Original Article

# Formulation and Evaluation of Controlled Release Gastro-Retentive *In situ* Gel for Diltiazem Hydrochloride

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## ABSTRACT

In present study is to develop Gastro-Retentive controlled release *in situ* gel using natural and synthetic polymers. Gastro-retentive controlled release *in situ* gels were prepared to controlled drug delivery, to improve bioavailability, stability, reducing side effects. For the present work $3^2$ factorial designs was selected. The two independent variables were selected sodium alginate ($X_1$) and ratio of polymers HPMC K4M: Gellum Gum ($X_2$) combined concentration of HPMC K4M and Gellum Gum was kept constant i.e. 2% and nine formulations were formulated as per experimental design, From evaluation of *in situ* gel formulation for factorial batches, formulation HPGG7 has show good gel strength, lag time (98 ± 0.57) sec, pH value (7.4 ± 0.20), drug contain (99.92 ± 0.04)%, viscosity before and after gel (32715 ± 1.15) and (39850 ± 1.73)cp respectively, total floating time more than 24 hours and also have good controlled release behaviour as it retard drug release up to (79.2 ± 0.50) % . Formulated *in situ* gel were stable at the selected temperature and humidity in storage for 3 month. Hence, from above it was concluded that formulation, *in situ* gel formulation HPPGG7 was containing sodium alginate (1.5%)w/v, HPMC K4M (0.5%)w/v, Gellum gum (1.5%)w/v, which could be most promising gastro-retentive *in situ* gel formulation. It was concluded that the prepared controlled release *in situ* gel of Diltiazem Hydrochloride may prove to be potential candidate for safe and effective controlled drug delivery for extended period of time.

**Key world:** Diltiazem HCL, Gastro-retentive *In situ* Gel, HPMC, Sodium Alginate, Tri-Sodium Citrate.

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## INTRODUCTION

Today the enhancement of bioavailability and development of continuous controlled release formulations has tremendous impact on the drug delivery field especially for drugs with a narrow absorption window.[1] However, conventional oral liquid dosage forms are limited by insufficient retention in the upper gastric region, thus lead to bioavailability complications. From this the requisites to prolong the residence time of such dosage forms in the stomach leads to an important approach including decrease in the density to stimulate floating in the gastric fluids and thus gastro-retentive sustained release dosage form is reached.[2] This new revolution that has been achieved in sustained drug delivery system represents today by floating *in situ* gel system. In this system, a solution of low viscosity can be easily applied; which upon reaching gastric contents it undergoes polymeric changes; thus producing a viscous *in situ* gel of density lower than the gastric fluids.[3]

Dosage forms for gastro-retentive drug delivery systems include floating; swelling; inflation; adhesion; high-density

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systems and low density systems that increase the gastric residence time.[4-6] Gastric retention is useful for those drugs which (i) Act Locally; (ii) Have a narrow absorption window in the small intestinal region; (iii) Unstable in the intestinal environment; and (iv) Low solubility at high pH environment.[7] Various dosage forms have been developed for gastric retention; these include, floating Tablets,[8] floating beads,[10] pellets,[11] floating granules,[12] and floating microspheres.[12]

*In situ* gel forming drug delivery is a type of muco-adhesive drug delivery system. *In situ* gel forming drug delivery system are a revolution in oral drug delivery. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These *in situ* gels have a characteristic property of temperature dependant and cation induced gelation.[13] these *in situ* gel preparations can be easily formulated in bulk, it gives site specific drug delivery and sustained action when compared to other conventional suspensions. The polymers which are used to prepare *in situ* gels can be termed as smart polymers. They are having the ability to change their physicochemical properties in response to the altered environmental conditions.[14] The *in situ gel* formation occurs due to one or combination of different stimuli like pH change, temperature change, ionic activation etc.[15]

Diltiazem Hydrochloride, a calcium channel blocker, is widely used for the treatment of angina pectoris, hypertension and arrhythmias.[16,17] It is administered orally in formulation such as (Tablets, Capsules, and Sustained Release Tablets/Capsules) and also parenterally (Intravenous). The usual dose of diltiazem Hydrochloride for antihypertension is 180-240 Mg/day.[14,16,18] The conventional Tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 6 hours. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional Tablet or capsules have been attenuated by modifying diltiazem in the form of sustained or controlled release Tablet or capsules.[16,19,14] The sustained or controlled release forms are administered two times a day due to its limited residence time in the gastrointestinal tract.[16,20]

The present research work was aimed to prepare controlled release gastro-retentive *In situ* gel for Diltiazem HCL to improve pharmacokinetic performance by using combination of Hydroxy Propyl Methyl Cellulose, Gellum Gum. The prepared formulation, *In situ* gel will become gel in contact with gastric pH and release drug in controlled manner up to 24 hours.

