Design and Evaluation of Glipizide Loaded In-situ Gel Formulation Using Natural Mucilages for Improved Bioavailability

Dalapathi Gugulothu*, Suraj Kumar Choudhary
Balaji Institute of Pharmaceutical Sciences
Laknepally (V), Narsampet, Warangal Rural, Telangana, 506331, India
Corresponding author: dalugugulothu@gmail.com
+91-9949127387

Abstract - This investigation aims to develop floating *in-situ* gel formulation of Glipizide (GLP) by employing natural mucilages such *Fenugreek* (FG) and *Colocasia esculenta* (CE) combination for improving oral bioavailability and patient compliance. For development of optimized *in-situ* gel formulation various trails were conducted by employing different concentrations of FG, CE and HPMC; additionally, Calcium chloride is used as cross linking agent and source of Ca^{2+} ions. Followed by *in situ* gels were subjected to evaluation of parameters like appearance, pH, floating lag time, floating duration, drug content, *in vitro* gelling capacity, *in vitro* drug release. Moreover, the final *in situ* gel formulation was evaluated to viscosity studies and *in vivo* pharmacokinetic study. The formulations resulted in optically clear, prolonged floating duration with controlled drug release profile. Consequently; the optimized formulation (F13) was exhibited optimal viscosity and *in vivo* pharmacokinetic studies exposed that higher T_{max} of *in situ* gel formulation compared to drug suspension which is allusive of slower absorption. However, the $AUC_{0-\infty\ ng/mL.h}$ was found to be approximately 3.93 folds higher than drug suspension. So; it is indicated that in combination of CE-FG (F13) could be excellent for development of *in situ* gel formulation. Finally, it was suggested that F13 could eliminate the repeated dose administration and improve the oral bioavailability of Glipizide.

Keywords: *Colocasia esculenta; Fenugreek*; Floating duration; *In situ* gel; Oral bioavailability.

1. Introduction

For a couple of decades numerous novel drug delivery systems have been developed to deliver the drugs for the controlled manner with a precise time intervals. The oral controlled release formulation can sustained the drug release and prolong the availability of the drug in gastrointestinal tract (GIT) for a period of required time [1, 2].Gastroretentive drug delivery (GRDDS) is an approach wherein, prolong the gastric residence time, therefore attain drug release in the upper GIT [3-6]. Gastroretentiveionic cross-linking *in situ* gels are liquid preparations for delivery of drugs into stomach [7-10]. Various scientists have been developed gastroretentive *in situ* gels for drugs like metformin [10], acyclovir [11], amoxicillin [12], clarithromycin [13] and nateglinide[14] and evaluated successfully. These formulations can be best suitable for paediatric and geriatric patients due to their ease of administration. These *in situ* gels are prepared in solution or suspension form and they undergo *sol-to-gel* transition after entering into the stomach; then they continuously float on the surface of the gastric fluid [15]. These systems are made up of ion-sensitive polysaccharide mucilages, such as gellan gum, carrageenan, and pectin, which undergo gelation as of interaction with various ions that are released in acidic pH [16-17]. Also, a combined use of a floating *in situ* gel system and mucoadhesive property will potentially improve contact time with the gastric mucosa and provide better controlled drug release with an abridged burst release rates. This investigation aims to develop Glipizide (GLP) (model drug) loaded *in situ* gel systems using in a combination of *Colocasia esculenta*(CE) and *Fenugreek*(FG) for improved gelation and controlled release property. Till now, there is no single literature reports have been available in the use of CE mucilage alone or combination of FG-CE as a gelling agent in novel drug delivery or *in situ* gel formulation. CE is an herbaceous succulent plant belonging to family *Araceae*; it is, widely cultivated in the humid areas of the globe. CE contain a high percentage of mucilage and are already established as mucoadhesive polymer, emulsifying agent and binding agent for tablet dosage forms[19,20]. Due to its swelling property, it is explored as excellent mucilage in development of controlled release formulations. Fenugreek gum (FG), is a naturally obtain galactomannan and isolated from the endosperm of methi seeds (*Trigonella foenum-graecum*). It is contain residues of α-(1-4)-β-D-mannan backbone with (1-6)-linked α-D galactopyranosyl. It is applied as hypoglycaemic and lipid lowering agent [21]. Due to the poor hydration rate of FG, it is difficult to achieve a homogeneous dispersion, hence negatively impact on its gel strength. Thus, a combination of CE-FG might be a capable process to improve its water solubility, swelling and drug release property [22].

GLP is a practically insoluble in water as well as acidic media. It is highly permeable and belongs to Bio pharmaceutical Classification System II [23]. The half-life of GLP is 2-5 hours; while administered as conventional solid dosage form, it does not get sufficient gastric residence time. In such cases it is to be administered in repeated doses 2.5 to 10 mg per day; and the site of absorption of GLP is stomach. Hence, the GLP loaded *in situ* gel formulation prepared with combination of CE-FG would clearly be advantageous as it improves drug efficacy and reduce dose necessities [24]. In the present study, a floating *in situ* gel system is considered for retention and expected to control the drug release in stomach. Thus, it would be an advantageous to develop Mucoadhesive *in situ* gel containing GLP using a combination of CE-FG, which may keep hold in the GIT for prolonged duration of time to enable a close adhesion with the absorbing surfaces of mucous membranes (i.e., mucoadhesion) for achieving maximum drug absorption and better oral bioavailability.

