

Preparation and *In-Vitro* Evaluation of Floating Oral *In- Situ* Gel of Montelukast Sodium (Conference Paper)

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Abstract

A polymeric drug delivery liquid system of oral *in situ* gel of montelukast sodium has been formulated by using natural ingredients like gellan, sodium alginate and pectin. There were several goals in this study, the most important of which was to formulate an oral liquid preparation (Ion sensitive floating oral *in situ* gel system for sustained delivery of montelukast sodium for pediatric patients) that would make administration easier, provide the correct therapeutic dose, and allow the drug to be released more slowly into the gastrointestinal tract (GIT) for better control. montelukast sodium *in situ* gels at different concentrations (w/v) of natural polysaccharides, gellan gum and sodium alginate and natural polymer pectin were formulated and characterized in the terms of appearance, viscosity and *in vitro* release.

As the concentrations of ion-sensitive gel-forming components, gellan gum, sodium alginate, and pectin, and gas-generating ingredients increased, the viscosity of formulations in solution was increased. *In vitro* release study showed that the release of montelukast sodium from these gels was characterized by an initial phase of high release (burst effect), followed by a more gradual release in the second phase.

The formulated oral *in situ* gel system of montelukast sodium can be regarded as a promising approach for oral delivery of montelukast sodium to pediatrics.

Keywords: Oral sustained drug delivery, Floating *in situ* gel, Montelukast sodium, Gellan gum.

تحضير وتقييم مختبري للهلام الفموي العائم موضعياً لعقار المونتيلوكاست صوديوم (بحث مؤتمر) #
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الخلاصة

تم تحضير الهلام الفموي العائم موضعياً لعقار المونتيلوكاست صوديوم على هيئة سائل بوليميري وباستعمال مواد طبيعية كصمغ الجيلان والجيلات الصوديوم والبيكتين. هناك العديد من الأغراض لهذه الدراسة أهمها هو تطوير مستحضر سائل عن طريق الفم (نظام هلام عائم موضعياً حساس للأطفال) مما يزيد من راحة الإعطاء وإعطاء الجرعة العلاجية الصحيحة للدواء، والسماح للدواء أن يتحرر ببطء إلى القناة الهضمية لتحكم أفضل من تحضير الهلام العائم موضعياً للمونتيلوكاست الصوديوم بتركيزات مختلفة (وزن / حجم) من متعدد السكريات الطبيعي (صمغ الجيلان والجيلات الصوديوم) والبوليمر الطبيعي (بيكتين) وتم تقييمها من حيث المظهر واللزوجة والتحرر داخل المختبر. صمغ حيث زادت لزوجة التركيبات في المحلول مع زيادة تركيزات مكونات الهلام الحساسة للأطفال (صمغ جيلان، أجيلات الصوديوم والبيكتين) وتركيز عامل توليد الغاز (كاربونات الصوديوم) وأظهرت دراسة التحرر في المختبر أن إطلاق مونتيلوكاست الصوديوم من هذه المواد الهلامية تميز بمرحلة أولية من الإطلاق العالي (تأثير الانفجار) تليها المرحلة الثانية من الإطلاق المعتدل التدريجي. يمكن اعتبار نظام الهلام العائم موضعياً للمونتيلوكاست الصوديوم أسلوباً واعداً لإعطاء عقار المونتيلوكاست صوديوم عن طريق الفم للأطفال.

الكلمات المفتاحية: توصيل الأدوية عن طريق الفم، هلام موقعي عائم في الموقع، مونتيلوكاست الصوديوم، صمغ الجيلان.

Introduction

Traditional oral dosage forms, which have low bioavailability because of the quick gastric transition from the stomach and necessitate higher dosing frequency, can be overcome using floating oral *in situ* gel. As a result, pharmaceutical researchers are highly interested in finding ways to boost the therapeutic benefits of this floating oral *in situ* gelling system. The floating oral *in situ* gel has the ability to overcome the drawbacks of conventional oral dosage forms, which have a limited bioavailability to small intestine. Because of its controlled release and site-specific drug

administration, the floating oral *in situ* gelling system is of tremendous interest to pharmaceutical researchers⁽¹⁾. The development of polymeric drug delivery systems has been the subject of extensive study. Last years have seen a significant increase in interest in the development of *in situ* gel systems⁽²⁾. Before administration, the *in situ* gel dosage form is a liquid, but when it comes into contact with gastric contents, it transforms into a gel. As soon as the gastric fluids come into contact with the low-viscosity solution, the polymeric conformation of the viscous gel changes, and it floats on the surface of the gastric fluids^(3,4).