## MATERIAL

**Diltiazem Hydrochloride** was obtained as gift sample from Pellet Pharma Ltd. Hyderabad. HPMC K4M was obtained as gift sample from colourcon Goa. Sodium alginate, gellum gum were procured from S.D. Fine chemicals, Mumbai, India. All other reagents used were of analytical grade commercially available from Merck Pvt. Ltd., Mumbai, India.

## METHOD

### Selection of Active Pharmaceuticals Agents

Diltiazem Hydrochloride, a calcium channel blocker, is widely used for the treatment of angina pectoris, hypertension and arrhythmias.[16,17] The conventional Tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 6 hours. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional dosage form.[16,19,14]

### Factorial Batch

A factorial designs is used to evaluate two or more factor simultaneously. The treatments are combination of level of factors. The advantages of factorial designs over one factor at a time experiments include theirs efficiency and deletion of interaction. Intervention studies with two or more categorical explanatory variable leading to numerical outcome variable are called factorial designs. A factor is simply a categorical variable with two or more value refers as levels. A study in which there are two factors with theirs three levels called $3^2$ factorial designs. For the present work $3^2$ factorial was selected. The two independent variables were selected Sodium Alginate ($X_1$) and ratio of HPMC K4M: Gellum Gum ($X_2$) combined concentration of HPMC K4M and Gellum Gum was kept constant i.e 2% and nine formulations were formulated as per experimental design. Amount variable in $3^2$ factorial designs batch and experimental design was shown in Table 1 and Table 2 respectively.

### Preparation of *In situ* Gel[21-24]

Sodium alginate solutions of concentrations (0.5%, 1% 1.5%)w/v were prepared in deionised water containing 0.3% w/v of Tri Sodium citrate and 1.8%w/v of sodium methyl paraben. Sodium alginate solutions were heated to 70°C with stirring. After cooling to below 40°C, gellum Gum, HPMC K4M was added with different concentration as per following formulation Table 3. After homogeneous dispersion calculated amount of

dose the drug and 1%w/v of calcium carbonate was added and dispersed well with continuous stirring.

## Evaluation of Controlled Release Gastro-Retentive *In situ* Gel

### Drug and Polymer Compatibility Studies[25,26]

**a) FTIR Spectroscopy**

The FTIR spectrum of drug was recorded on an infrared spectrophotometer (Shimadzu Affinity-1). IR spectrum of drug, polymers, and physical mixture of drug and polymer were recorded in the frequency range 400-4000 $cm^{-1}$. The recorded significant peaks were noted and were matched with standard FTIR of drug. The FTIR spectrum was shown in Figure 1.

**b) Differential Scanning Calorimeter Analysis**

Thermal analysis was performed using system with differential scanning calorimeter equipped with a computerized data station. All samples were weighed and heated at a scanning rate of 10°C/min between 30 and 300°C and 40 ml/min of nitrogen flow. The differential scanning calorimetry analysis gives an idea about the interaction of various materials at different temperature. It also allows us to study the possible degradation pathway of the materials. The DSC spectrum was shown in Figure 2.

### Standard Calibration Curve of Diltiazem HCl in 0.1N HCL[25,26]

From solution having concentration 100 µg/ml aliquots of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2,1.4, 1.6, 1.8, and 2 ml were pipette out into 10ml volumetric flasks. The volume was made up to the mark with 0.1N HCL to get the final concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/ml respectively. The absorbance of each concentration was measured at 236 nm. A graph of absorbance versus concentration was plotted and it is shown in Figure 3. It shows straight line meaning the calibration curve obeys Beers law.

### pH Measurement[21,27]

The pH was measured in each of the solution of sodium alginate based *in situ* solutions, using a calibrated digital pH meter at 27°C. The measurements of pH of each data were in triplicate and the average values are given in Table 4.

### *In vitro* Floating Study[28]

The *in vitro* floating study was carried out using USP dissolution apparatus II having 500 ml of 0.1N HCl (pH 1.2) .The medium temperature was kept at 37°C. Accurately weighed 10 mL of the prepared *in situ* gel formulations were drawn up using disposable syringe and placed into the Petridis (4.5 mm internal diameter) and finally the Petridis containing the formulation was kept in the dissolution vessel containing medium without much disturbance.