2. Material and Methods

2.1.Materials

GLP was obtained from Yarrow Chem Products Limited, Mumbai, India, Calcium carbonate, Sodium citrate, Calcium chloride, HPMC K4, Propyl paraben and Methyl paraben were purchased from Qualikems Fine Chem Pvt Ltd, Vadodara. Gujarat, India. FG and CE were procured from local market, Narsampet, Warangal, India and mucilage was extracted by using solvent precipitation technique [25]. All other solvents and chemicals were of analytical grade.

2.2. Preparation of in situ gel formulation

Required quantity of GLP, sodium citrate, calcium carbonate, calcium chloride, methyl paraben, FG, CE, and HPMC were weighed accurately. Formulation trails have been reported in Table1. Therefore, required concentration of CE, FG, CE-FG and HPMC was added in about 30 ml of deionized water. Followed by solutions was heated to 60ºC with continuous stirring. Subsequently cooling to below 40ºC, calcium carbonate, calcium chloride, sodium bicarbonate, GLP and sodium citrate were added and dispersed well by an incessant stirring, followed by solution of methyl paraben and propyl paraben were added. Finally, the formulations have been an adjusted to required volume, filled and stored in an amber colored bottles until further use [26].

Table1.Formulation trials for GLP loaded *in situ* gel formulation.

Ingredients	F1	F2	F3	F4	F5	F6	F7
GLP (mg)	100	100	100	100	100	100	100
FG(% w/v)	0.5	1	1.5	2	-	-	-
CE(% w/v)	-	-	-	-	0.5	1	1.5
HPMC K4M(% w/v)	-	-	-	-	-	-	-
$CaCO_3$(%w/v)	2	2	2	2	2	2	2
$CaCl_2$(%w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
$NaHCO_3$ (%w/v)	2	2	2	2	2	2	2
Sodium citrate(%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propyl paraben(%w/v)	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Methyl paraben(% w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water Qs to	100	100	100	100	100	100	100

$CaCO_3$: Calcium Carbonate; $CaCl_2$: Calcium Chloride; CE: Colocasia esculenta; FG: Fenugreek; GLP: Glipizide; HPMC: Hydroxyl Propyl Methyl Cellulose; $NaHCO_3$: Sodium bicarbonate

2.2.1. Characterization of the developed in situ gel formulations

2.2.1.1. Appearance

All formulations were subjected to evaluation of clarity by visual observation against a black and white background.

2.2.1.2.pH

The pH values of various formulations were measured using a digital pH meter at room temperature in triplicate [27].

2.2.1.3.In vitro gelation studies

Gelation study for *in situ* gel solution was performed by taking 15 ml Hydrochloric acid (HCl; pH 1.2) in 25 ml test tube. 10 ml solution was added to HCl with mild agitation to avoid the breaking of a formed gel. Gel was perceived visually by qualitative measurement [28]. Gel residence time is the time for which gel system remains stable in floating without getting dispersed. Then floating gel was disturbed using a glass rod to ensure the strength of the gel system [28]. The gel is considered to have good strength if it remains integrated even after disturbance [29].

2.2.1.4. Determination of drug content

Drug content in each in *situ* gel formulation was performed by UV spectroscopy. The UV absorbance of the sample was determined at a wavelength of 277 nm. The drug content for all batches was measured in triplicate and the average values were reported [29, 30].

2.2.1.5.In vitro floating studies

In vitro floating studies for *in situ* gel solutions were carried out in 500 ml of 0.1NHCl (pH 1.2) in a beaker. 10 ml of gel solution was transferred to HCl with mild agitation. Time required for floating on the surface after adding solution (floating lag time) and total floating time were reported [29, 30].

2.2.1.6.In vitro drug release studies

In vitro release studies for in *situ* gel formulation was performed in USP apparatus II, fitted with paddle (50 rpm) at 37 ± 0.5°C.0.1N HCl (500 ml). The speed was kept slow adequate to avoid the breaking of gel formulation under mild agitation conditions mimic to physiological salt conditions. A 5 ml sample was withdrawn and filtered through a 0.45μm membrane filter. At the various time intervals the samples were analysed at 277 nm using a Shimadzu UV-double-beam spectrophotometer. Percentage cumulative drug release (%CDR) was determined using an equation obtained from a calibration curve [29, 30].

2.2.1.6. Measurement of viscosity of in situ gel solution

The viscosity of an optimized gel formulation (F13) was performed by digital brook field viscometer. The samples (100 ml) were sheared at a rate of 100 rpm using suitable spindle at room temperature. Viscosity measurement for each sample was performed in triplicate; though every measurement was taken approximately for 30 seconds [28, 29].

2.3. Pharmacokinetic studies

2.3.1. Animals

In vivo studies were performed in male Wister rats weighing between 250 and 300g. The rats were purchased from National Institute of Nutrition, Hyderabad, India. The rats were kept in polypropylene cages and housed in the animal house of Balaji institute of Pharmaceutical Sciences under standard environmental conditions (23.0±1°C, 55±5% humidity, and 12 h/12 h light/dark cycle). The animals had *ad libitum* access to standard animal diet and water. The protocols of the animal studies were permitted by the Institutional Animal Ethical Committee (IAEC 01/2017) and the experiments were performed according to CPCSEA guidelines. RP-HPLC (Shimadzu, LC solution software) was used for pharmacokinetic study. The mobile phase consisted of 20 mM monobasic potassium dihydrogen orthophosphate in water, which was adjusted to pH 3.5 with phosphoric acid, and acetonitrile in the proportion of 65:35v/v. The mobile phase was filtered through 0.22 µm membrane filter. The flow rate was 1 ml/min and the effluent was monitored at 275 nm. The total run time of the method was set at 25 min [31, 32].