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For prolonged drug delivery, *in situ* gel forming polymeric delivery systems have been extensively studied. This is in addition to other advantages of *in situ* forming polymeric delivery systems such as simplicity of administration, lower dose frequency, enhanced patient compliance and comfort⁽⁵⁾.

An *in situ* gel undergo a sol-to-gel phase transition when certain physicochemical factors, including ionic strength, temperature, or pH, are altered⁽⁶⁾. When compared to a traditional liquid dosage form, a gastroretentive *in situ* gelling technology can help boost medication bioavailability. Polymer-based gels, which are lighter than gastric fluids, float over the stomach contents or stick to the gastric mucosa, resulting in increased gastric retention of dose forms and a longer period in the gastrointestinal tract of the drug⁽⁷⁾. The formulation of floating *in situ* gelling solution may sustain and prolong drug action, enhance patient compliance, and lower the frequency with which the drug is administered. Because of the system decrease in density, it initially sink in the stomach before absorbing water, swelling, and finally floating⁽⁸⁾.

Polysaccharides and polymers of various sorts, as well as their gel-forming mechanisms, are being studied as part of this effort to build a stomach-specific gelling system. Gellan gum is an anionic deacetylated, exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit. Double-helical junction zones are formed in the gelation process, followed by aggregation of the double-helical segments into a three-dimensional network via complexation with cations and hydrogen bonding with water⁽⁹⁾.

Because it works as a gelling agent, sodium alginate can produce a wide range of gel textures in the finished product. As a result of the free Ca²⁺ ions being trapped in sodium alginate polymeric chains, the polymer chains cross link to form a matrix structure. The gelation process begins with the production of double helical junction zones, which are then re-aggregated to create a three-dimensional network through complexation with cations and hydrogen bonding with water⁽¹⁰⁾.

Water-soluble and pH-sensitive anionic acidic pectin polysaccharide isolated from fruit. Because of its natural gelling, stabilizing, and thickening properties, it is an excellent drug delivery vehicle. An efficient delivery system can be achieved by using pectin polysaccharide-based medication carriers⁽¹¹⁾.

montelukast sodium (MK) is a selective leukotriene receptor antagonist. Chronic asthma, exercise-induced asthma, and other leukotriene-related disorders like capsular contracture and obstructive sleep apnea can all benefit from this medication⁽¹²⁾. There is only a 10 mg/day dose for adults and a 4–5 mg/day dose for children with MK. Acute asthma attacks should not be treated with this medication⁽¹³⁾. MK bioavailability after oral administration is

around 62%, and its half-life in the human body is approximately 6.7 hours⁽¹⁴⁾.

Gellan, sodium alginate or pectin solution was proposed with calcium carbonate and sodium citrate, which complexed free calcium ions so that they could only be liberated in a stomach acidic environment. The formulation was kept liquid until it was swallowed, at which point it immediately turned into a gel.

There were several goals in this study, the most important of which was to formulate an oral liquid preparation (Ion sensitive floating oral *in situ* gel system for sustained delivery of MK for pediatric patients) that would make administration easier, provide the correct therapeutic dose, and allow the drug to be released more slowly into GIT for better control.

Materials and Methods

Materials

Montelukast sodium was purchased from Hangzhou Hyper Chemical Limited, China. sodium alginate was purchased from Himedia laboratories, India. Gellan gum and pectin were purchased from Hangzhou Hyper Chemical Limited, China. Only commercially analytical-grade reagents were used for the experiment.

Preparation of *in situ* gel

In situ gel formulations were made using the ingredients listed in Table (1). Gellan gum and sodium alginate were dissolved in distilled water containing 0.17 percent w/v sodium citrate and heated to 90°C using a heating magnetic stirrer (Labtech, Korea) while stirring to produce solutions of 0.25, 0.50, and 1.0 w/v percent. Before dissolving the calcium carbonate 0.75% w/v and MK in the solution, it was cooled down to the desired temperature of less than 40°C⁽¹⁵⁾. Afterward, the solution was cooled to room temperature and the stirring was halted. Distilled water was added up to 100 ml which was the volume of the final formulation⁽¹⁶⁾.

