

IN SITU GEL AS PLATFORM FOR KETOCONAZOLE SLOW RELEASE DOSAGE FORM

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ABSTRACT

Objective: The aim of this study was to formulate ketoconazole (keto) as oral floating *in situ* gel to slow the release of keto in the stomach.

Methods: Sodium alginate (Na alginate) was used as a primary polymer in the preparation of the *in situ* gel and was supported by the following polymers: guar gum (GG), hydroxypropyl methylcellulose (HPMC) K4M, K15M and carbapol 940 as viscosity enhancing agents. As a consequence, and to complete the gelation process of above formulations was by adding the calcium carbonate (CaCO₃). The *in situ* gels were investigated by the following tests: floating lag time, floating duration, viscosity, drug content, *in vitro* gelling studies and *in vitro* release study.

Results: The study showed that the faster release was obtained with F1 which contained Na alginate alone. Additionally, reduction in Na alginate concentration resulted in significant increase in drug release. It was also noted that the increase in GG (viscosity enhancing polymer) concentration resulted in non-significant decrease in percent drug release and the reduction in CaCO₃ concentration led to significant increase in drug release. Moreover, the release of drug was also affected by grade of viscosity enhancing polymer, the faster release was observed with the formula which contained a polymer of low viscosity (HPMC K4M) and an opposite result was with the high viscosity polymer (HPMCK15M).

Conclusion: This study showed the formulation of Na alginate with GG and CaCO₃, led to gain floating *in situ* gel and a sustained release of keto.

Keywords: Ketoconazole, *In-situ floating gel*, Sodium alginate, Guar gum, HPMCK4M, HPMCK15M

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INTRODUCTION

Recently, gastro retentive dosage forms (GDF) have been studied extensively by researchers due to their essential characteristic of staying in the stomach for prolonged period of time which enabled slowing and sustaining the release of the selected drug in the stomach [1]. Also, this distinctive characteristic of GDF helped in solving many problems were associated with pharmaceutical formulations such as the narrow window absorption of the upper part of the gastrointestinal tract, drugs with short half-lives, unstable drugs in the environments of lower segment of the gastrointestinal tract, drugs for local target activity in the upper region of gastric tract and the low solubility of specific drugs in the basic gastric pH [2].

The GDF can be prepared by different techniques such as the dosage of low density to gain floating delivery system or high density dosage form that retain the dosage form in the lower part of the stomach. Additionally, the GDF can be obtained by formulating an adhesion form to the stomach mucosa or in a different way by expansion the size of the formulation to delay the emptying from the upper part of gut or by using ion exchange resin to gain adherence to the stomach mucosa [3]. The *in situ* gel preparation is one of the GDF that provide a controllable drug release in the stomach. This preparation is gelled upon contact to the stomach content and floats on the stomach surface fluid due to the influence of excipients having a lower density than the stomach fluid [4]. These properties were as a guide for many researchers to develop formulations that increased the efficacy of many drugs such as Rajinikanth et al. who utilised amoxicillin as a model for *in situ* gelling and they found a better eradication of *H. pylori* in comparison with amoxicillin suspension [5]. This was due to the prolonged release in the stomach. Also, Darekar et al. prepared *in situ* gel incorporated with levocitrazine dihydrochloride to gain a prolonged release and to control the allergy symptoms [6]. In this current study, we focused on keto due to its systemic importance in mycoses treatment as this drug is classified as a fungistatic. The antifungal mechanism is by inhibiting cytochrome P450 enzyme leading to block the demethylation of primary sterols of the fungal membrane. By the aid of this mechanism, a distortion of the membrane structure is followed to retard the fungus growth. Also, keto as antifungal is a broad spectrum, inhibits a plenty of gram-positive bacteria and protozoa [7].

Also, it was reported that 90% of keto binds to plasma albumin and its elimination showed biphasic behaviour of 2 h and 8 h as initial and terminal half-lives respectively. Usually, keto is metabolised to an inactive metabolite in the liver as both the later and the unchanged form of a drug are excreted via the renal route [8].

Additionally, keto is formulated for oral route and its absorption increases at stomach low pH [9]. A part of our work novelty and according to our knowledge, no study has investigated and formulated keto as *in situ* gel. This study used advantage of the increasing solubility of keto at the low pH of stomach as this guarantees a better bioavailability due to the slow release by the *in situ* gel. Thus, many studies have been done in this work to explore the *in situ* gel of keto such as determination of keto content in different formulations. Also, the examination of the *in vitro* of both gelation and floating and this is followed by viscosity measurements. These studies were supported by studying the effect of different concentrations of CaCO₃ as a crosslinking and gas generating agent and polymer to polymer ratio of both the Na alginate and GG. Additionally, the effect of addition of different grade of HPMC in the presence of Na alginate on the release of keto was studied too.