Pharmacokinetic evaluation in wistar rats

The overnight fasted rats (n=5) were administered with a single oral dose of carrying 1.5 mg of GLP suspension and GLP loaded *in situ* gel formulation. The blood samples were withdrawn at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12, and 24hr) through the retroorbitral vein in heparinised tubes. The plasma was separated by centrifuging at 5000 rpm and stored at -4°C until further analysis. A rat plasma sample of 0.2 ml and 0.2 ml of 0.1 N HCl were vortexed for 3 min and then 6 ml of benzene was added for the precipitation of plasma proteins. The mixture was efficiently shaken using a cyclomixer for 5 min followed by centrifugation for 10 min at 6000 rpm and the precipitates were removed by syringe filter (0.22 µm). The organic phase was evaporated and the residue was thawed with 0.2 ml of mobile phase by vortex mixing. A sample of 20 µl was injected into the HPLC column [31, 32].

Statistical analysis

The pharmacokinetic data were analysed by student'sun paired t-test using Graph Pad Prism 9 software. P values <0.05 were considered significant.

3. Results and Discussion

3.1. Formulation of in situ gelling system

In situ gel formulations are an uprising approach in oral drug delivery. These are liquids at room temperature followed by undergo gelation, in presence of body fluids or change in pH. These encompass a distinguishing character of temperature dependant and cation induced gelation. A gel formation includes progress of the double helical junction zones followed by aggregation of the double helical segments to create a three-dimensional network by complexation with cations as well as hydrogen bond [33].The present explorations, different concentrations of FG, CE, HPMC K4M alone and in combination were employed for preparation of sustained release *in situ* gel formulations. Formulation trails of *in situ* gel were illustrated inTable.1-2. *In-situ* gel formulation should maintain proper viscosity for it to be administration into oral cavity. After swallowing; it is undergoes *sol–gel* transition quickly due to their ionic interactions. The formed gel was floated promptly in the GI pH conditions. *Sol-to-gel* renovation of *in situ* gel result in the occurrence of either monovalent or divalent cations in reaction with gastric pH [33, 34].The calcium carbonate is existing as an insoluble dispersion in preparation and dissolved and reacted with acid then released the CO_2. The released CO_2 was attentive in the gel network of the formulation, and the gel encouraged ascending to the surface of the dissolution medium. The same can occur in the GI tract also. It was expected that *in situ* gel formulation comprising calcium carbonate create a significantly strong gel [35]. This may be due to the internal ionotropic gelation effect of calcium on FG-CE.

Table 2.Formulation trials for GLP loaded *insitu* gel formulation.

Ingredients	F8	F9	F10	F11	F12	F13
GLP (mg)	100	100	100	100	100	100
FG(% w/v)	-	-	-	-	-	0.5
CE(% w/v)	2	-	-	-	-	0.5
HPMC K4M(% w/v)	-	0.5	1	1.5	2	-
$CaCO_3$(%w/v)	2	2	2	2	2	2
$CaCl_2$(%w/v)	0.2	0.2	0.2	0.2	0.2	0.2
$NaHCO_3$ (%w/v)	2	2	2	2	2	2
Sodium citrate(%w/v)	0.5	0.5	0.5	0.5	0.5	0.5
Propyl paraben(%w/v)	0.02	0.02	0.02	0.02	0.02	0.02
Methyl paraben(%w/v)	0.1	0.1	0.1	0.1	0.1	0.1
Water Qs to	100	100	100	100	100	100

$CaCO_3$: Calcium Carbonate; CaCl2: Calcium Chloride; CE: Colocasia esculenta;FG: Fenugreek; GLP: Glipizide; HPMC: Hydroxyl Propyl Methyl Cellulose; $NaHCO_3$: Sodium bicarbonate

3.2. Evaluation of in situ gel formulation

Developed *in situ* gels were resulted optically clear and pH was in alkaline nature (Table 3). The formulation F1 showed slow gelation after contact by SGF. Whereas, formulations F2-F8 and F11-F12 exhibited instant gelation when contact with SGF (Table 3). The formulation comprising a combination of FG-CE exhibited more promptly than that of the formulation not comprising combination (Fig.1). The formulation comprising low concentration of FG (F1) has slow gelation and formed weaker gelation, although formulation containing HPMC concentration of 0.5 % (F9) and 1 %(F10) has medium gelation as shown in Fig.1 and Table 3. This might be expounded by the statement that low concentration of FG and HPMC thus formed weaker gels. Furthermore, weak gel formulations can be removed quickly from the stomach by the peristaltic movements. Thus, the weak gel formulations cannot suitable for oral administration. Therefore, formulations with high concentration of FG, CE and HPMC and combination of CE-FG developed a strong gel in diminutive gelation time in stomach. Furthermore, a combination of CE-FG revealed excellent gel strength when constrained with a pair of fine forceps, viewing that they can endure the shear forces possible to be encounter in the GI tract. Consequently, these vehicles might have extended residence time than solutions [36]. The drug content of selected formulation was found to be 99-100%. The results are revealed in Table 3.CO_2 was released after dissolving calcium carbonate in GI fluid. Followed by calcium ion are interacted with mucilage to form a strong stable gel layer while the $CO_2$was trapped within the gel network. Then, liquid gel formulations were added to 0.1NHCl (pH 1.2); they dropped to the bottom of medium. Subsequently, gel moved up and retained on the surface of the medium once the CO_2 was released. The floated gel was also useful as it acted as a barrier to prevent reflux of the gastric fluid into the oesophagus [37]. The floating lag time and duration of floating was revealed in Table 3. The floating time of F1, F5, F6, F9 was exhibited around 10s, whereas F2, F7, F8, F10, F11 resulted less than 60s and F3, F4, F12 and F13 revealed

