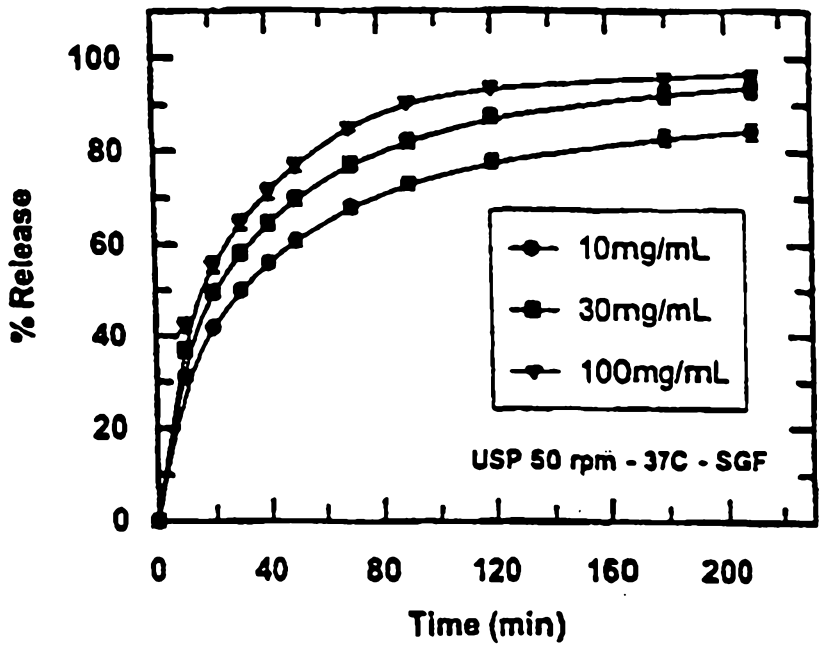

Figure 6: Effect of active dose on the release of Vitamin C from 0.5% (6 mM Ca) GELRITE gels. USP 50 RPM, 37°C in simulated gastric fluid (pH 1.2). Average of 3 gels for each curve.

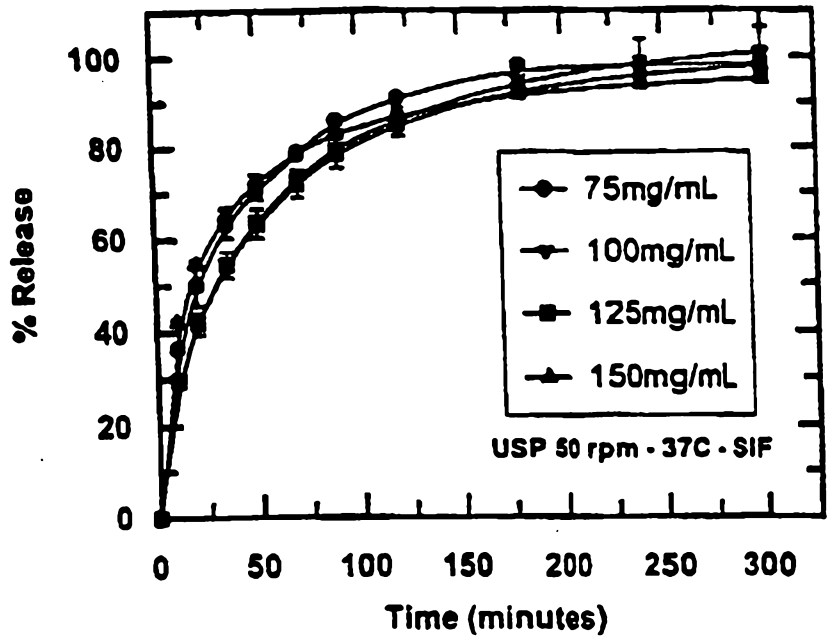

Figure 7: Effect of active dose on the release of Ibuprofen from 0.75% (No calcium added) GELRITE gels. USP 50 RPM, 37°C in simulated intestinal fluid (pH 6.8). Average of 3 gels for each curve.