MATERIALS AND METHODS

Materials

Keto was purchased from (Shanghai Macklin Biochemicals Co. Ltd, China), Na alginate and CaCO₃ (Sinopharm Chemical Reagent Co., Ltd. China), GG (Samara Drug Industry, Iraq), HPMCK4M and HPMCK15M (Alladin Industrial Co., Shanghai, China), carbapol 940 (Himedia lab., India.), Methyl paraben and propyl paraben (BDH Ind., India).

Methods

Keto preparation as floating *in situ* gel

Different compositions of Keto formulations of floating *in situ* gel as shown in table 1 were prepared by a gradual addition of Na alginate to a specific portion of water at 100 °C. This helps to solubilise Na alginate with the aid of stirring by using hot plate magnetic stirrer. Then this followed by addition of GG and in a different beaker, the parabens were dissolved in another portion of water at 100 °C. This

followed by addition of keto to the contents after mixing of the two beakers with continuous stirring and cooling. After 15 min of keeping as a waiting period for the preparation, the CaCO₃ was

added with continuous stirring until a homogeneous dispersion was gained. This formulation was allowed to cool at room temperature with volume adjusting using water to 100 ml [10].

Table 1: The composition of keto *in situ* floating gel different formulas

Formulation code ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Keto	2000	2000	2000	2000	2000	2000	2000	2000	2000
Na alginate	2000	2000	1000	1000	2000	2000	2000	2000	2000
GG	----	500	500	500	500	1500	----	----	----
CaCO ₃	1000	1000	1000	500	2000	2000	1000	1000	1000
Methyl paraben	90	90	90	90	90	90	90	90	90
Propyl paraben	10	10	10	10	10	10	10	10	10
HPMC k4 M	---	---	---	---	---	---	500	---	---
HPMC K 15 M	----	---	---	---	---	---	---	500	----
Carbapol 940	----	---	---	---	---	---	---	----	500
D. W (ml) up to	100	100	100	100	100	100	100	100	100

Evaluation of prepared keto *in situ* floating gel

Physical appearance and pH

All formulations were screened to check the presence of foreign particles or not. Also, the pH of all formulations was measured using a digital calibrated pH meter [11].

Determination of drug content

By the aid of sonication, a dissolved *in situ* solution was obtained by adding 10 ml of *in situ* solution to 0.1N hydrochloric acid (HCl) and then top up with 0.1N HCL to 100 ml. The keto content was measured by using UV-spectrophotometer (Shimadzu, Japan) at λ_{max} 270 nm and this needed a proper dilution using 0.1 N HCl [6].

In vitro gelation study

The capability of *in situ* solution to gel was evaluated visually by pouring 10 ml of the *in situ* solution to 100 ml of 0.1N HCl (pH 1.2). This was followed by watching and counting the time needed by *in situ* solution to be solid and for how long persisted intact where this technique was graded to 3 classes:

(+)-Dispersed quickly within few minutes once gelation occurred.

(++)-Persistent intact for 12 h after instant gelation.

(+++)-Persistent intact for more than 24 h after instant gelation [12].

In vitro floating study

This was executed in stagnant condition at 37 °C by pouring 10 ml of liquid formulations into 100 ml of 0.1N HCL contained in a beaker.

This study assisted to evaluate firstly, the floating lag time which indicates the actual time for the gelling formulation to rise to the surface of media and secondly, the duration of floating which represents the period of floatation persistence [13].

Viscosity measurement of the In-situ gelling solutions

Viscosity of the solutions of *in situ* gels was determined using a Brookfield digital viscometer. 50 ml of prepared solutions were sheared at a rate of 100 rpm/min using spindle number 2 at room temperature [14].

In vitro release study

To evaluate the release of keto from *in situ* gel, 10 ml of *in situ* liquid was added to 900 ml of 0.1N HCl (pH 1.2) as this study was run at 37 °C (body temperature) and stirring rate was 50 rpm to mimic the mild agitation of stomach and keeping formulation solid by using type II (paddle method) dissolution apparatus. A withdrawn sample of 5 ml was replaced by the same volume of fresh 0.1N HCL to keep the sink condition within time course of the study and filtered by Whatman filter paper. These samples were diluted then keto quantified at λ_{max} 270 nm [15].