The time the formulation took to emerge on to the medium surface (Floating Lag Time) and the time over which the formulation constantly floated on the dissolution medium surface Duration of Floating) were noted. The measurements of floating lag time and total floating time of each data were in triplicate and the average values are given in Table 4.

### Characteristics of *In situ Gel/ Gel Strength In-vitro* Gelling Capacity[29]

To evaluate the formulations for their *in-vitro* gelling capacity by visual method, colored solutions of *in situ* gel forming drug delivery system were prepared. The *in-vitro* gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37 ± 1°C temperature. One ml of colored formulation solution was added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which they formed gel remains as such. Color was added to give visualized appearance to formed gel. The *in-vitro* gelling capacity was graded in three categories on the basis of gelation time and time period for which they formed gel remains.

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for few hours

(+++) Gelation immediate remains for an extended period.

### Determination of drug content (%)[30]

A known quantity 5 ml of the prepared solutions was stirred with 100 ml of 0.1N HCl for 2 hrs. The sample was then centrifuged at 2000 rpm and the filtrate was measured by using UV spectrophotometer at 236 nm. The measurements of drug content of each data were recorded in triplicate and the average values are given in Table 4.

### Viscosity Measurement of the *In-situ* Gelling Solutions[31,32]

Viscosity before gel (Sol) were determined using a brookfield digital viscometer (Model no LVDV 2P230)

with the spindle number 5. The temperature of the 25 mL samples was kept at 25 ± 1 °C during each measurement which lasted 60 sec, and the experiments were performed in triplicate. The average values are given in Table 4.

Viscosity after gel (gel) were determined using a Brookfield digital viscometer (Model no LVDV 2P230) with the spindle number 6. 10 ml of 0.1N HCL was added to 25 ml of *in situ* gel for gelation after 2 min sample was analysed. The temperature of samples was kept at 25 ± 1 °C during each measurement which lasted 60 sec, and the experiments were performed in triplicate. The average values are given in Table 4.

### *In vitro* Drug Release Studies[28,31,33]

Cumulative drug releases of the *in-situ* gelling preparations were carried out with some modification using USP 2 dissolution test apparatus with paddle stirrer at a rate of 50 rpm. The slow speed prevented breaking of the gelled formulation and ensured a low level of agitation. The dissolution medium used was 900 mL of a 0.1 N solution of HCL (pH 1.2), and the temperature was kept at 37°C ± 2°C. A 10 mL sample was withdrawn using a disposable syringe; the needle was then wiped clean and the excess sample removed from the needle end. The sample was then gently transferred into a Petridis which was then immersed into the dissolution medium without much turbulence. At hourly intervals, an accurately measured 10 mL sample of the dissolution medium was removed with the help of a hypodermic syringe, diluted to 50 mL with 0.1N HCL and absorbance of the sample was read at 236 nm using a UV spectrophotometer for analysis of drug. Each time, the sample withdrawn was replenished with the same amount of the pre-warmed 0.1N HCL. Each experiment was continued for a period of 24 hours in triplicate. The experiments were performed in triplicate. The cumulative drug release of factorial batches is shown in Table 5 and Figure 4.

### Rheological Studies[21,28]

A rheology study for *In situ* gel for gastro-retentive system by using brookfield viscometer was studied. 25 ml of *in situ* gel formulations were placed in nescller cylinder which properly cut for required quaintly. The viscosity measurements were done at rpm of 10, 20, 30, 40, 50 60 and up to 100 for 60 sec agitation at temperature of 37°C ± 2°C and similarly viscosity measurement were done reverse order. Experiments were performed in triplicate. Rheograms were constructed by plotting the dial readings on the x-axis and rpm values along the y-axis. The rheological behavior of factorial batches is shown in Figure 5.

### Kinetics of Drug Release[34]

Dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Pepas to ascertain the kinetics modelling of dug release by using a PSP Disso version 2.08 and the model with higher correlation was consider to be the best model observation were submersed in Table 6.

In order to know drug release mechanism the data was further analysed by korsmeyer pepas equation and value if n i.e. release exponent was calculated. The n value is used to interpret the release mechanism as is shown in Table 6.

### Stability Studies[35-37]

In the present study, stability studies were carried out at 40°C ± 2°, 75 ± 5% RH), (25°C ± 2°C ,75% ± 5% RH) and (40°C ± 2°C, 75% ± 5% RH) for a specific time period up to 3 month for the optimized formulation. The optimized formulation was analyzed for the drug contents study, pH, lag time (sec), floating time (hours), viscosity before gel (cp), viscosity after gel (cp), cumulative drug release (%). Experiments were performed in triplicate and average values are noted. The Stability Studies data was shown in Table 7.