70.00±14.23s, 50.0±11.23s, 120.0±9.8s, 80.0±26.3s respectively. The floating duration for F1, F5 and F9 was up to 12h and rest of formulation was more than 12h. The floating lag time is the time taken for the release of CO_2 from the gel system which helps in the floating of the gel system. Floating lag time was decreased with increasing the concentration of mucilage. Whereas as, formulation F13 (combination of CE-FG) floated on the surface in less than 100s and floating duration was more than 24h. The gel bundle of F1, F5, and F9 formulation was disappeared within 12h and for F2-F4; F6-F12 was remain stable for 12h. The combination of CE-FG at concentration of 0.5% each affected the floating lag time and floating duration.

Table 3.Characterization of the prepared*insitu*gel formulations.

Formulation Code	Appearance	pH±SD	*In vitro* gelation study± SD	Drug content± SD	Floating log time(S)±SD	Duration of floating (h)
F1	Optically clear	10.0±0.02	+	9.36±0.18	10.0±1.2	<12
F2	Optically clear	10.0±0.013	+++	99.68±0.56	60.0±5.2	>12
F3	Optically clear	10.0±0.010	+++	96.87±0.45	70.0±14.23	>12
F4	Optically clear	10.0±0.012	+++	100.33±0.45	50.0±11.23	>12
F5	Optically clear	10.50±0.025	+++	100.00±0.41	10.0±1.0	<12
F6	Optically clear	10.50±0.014	+++	100.00±0.78	15.0±1.5	>12
F7	Optically clear	10.50±0.045	+++	100.00±0.47	30.0±2.3	>12
F8	Optically clear	10.50±0.010	+++	99.78±0.28	40.0±2.1	>12
F9	Optically clear	10.50±0.015	++	99.15±0.99	5.0±0.58	<12
F10	Optically clear	10.50±0.030	++	99.25±0.57	20.0±1.5	>12
F11	Optically clear	10.50±0.062	+++	100.02±0.15	60.0±2.5	>12
F12	Optically clear	10.50±0.080	+++	99.87±0.28	120.0±9.8	>12
F13	Optically clear	10.50±0.018	++++	99.98±0.47	80.0±26.3	>24

+: Very poor gelation; ++: Poor gelation; +++: Gelation for 12 hr; ++++: gelation for 24 hr

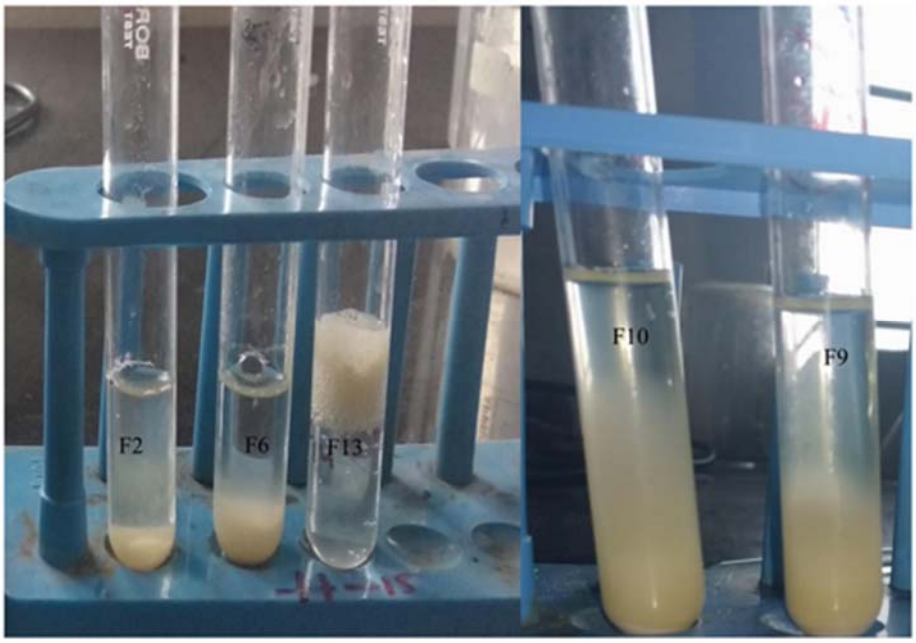

Fig1. *In vitro* gelation study of in situ gel formulation in simulated gastric fluid.