Statistical analysis

ANOVA test (one way analysis of the variance) was applied for statistical analysis. Significant statistical differences were considered when (p<0.05).

RESULTS AND DISCUSSION

Evaluation of ket floating *in-situ* gel

In this current study, the formulations that contained keto for floating *in situ* gel were nine composed of Na alginate which is the main polymer that form gels. Additionally, GG, HPMC K4M, HPMC K15M and carbapol 940 were added to the solution of Na alginate to enhance its viscosity and to retard the release of keto upon gelation. Furthermore and to complete the gelation process, CaCO₃ was added which also act as a gas generating agent. The last one was used in different concentrations to optimise the concentration for better gelation. Different parameters were investigated for formulations (F1 to F9) as demonstrated in table 2 and discussed in details below.

Table 2: Evaluation of keto floating *in-situ* gel

Formulation code	pH	Gelation time (sec)	Drug content	Floating lag time (sec)	Duration of floating (h)	Viscosity (cp)
F1	7.5	++	93.8±0.43	130±0.15	>12	336±0.33
F2	7.75	+++	94.3±0.23	138±0.19	>12	678±0.56
F3	8.81	+++	95.1±0.17	131±0.09	>12	473±0.3
F4	8.81	+++	92.33±0.1	139±0.13	>12	538±0.14
F5	7.79	+++	89.5±0.36	145±0.05	>12	574±0.26
F6	8.34	+++	95±0.3	157±0.2	>12	1360±0.1
F7	8.1	+++	90.9±0.21	133±0.2	>12	450±0.05
F8	8.2	+++	89.1±0.4	132±0.26	>12	511±0.22
F9	---	---	----	---	---	1515±0.4

(mean±SD, n=3)

Physical appearance and pH

The nine formulations appearance was screened and found that all the liquid formulations were light brown, smooth and free from lumps or clots.

Also, the pH was investigated to make sure that the formulation pH is far from acidic or basic pH that harms the throat [16]. As shown in table 2, the pH of the eight formulations was within this range (7.75-8.81) which indicates a neutral or light alkaline pH and this is compatible with desired pH for oral formulations as no need for further pH adjustment [17].

In vitro gelation time

The process of gelation starts after the CaCO_3 in liquid formulations being in contact with the acidic medium which is then followed by the release of gas and calcium ions. An instantaneous hardening to the liquid formulation occurs once the interaction happens between calcium ions and sodium alginate (the anionic polymer) giving a reservoir of three dimensional (3D) solid structure that slows the release of keto [18]. This was shown in table 2 where the gelation time study was executed using 0.1N HCl (pH 1.2). The results revealed that all formulations showed an instant gelation and staying as an intact 3D structure for more than 24 h except the F1 that gelled instantly but remained intact not more than 12 h. This could be explained that F1 composed of just Na alginate and free from viscosity enhancing agent, thus F1 showed rapid vanishing and this might be owing to the Na alginate gel is a porous scaffold. Obviously, this scaffold permits an ease water entrance leads to speed up the gel dissolution [19].

Drug content

The uniform distribution of keto in the formulations was studied as shown in table 2 and it was found that the drug content within this range (89.1-95.1%). This was within the acceptable limits that are determined by USP (not <85% and not >115%) [20].

In vitro floating study

The buoyancy of the *in situ* gels is due to the presence of CaCO_3 which generates gas upon contact with the acidic medium which helps gels to float [21], and as the residence time of gels increased as this guarantees the absorption of drug in the stomach [22, 23]. This was investigated via *in vitro* study as shown in table 2. All formulations floated for more than 12 h and the longest floating period was 157 seconds for F6 whereas F1 showed the least floating time which was 130 seconds.

Viscosity study

The liquid gels formulations that contained the viscosity enhancing agent helps to gain an appropriate viscosity and permit an easy swallowing. Also, as these agents facilitate the solid gels formulations to be coherent and solid enough to slow the release of keto.

The results of viscosity for formulations F1 to F9 were demonstrated in table 2 as F1 showed the lowest viscosity value 336 cp and this might be due to the F1 contained no viscosity enhancing agents. On the other hand, the F9 showed the highest viscosity value 1515 cp and this high value could be as a result of the presence of the carbapol 940. This made F9 non pourable and no further investigation was followed this study on F9. Generally, the formulation's viscosity showed the following order $F9 > F5 > F8 > F7$ that contained carbapol 940, GG, HPMCK15M and HPMCK4M respectively. Besides the impact of GG on the viscosity of *in situ* gels, increasing its concentration led to increase the viscosity of F5 and F6 and this might be as a result of the increase in the interaction amongst the polymers [24].