Evaluation

Appearance

A black-and-white background was used to evaluate the clarity of each formulation⁽¹⁷⁾.

Rheological study of *in situ* gel

Brookfield viscometer DV-III (Brookfield, USA) spindle number 21, cup and bob setting at 50 rpm was used to measure the viscosity of formulations after gelling in artificial gastric fluid⁽¹⁴⁾. Each sample's viscosity was measured three times, with each measurement taking about 30 seconds⁽¹⁸⁻¹⁹⁾.

pH measurement

A calibrated digital pH meter (Schott Gerate, Germany) was used to measure the pH levels of the produced mixtures⁽¹⁶⁾.

In vitro floating study

The time the formulation took to emerge on the medium surface (floating lag time). Time in seconds was used to calculate the floating lag time, which was calculated by introducing 5 mL of formulation into a beaker containing 100 ml of 0.1N HCl, pH 1.2, at 37°C⁽²⁰⁾.

The time the formulation constantly floated on surface of the dissolution medium (duration of floating) were recorded. Ten milliliters of the formulation were added to the container of 100 milliliters (0.1N HCl, pH 1.2) at 37 ° C for the in-vitro floating study and the time it remained on the surface (duration of floating) were documented⁽²¹⁾.

In-vitro gelation study

For in vitro gelling evaluation, 10 mL of each formulation was added to 100 mL of 0.1N hydrochloric acid (HCl, pH 1.2) at 37°C in a beaker with gentle agitation that avoided breaking the gel. The ability to gel in vitro was divided into three categories based on the stiffness of the generated gel, the time it took to gel, and the length of time the gel stayed firm as such.

- (+) Gels after few minutes, dispersed rapidly
- (++) Gelation immediate remains for few hours
- (+++) Gelation immediate remains for an extended period⁽²²⁾.

Determination of drug content

For 1 hour, a magnetic stirrer was used to stir 5 ml of the solution into pH-1.2 simulated stomach fluid 0.1N. Once the solution was filtered

and sufficiently dilute with simulated gastric fluid, a UV-visible spectrophotometer (Biotecheng. UV-9200, UK) at 357 nm was used to measure the drug concentration in comparison with an appropriate blank solution by using calibration curve equation⁽²³⁾.

Measurement of drug release rate from gels

Dissolution test apparatus (Pharma-Test, Germany) USP type II (Paddle Method) was used to perform an in vitro release investigation in the Laboratory. The formulations' in vitro dissolution rates were measured using the procedure outlined below. The dissolution of MK from the formulations was measured using a paddle stirrer at 50 rpm in a USP Type II dissolution test device. A 900 ml solution of (0.1N HCL, pH 1.2) was employed as the dissolution media, and the temperature was maintained at 37°C. A 0.1N HCL solution was carefully added to the dissolution vessel without disturbing the petri plate after 10 ml of the formulation had been placed in it to prevent breaking of the gel formulation. Dissolution medium was pipetted out and refilled at regular intervals to ensure that the samples were accurately quantified. The UV-Spectrophotometer (Shimadzu UV – 2201, Japan) was used to measure the aliquot's montelukast sodium concentration spectrophotometrically at 357nm⁽²⁴⁾.

Using a graph with cumulative drug release on the y-axis and time on the X-axis, the raft formulation's dissolving profile may be plotted⁽²⁵⁻²⁶⁾.

Table 1. Floating in situ gel formulations of montelukast sodium

Formulation code	Montelukast sodium (mg)	Gellan gum (% w/v)	Sodium alginate (% w/v)	Pectin (% w/v)	CaCO ₃ (% w/v)	Sodium citrate (% w/v)
F1	4.2	0.25			0.75	0.17
F2	4.2	0.5			0.75	0.17
F3	4.2	1.0			0.75	0.17
F4	4.2		0.25		0.75	0.17
F5	4.2		0.5		0.75	0.17
F6	4.2		1.0		0.75	0.17
F7	4.2			0.25	0.75	0.17
F8	4.2			0.5	0.75	0.17
F9	4.2			1.0	0.75	0.17
F10	4.2	1.0			1.5	0.17

* All formulations were made as 100 ml volume with D.W where each formula contain 4.2 mg of montelukast sodium in each 5 ml.