3.3.In vitro drug release study

In vitro drug release study profile of the developed *in situ* gel formulations i.e. F1, F2, F5, F6, F9, and F10 exhibited 100% drug release in the period of less than 12h. Therefore, formulations F3, F4, F7 and F8 showed 90-100% drug release in the period of 12h (Fig.2A-C). The combination of CE- FG (F13) mucilage revealed to sufficient controlled release, whereas; *in situ* gel developed by using HPMC with various concentrations like 1% and 2% also exhibited controlled release profile. It may be accredited to the encapsulation of GLP into the CE-FG gel layer with reducing the amount of drug close to the surface and available for the dissolution medium with an ensuing decrease in the percentage of drug release [12]. Normally, it was reported that, increasing the concentrations of the polymers in formulations decreases the burst effect and sustains the release of the drugs [13], by snowballing the diffusion path length that should be navigated by drug molecules [40].Furthermore, it was advised that higher % of GLP release was observed in HPMC based formulation (Low concentration) alone. This might be due to the amount of HPMC was inadequate to control the release of GLP, thus a combination of FG-CE was the major effect for controlled release effect of GLP through the formed *in situ* gel. The mechanism of drug release from formulation F3 and F4was exhibited higuchi model with non fickian super case (besides swelling-based drug release); this might be associated to the higher viscosity and gel strength of the formed gel of F3 and F4. Whereas, F7, F8, F11 and F12 exhibited was zero order with quasi fickian. It may be caused by partially diffusion through a swelling of *in situ* gel. However the release from F13 was zero order with non fickian (diffusion besides swelling-based drug release); this can be related to the higher viscosity and high gel strength CE-FG combination. The controlled release manner of *in situ* gel formulation could be ascribed to the encapsulation of the drug inside the mucilage matrix and its release is a controlled pattern with time as a result of its diffusion through the mucilage matrix of the formed *in situ* gel [38].Therefore, based on all physicochemical evaluation data and *in vitro* drug release study, F13 was selected as an optimized formulation and subjected to viscosity study and pharmacokinetic study.

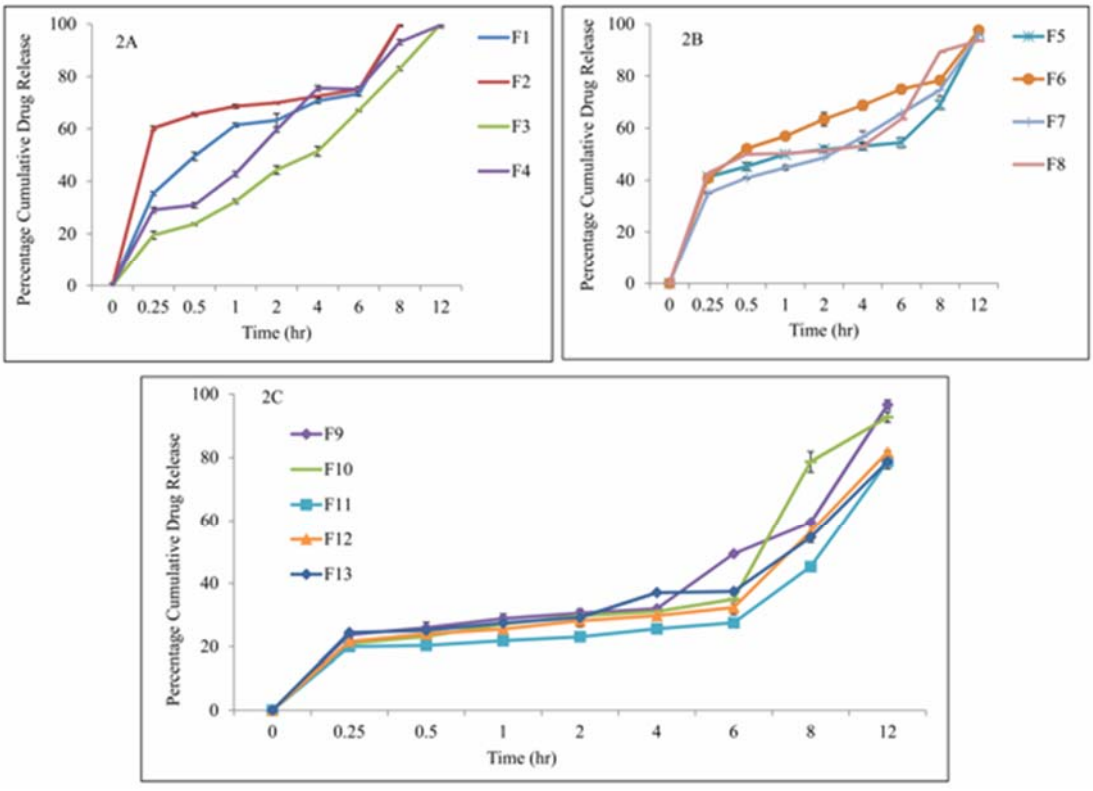

Fig2. Comparative *in vitro* release profile of GLP Insitu gel formulation.

3.4. Measurement of viscosity

An effective *in situ* gel formulation have to accomplish optimal viscosity of the prepared liquid solutions that resolve let easy to swallow, followed by undergoes a rapid *sol-gel* change and floating after ionic interaction. Also, a prepared *in situ* gel can preserve its integrity without dissolving or eroding throughout *buoyancy* for a longer period of time to endorse sustained-drug release. A combination of CE-FG could transform from *sol to gel* in the incidence of either divalent or monovalent metal ions [39]. The divalent as cationic calcium ions can greater to monovalent cations in endorsing the gelation of the polysaccharide, as of the internal ionotropic gelation power of divalent cations on the gel-forming polymers [40]. The formulation of CE-FG combination exhibited an enhanced in viscosity. This result can be inferred in terms of the structural features of the CE-FG combination

upon interface with calcium ions [41].The rheological properties of formulation F13 exhibited pseudoplastic flow or a shear thinning behaviour (Fig.3) and suitable for oral administration [12].