Also, it was noticed that the increase in the molecular weight of HPMC led to increase in the viscosity of the formulations as shown in F7 and F8. Another finding was the increase in CaCO_3 concentration led to increase in the viscosity and this might be due to the increase in the dispersed amount of CaCO_3 through the whole formula which helped in more hardening to the Na alginate gels [25].

In vitro release study

The release of keto was studied for 3 h for different formulations using USP paddle type apparatus. The keto concentration was calculated by the following equation of the calibration curve ($y=2.43x+0.0341$) which was constructed from serial dilutions of keto in 0.1N HCl solution (pH 1.2). These dilutions were read by spectrophotometer at λ_{max} of keto which was 270 nm. The main polymer in this work is the Na alginate, thus the effect of different amounts of the main polymer was investigated using F1, F2 and F3 and it was found as shown in fig. 1, the F1 released 99% (w/w) of keto within 30 min. This fast release referred to the low viscosity of F1 and probably due to the lack of GG which in turn reflected the low solidity of the formulation upon gelation. As well and in the presence of 0.5% (w/w) of GG, a significant increase ($p < 0.05$) in the release of keto was observed as the amount of Na alginate was reduced from 2% (w/w) (F2 around 49%) to 1% (w/w) (F3 around 58%) and as shown in fig. 1. This result was similar to the preparation of ranitidine *in situ* gels by Rohith et al. study as they increased the Na alginate concentration from 0.5% (w/w) to 1% (w/w), the release of ranitidine decreased from 96.5% to 74% within a frame time of 8 h respectively [26].

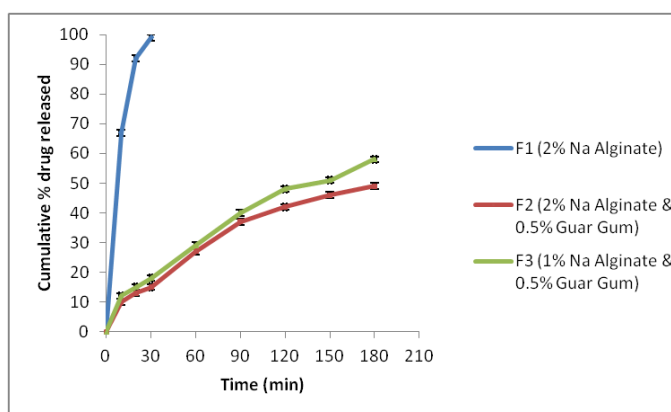


Fig. 1: Effect of Na alginate concentration on drug release (mean \pm SD, n=3)

The effect of GG content was also studied as shown in fig. 2 and it was found a non-significant ($p > 0.05$) decrease in the keto release of F5a 43% compared with 40% of F6 after 180 min as changes in the concentrations of GG was 0.5% (w/w) and 1.5% (w/w) respectively. The role of the presence of another polymer besides the main polymer in the formulation of *in situ* gels was investigated by

Maheswaran *et al.* They also found as they increased the HPMC content in Na alginate formulations as the release of diltiazem decreased [27]. This could be clarified that the presence of two polymers leads to increase the density of gelled formulations which consequently slows the diffusing molecule through this kind of matrix [24].

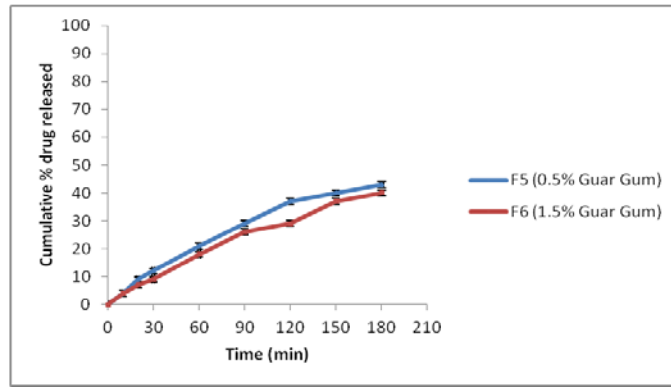


Fig. 2: Effect of GG concentration on drug release (mean±SD, n=3)

Additionally and it was obvious the importance of CaCO₃ in the gelation of Na alginate, hence the different contents of CaCO₃ were investigated in F3 and F4. As shown in fig. 3, the release of keto decreased from 62% to 58% as the CaCO₃ increased from 0.5%

(w/w) to 1% (w/w) in F4 and F3 respectively. This could be made clear that the increase in the calcium ions due to the increase in the CaCO₃ content enhances sufficient crosslinking sites between sodium alginate molecules [28].