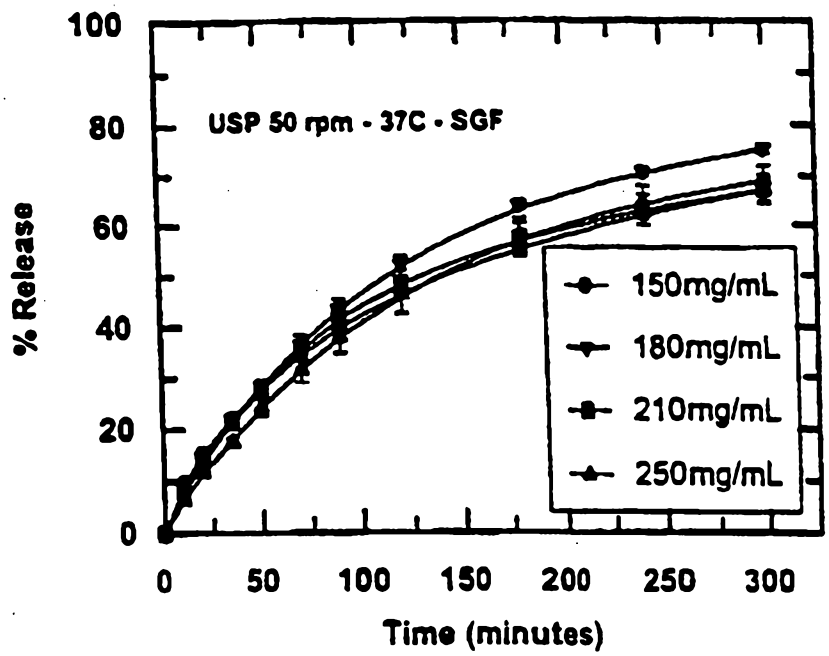

Figure 8: Effect of active dose on the release of sodium salicylate from 0.75% (No calcium added) GELRITE gels. USP 50 RPM, 37°C in simulated gastric fluid (pH 1.2). Average of 3 gels for each curve.

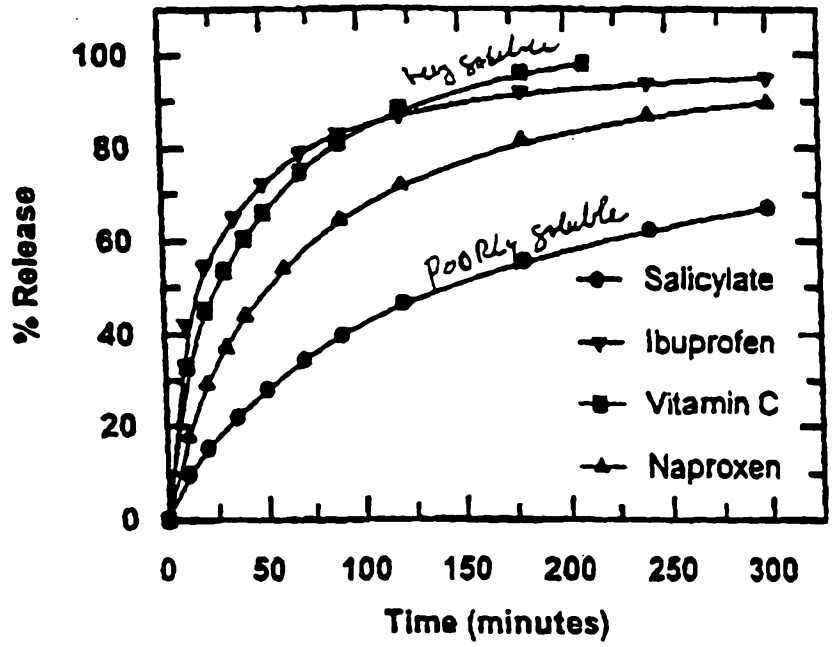

Figure 9: Effect of release medium / solubility on the release characteristics of small molecular weight active ingredients from 0.75% (No calcium added) GELRITE gels. USP 50 RPM, 37°C in simulated gastric fluid (pH 1.2) for Vitamin C and sodium Salicylate, in simulated intestinal fluid (pH 6.8) for sodium Naproxen, and in phosphate buffer for Ibuprofen. Active dose is 150 mg/mL in all cases except for Vitamin C which is 100 mg/mL. Average of 3 gels for each curve.