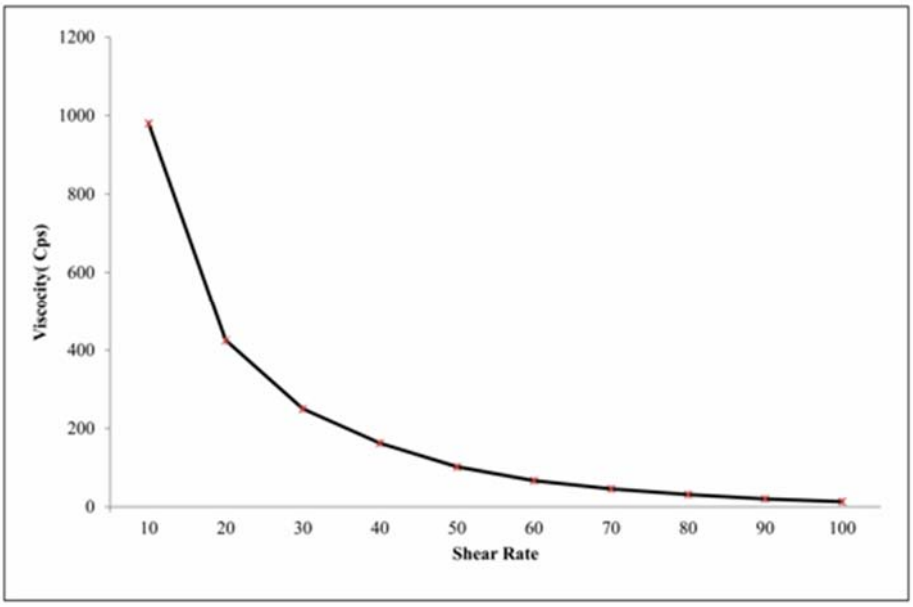

Fig3. Rheology study of formulation F13.

3.5.In vivo pharmacokinetic study

In vivo pharmacokinetics were studies to estimate plasma concentration of GLP following administration of *in situ* gel formulation and GLP suspension orally. All pharmacokinetic parameters were shown in Table 4. The plasma concentration verses time profile for pure drug in suspension and *in situ* gel formulation was represented in Fig.4. The increase of T_{max} for *in situ* gel formulation is indication for delayed absorption and slow release of drug from formulations. The enhanced in $AUC_{0\text{-}24}$ng/ml is indication of superior oral bioavailability. For GLP suspension, peak plasma concentration (C_{max}) was found to be 450±23 ng/ml at 4h (T_{max}) and $AUC_{0\text{-}\infty}$ng/ml.h was calculated as 03447.91± 102.80 ng/ml.h. For controlled release floating oral *in situ* gel, the (C_{max}) was found to be 1540±39 ng.mL^{-1} at 8 hr (T_{max}). The $AUC_{0\text{-}\infty}$was found to be 13566.70±523 ng/ml.h, which were significantly 3.93 folds higher than that for GLP suspension. However GLP was an existing in plasma within 4 h subsequent to its oral administration for GLP suspension. The plasma profile indicated an unremitting decrease in 2-12h, while for the *in situ* gel a stable increase was an obvious reaching a peak at 8h followed by an additional steady reduces in plasma concentration. Thus, we assume that *in situ* gel of GLP, since a sustained release system by using a combination of CE-FG *in situ* gel system efficiently.

Table 4. Mean pharmacokinetic parameters of GLP*in-situ* gel systems and GLP suspension after single dose administration (1.5 mg/kg; *n* = 5).

Pharmacokinetic parameters	**GLP suspension**	**GLP *In-situ gel***	**Ratio (In-situ gel / GLP suspension)**
$AUC_{0\text{-}t}$ (ng/ml.h)	3168± 63	12452.87±318	3.3.93
$AUC_{0\text{-}\infty}$ (ng/ml.h)	3447.91± 102	13566.70±523**	3.93
C_{max} (ng/ml)	450±23	1540±39	3.40
T_{max} (h)	4±0.058	8±0.98	2.00
$T_{1/2}$(h)	2.42±0.67	4.12±0.057	1.70