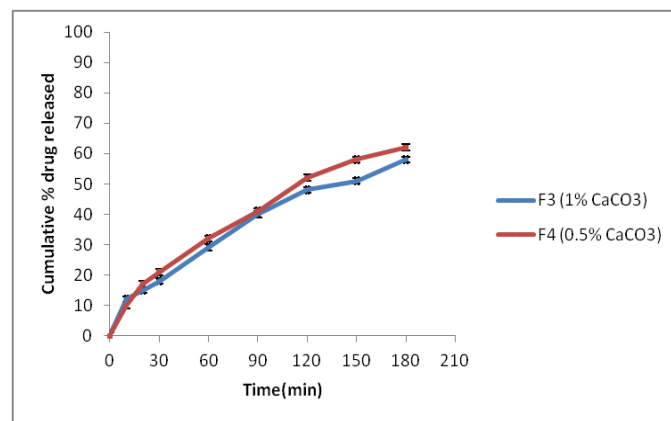


Fig. 3: Effect of CaCO₃ concentration on drug release (mean±SD, n=3)

The clear impact of GG in retarding the keto release from Na alginate formulations was encouraging to investigate other polymers as viscosity enhancing polymers. This was done by choosing a base formulation containing 2% (w/w) Na alginate, 0.5% (w/w) GG as in F5, further to, selective polymers the HPMC K4M and the HPMC K15M were added as in F7 and F8 respectively. As shown in fig. 4, the slow release order of these formulations was in the following order F5>F8>F7 and significant (p<0.05) decrease in the release rate of keto as F5 compared with F8 and F8 compared with F7. This could be clarified on the base of the effect of polymer grade of HPMC on

the release of keto which was observable and showed an inverse relationship. As well, Li *et al.* obtained the same finding and they found the high grade of HPMC K4M in combination with carbopol slowed the release of calcium as compared with the formulation of low grade of HPMC K100LV with carbopol [29].

Based on the above results, the prepared in situ floating gel of F3 which showed pH 8.81, floating lag time of 131±0.09, floating duration of >12 and viscosity 4730 cp can be considered as the optimum formulation that met the aim of our work.

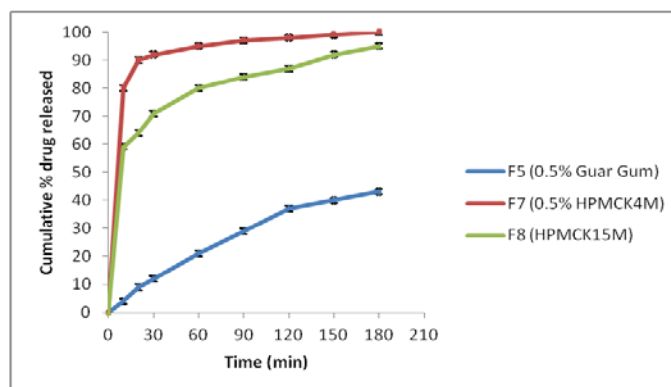


Fig. 4: Effect of viscosity enhancing polymers concentration on drug release (mean±SD, n=3)

CONCLUSION

The enormous interest in studying the GDF was due to the ability of these formulations to stay in the stomach for a long time hence we focused in this work on the *in situ* gel formulation selecting the keto as a model. This was to study the capability of *in situ* gel formulation controlling the drug release and enhancing the solubility of keto in the stomach media. The results revealed that F1 showed 99% of keto released within 30 min which contained just Na alginate. Also, the reduction in Na alginate concentration in the presence of 0.5% w/w GG from 2% w/w as in F2 to 1% w/w as in F3 led to increase the release of keto from 49% to 58% within 180 min respectively. Furthermore, it was found when the CaCO₃ amount was reduced in F3 from 1% w/w to 0.5% w/w as in F4, the release of keto increased from 58% to 62%. Additionally, the higher concentration of GG 1.5% w/w in F6 showed a slower release to 40% of keto as compared with the lower concentration of 0.5% w/w GG as in F5. Moreover, other than GG as viscosity enhancing agents, the addition of HPMC K4M effect was studied as in F7 which gave a higher release in comparison to the F8 that contained a higher grade the HPMCK 15K. Thus, the above different parameters showed the capability and feasibility to control the release of keto while the *in situ* gel formulation floating in the stomach.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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