Results**Characteristic of in situ gel**

As a result, the in situ gels that were created were completely transparent. An in situ gelling system can be achieved by developing formulations that behave like a fluid yet harden when exposed to gastric acid (Figure 1).

Calcium carbonate in the formulation was dissolved and released carbon dioxide when it came into contact with the stomach's acid. The calcium ions

that had been released in situ formed a gel that floated.

Measurement of viscosity of in situ gel

Table 2 shows a significant rise in viscosity with increasing polymer concentration.

pH measurement

Oral medication is necessary to avoid throat discomfort.

Everything in this recipe has a neutral or slightly alkaline pH. According to Table 2, a range of 7.1-7.86 for the pH of the formulations was obtained.

Floating behavior

In (0.1N HCl, pH 1.2) solution, the



Figure 1. Photographs taken during the in vitro floating study of Formulae (a: F3, b: F2, C: F1) in 100 mL 0.1 N HCl (pH 1.2)

In-vitro gelation study

Drug content

For each formulation, a percentage of the total drug content was calculated and is given in Table 2. The drug content was found to be in the range of 90.2-94.4% for all the formulations indicating a consistent distribution of the medicine.

In vitro drug release

Figure 2 depicts the impact of polymer type and concentration on in vitro drug release from in situ gels. MK was shown to be released from these gels in phases, with the initial phase being characterized by significant release rates (burst effect) followed by a second phase of moderate release. Matrix diffusion kinetics has a unique biphasic pattern of release. In addition, the polymer type and concentration had an effect on the release rate. Release rates from F1-F9 formulations showed that the release of MK was different when different polymer types were used, and this release was ranked in the following order: pectin > sodium alginate > gellan: Polymer concentrations range from 0.25 to 1.5%, with the longest sustained release achieved by 1% gellan containing formula F3. Figure 3 depicts the impact of in vitro drug release from in situ gels of various concentrations of gas-generating agent (CaCO₃). Formulae F3 and F10, for example, show a slower release of the drug when the concentration is increased from 0.75% to 1.5%.

Discussion

Three distinct polymer kinds and concentrations were used to make in situ gels in this investigation. In situ gelling systems must have optimal viscosity and gelling capability as prerequisites (speed and extent of gelation). The ideal viscosity for the formulation is one that is easily swallowed as a liquid, and then rapidly transforms into a gel due to ionic contact. Because they will be administered orally, the solutions' rheological qualities are critical.

floatability of the produced formulations was tested. The floating lag time. A thick gel with a good floating tendency was formed when the formulation floated for 12 hours on the surface of the dissolving medium (duration of floating)⁽²⁷⁾.

In order to explain the correlation between viscosity and concentration, it has been hypothesized that as the polymer concentration increased, the polymer chains got closer and the number of contacts between the polymer chains increased, leading to a denser 3-D network structure⁽²⁸⁾.

Depending on the formulation parameters, the floating lag time changed significantly ($p < 0.05$). When calcium carbonate is added to a formulation, the amount of CO₂ that may be trapped in the gel increases, resulting in a rising in the time it takes for buoyancy.

As a gas producing agent and a source of cations for gelation, calcium carbonate was included in the formulation. In formulae F1-F9, 0.75 percent CaCO₃ was employed to achieve the required floating duration, however larger concentrations were used in an effort to provide a more retarded release of the medication⁽²⁹⁾.

To achieve the necessary floating time, the formulas comprising 0.75 and 1.5 percent CaCO₃ were used, however larger concentrations were used in an effort at a more delayed drug release, as illustrated in figure 3. Formulas having 1.5% of CaCO₃ released drugs more slowly than those containing less of the compound⁽²³⁾.

In other words, as the formulation's calcium carbonate concentration grew, the drug's release reduced. Due to the fact that cross-linking occurs when calcium ions are present in higher concentrations, this behavior can be linked to a stronger gel being formed, which results in a more restricted and slower release of the drug.

Table 2. MK *in-situ* gelling compositions' properties.