**Statistically Significant ($P < 0.05$)

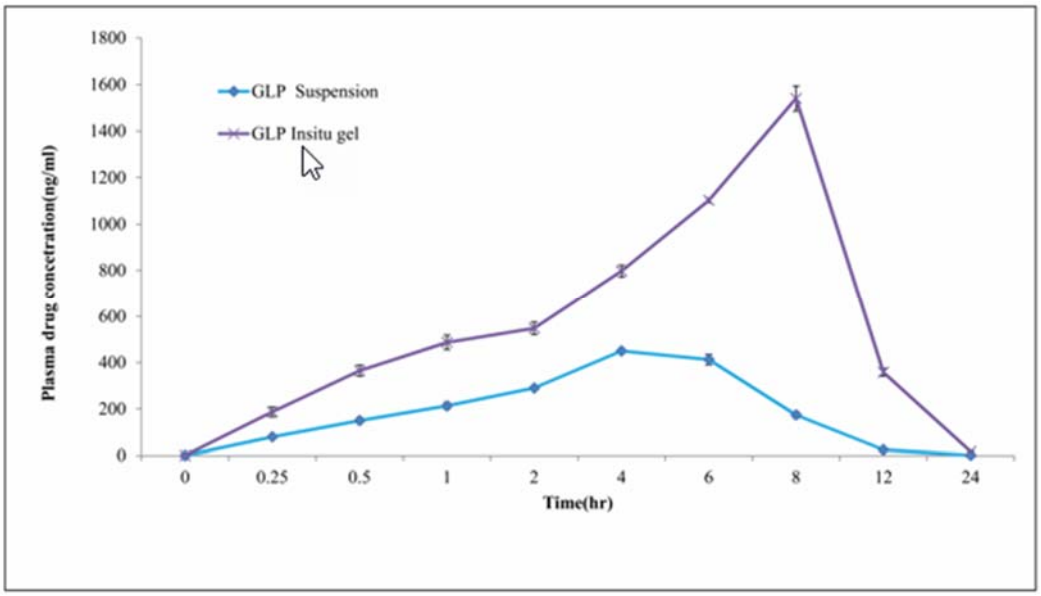

Fig.4. Mean plasma concentration–time curves of GLP Insitu gel and GLP suspension after single dose administration (1.5 mg/kg; n = 5).

4. Conclusions

The sustained release floating in *situ* gel of GLP was effectively formulated using natural mucilage of CE-FG combination, which on transfer into SGF formed viscous gel that floated on surface of SGF for the period of 24 h and exhibited sustained release for the period of 12 h. Furthermore, it has shown psuedoplastic behaviour and improved oral bioavailability with half-life of 1.72 folds higher than GLP suspension. According to the pharmacokinetic data it could be administered once a day instead of 2-3 times a day with improved patient compliance. Therefore, an anticipated formulation is a promising approach in the treatment of non-insulin dependent diabetes.

Competing interests: Authors declare that there is no competing of interest.

Acknowledgements: Authors are thankful to Science and Engineering Research Board, Department of Science and Technology (SERB-DST), Government of India, New Delhi(Project File No.ECR/2017/000175) for funding this project. The authors also would like to acknowledge Balaji Institute of Pharmaceutical Sciences, Narsampert, Warangal, India for providing basic infrastructural support to carry out the project.

References

[1] P.L. Bardonnet, V. Faivre, W.J. Pugh, et al. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J. Control. Release., 2006, 111:1–18.
[2] S. Arora , J. Ali, A. Ahuja, et al. Floating drug delivery systems: a review. AAPS PharmSciTech., 2005, 6: E372–390.
[3] U.K.Mandal, B.Chatterjee, F.G, Senjoti. Gastro-retentive drug delivery systems and their in-vivo success: a recent update. Asian. J. Pharm. Sci., 2006, 11:575–584.
[4] A.A.Deshpande, N.H.Shah, C.T. Rhodes, et al. Development of a novel controlled-release system for gastric retention. Pharm. Res., 1997, 14:815–819.
[5] E.A. Klausner, E. Lavy, M.Friedman, et al. Expandable gastroretentive dosage forms. J.Control.Release., 2003, 90:143–162.
[6] G.Ponchel, J.M.Irache. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract.Adv. Drug. Deliv. Rev., 1998, 34 (2-3):191–219.
[7] L.H. Kircik. Microsphere technology: hype or help?.J.Clin.Aesthet. Dermatol., 2011, 4:27–31.
[8] N.Nagahara, Y. Akiyama, M. Nakao, et al. Mucoadhesive microspheres containing amoxicillin for clearance of Helicobacter pylori. Antimicrob. Agents. Chemother., 1998, 42: 2492–2494.
[9] A.Vaidya, A. Jain, P. Khare, et al. Metronidazole loaded pectin microspheres for colon targeting. J. Pharm Sci., 2009, 98:4229–4236.
[10] R.C. Nagarwal, A.Srinatha, J.K. Pandit. In situ forming formulation: development, evaluation, and optimization using 33factorial design. AAPS Pharm SciTech., 2009, 10:977-984.
[11] B. Singh, A. Kaur, S.Dhiman et al. QbD-enabled development of novel stimuli-responsive gastroretentive systems of acyclovir for improved patient compliance and biopharmaceutical performance. AAPS PharmSciTech. 2016, 17:454-465.
[12] P.S.Rajinikanth, J.Balasubramaniam, B.Mishra. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. Int .J. Pharm., 2007, 335:114-122.
[13] P.S.Rajinikant, B. Mishra. Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H. pylori. J.Control. Release., 2008, 125: 33–41.
[14] G.M.Maghraby, A.E.Elsisi, G.A.Elmeshad. Development of liquid oral sustained release formulations of nateglinide: in vitro and in vivo evaluation. J. Drug. Deliv. Sci .Technol., 2015, 29:70-77.
[15] J.K.Patel, J.R.Chavda, M.K. Modasiya. Floating in situ gel based on alginate as Carrier for stomach-specific drug delivery of famotidine. Int. J. Pharm. Sci. Nanotechnol., 2010, 3:1092-1104.
[16] S.Sangeetha, G.Harish, R. Medapati, et al. Oral sustained delivery of salbutamol using in situ gelation of sodium alginate. Int.J. Curr. Pharm. Res., 2010, 2:61-64.
[17] J.Hao, J. Zhao J, S.Zhang, et al. Fabrication of an ionic-sensitive in situ gel loaded with resveratrol nanosuspensions intended for direct nose-to-brain delivery. Colloids. Surf B. Biointerfaces., 2016, 147:376-386.

[18] S.Selvakumaran, I.I.Muhammad, S.I.Razak. Evaluation of Kappa carrageenan as potential carrier for floating drug delivery system: effect of pore forming agents. Carbohyd. Polym., 2016, 135:207-214.
[19] C.A. Alalor, J.A.Avbunudiogba, K.Augustine. Isolation and characterization of mucilage obtained from colocasia esculenta. Int. J. Pharm. Bio. Sci., 2014, 4: 25-29
[20] N.Y. Njintang, T.Boudjeko, L.N.Tatsadjieu, et al.. Compositional, spectroscopic and rheological analyses of mucilage isolated from taro (Colocasia esculenta L. Schott) corms. J. Food. Sci. Technol., 2014, 51(5): 900–907.
[21] H.Bera, C.Gaini, S.Kumar, et al. HPMC-based gastroretentive dual working matrices coated with Ca+2 ion cross linked alginate-fenugreek gum gel membrane. Mater.Sci. Eng C., 2016, 67170–67181.
[22] H. Bera, S.Mothe, S. Maiti, et al. Carboxymethyl fenugreek galactomannan-gellan gum-calcium silicate composite beads for glimepiride delivery. Int. J. Biol. Macromol., 2018, 107:604-614.
[23] T. Prannoy, P.K.Lakshmi. Design and optimization of hydrodynamically balanced oral in situ gel of glipizide. J.Appl. Pharm.Sci., 2015, 503:1-8.
[24] S.Jamzad, R. Fassihi. Development of a controlled release low dose class II drug-Glipizide. Int.J. Pharm., 2006, 312:24–32.
[25] M. Barbouchi, K.Elamrani, M. Idrissi, et al. Comparative study on phytochemical screening, quantification of phenolic contents and antioxidant properties of different solvent extracts from various parts of Pistacia lentiscus L. J. King. Saud. Univer . Sci., 2020, 32(1):302-6.
[26] N.C.J. Anyanwu, L.Y. Adogo, B.Ajide. Development and evaluation of in situ gelling gastroretentive formulations of meloxicam. Univers. J. Pharm. Res., 2017, 2(3):11-14.
[27] R.Ganapati,K.S. Bhimgoni, S.Anegundha. Floating drug delivery of a locally acting H2-antagonist: an approach using an in situ gelling liquid formulation. Acta. Pharm., 2009, 59: 345–354.
[28] M.Patel, D.K.Patel , C.N.Patel . Formulation and evaluation of floating oral in situ gelling system of amoxicillin. I.S.R.N Pharm., 2011, 5402: 276250.
[29] P.S.Rajnikanth,B.Mishra. Floating in situ gelling system of acetohydroxamic acid for clearance of H.pylori. Drug. Dev. Ind. Pharm., 2008, 34: 577–587.
[30] P.S.Rajnikanth, J. Balasubramanium, B.Mishra. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. Int. J. Pharm., 2007, 335: 114–122.
[31] S.Mutalik, N.Udupa, S.Kumar , et al. Glipizide matrix transdermal systems for diabetes mellitus: Preparation, in vitro and preclinical studies. Life. Sci., 2006, 79:1568-1577.
[32] V.K. Kamboj, P.K. Verma. Palmitic Acid-Pluronic F127-palmitic acid pentablock copolymer as a novel nanocarrier for oral delivery of glipizide. Turk. J. Pharm. Sci., 2019, 16(3):265-272.
[33] N.N.Bobade, S.D Pande. Formulation and evaluation of controlled release gastro-retentive in situ gel for diltiazem hydrochloride. Ind. J. Pharm. Ed. Res., 2016, 50 (3): S254-S265.
[34] S.Miyazaki, H.Aoyama, N.Kawasaki . In situ gelling gellan formulations as vehicles for oral drug delivery. J. Control. Release. 1999, 60:287–295.
[35] D.J. Singhavi, R.S.Pundkar, S.Khan . Famotidine microspheres reconstituted with floating in situ gel for stomach-specific delivery: Preparation and characterization. J.Drug. Deliv . Sci.Technol., 2017, 41: 251-259.
[36] B.E.De Spiegeleer, G.Wattyn G, P. Slegers. The importance of the cosolvent propylene glycol on the antimicrobial preservative efficacy of a pharmaceutical formulation by DOE ruggedness testing. Pharm. Dev. Technol., 2008, 11:275-284.
[37] D.B.Mahmoud, M.H.Shukr, A.N. Meshad. Gastroretentive cosolvent-based in situ gel as a promising approach for simultaneous extended delivery and enhanced bioavailability of mitiglinide calcium. J. Pharm.Sci., 2018, 108: 897-906.
[38] Y.Lu, S. Kim, K.Park. In vitro-in vivo correlation: perspectives on model development. Int. J . Pharm., 2011, 418:142-148.
[39] S.Sakore, B. Chakraborty. In vitro-in vivo correlation (IVIVC): a strategic tool in drug development. J. Bioequiv.Availab., 2011, S3-15.
[40] N.A.H.Abou Youssef, A.A.Kassem, M.A.E. El-Massik, et al. Development of gastroretentive metronidazole floating raft system for targeting Helicobacter pylori.Int J Pharm. 2015; 486(1-2):297-305.
[41] B. Choi, H.J. Park, S. Hwang et al. Preparation of alginate beads for floating drug delivery system: effects of CO2 gas-forming agents. Int. J. Pharm., 2002, 239(1-2): 81-91.