Formulation code	Drug Content (%)	pH	Graded Gel response	Floating lag Time (sec)	Duration of floating (hr)	Viscosity (cp)
F1	90.20±0.22	7.26±0.02	+++	8±0.12	> 12 hr	244.86±1.2
F2	93.45±0.43	7.10±0.11	+++	8.5±0.16	> 12 hr	326.62±0.21
F3	92.40±0.24	7.33±0.22	+++	14±0.26	> 12 hr	522.34±0.88
F4	90.35±0.35	7.34±0.02	+++	9.5±0.42	> 12 hr	210.55±0.24
F5	94±0.12	7.22±0.18	+++	8.4±0.04	> 12 hr	287.32±0.1
F6	91.8±1.2	7.10±0.36	+++	12±0.05	> 12 hr	386.99±0.13
F7	92.6±0.3	7.32±0.4	++	10.5±0.11	> 12 hr	205.24±0.5
F8	90.3±1.1	7.24±0.21	++	12±0.02	> 12 hr	264.76±0.35
F9	92.8±0.16	7.16±0.02	++	15±0.3	> 12 hr	354.66±0.24
F10	94.4±0.42	7.30±0.24	+++	5±0.02	> 12 hr	725.35±0.33

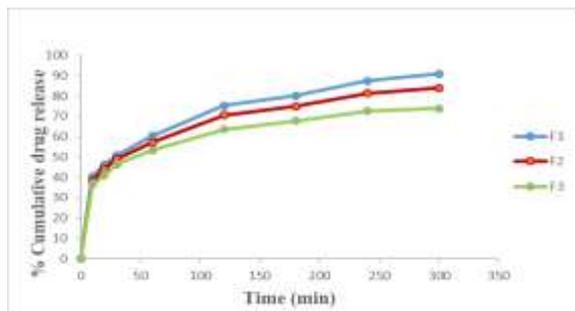


Figure 2 a. Formulations containing gellan gum

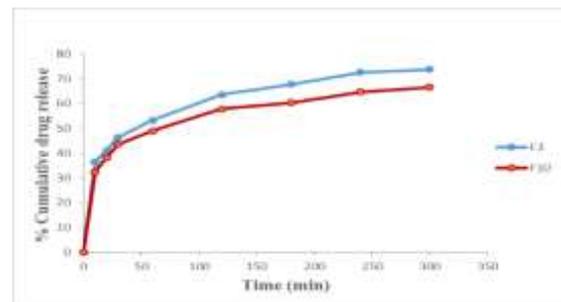
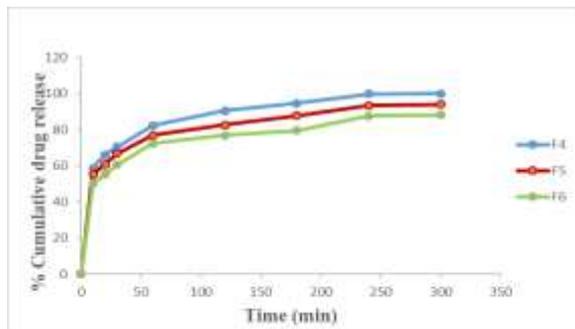
Figure 3. Comparison of two CaCO₃ concentrations, 0.75% and 1.5%, in F3 and F10, respectively, by an *in vitro* release test.

Figure 2 b. Formulations containing sodium alginate

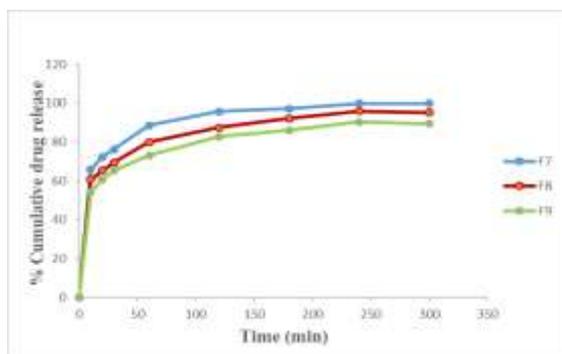


Figure 2 c. Formulations containing pectin.

Figure 2. F1 to F9 dissolution patterns were compared by an *in vitro* release test.

Conclusion

MK *in situ* gelling liquid oral formulations were developed in this investigation. It was found that the release rate could be changed by altering variables including the kind and concentration of ion-sensitive polymer and the concentration of the gas-generating agent (CaCO₃). The changes were non-significant ($p > 0.05$). Drug release from MK floating *in situ* gel may be sustained while it is still in the stomach. As a stomach-specific delivery method for montelukast sodium, it appears to be promising in the treatment of persistent asthma, prevention of exercise-induced asthma, and treatment of other illnesses in children.

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