## RESULTS AND DISCUSSION

Diltiazem Hydrochloride, a calcium channel blocker, is widely used for the treatment of angina pectoris, hypertension and arrhythmias. The conventional Tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 6 hours. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional dosage form.

*In situ* gel forming drug delivery systems are a revolution in oral drug delivery. These hydrogels are liquids at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependant and cation induced gelation. This gelation involves formation of the double helical junction zones followed by aggregation of the double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding. In present works, sodium alginate, HPMC K4M, gellum gum were used for development of controlled release formulations with various concentrations of the polymers.

Alginic acid is a linear block polysaccharide copolymer made of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues joined by 1,4 glycosidic linkages. The

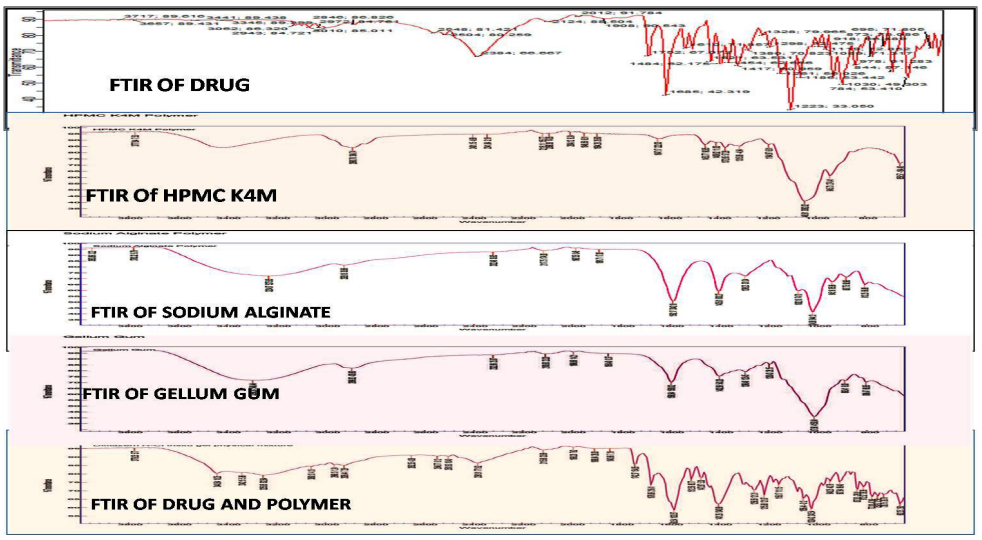


**Figure 1: FTIR Spectra of Drug, Polymer and Physical Mixture.**

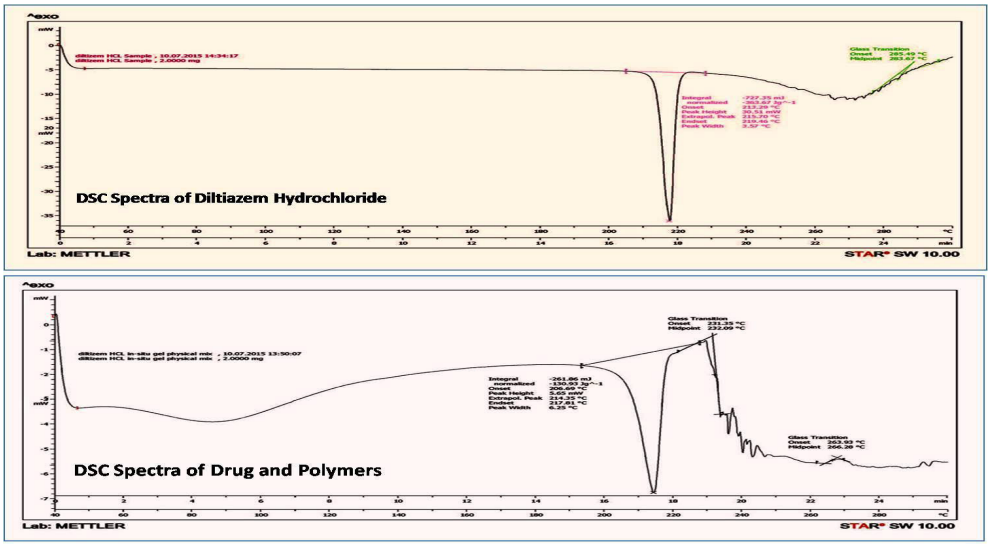


**Figure 2: DSC Spectra of Drug and Physical Mixture.**

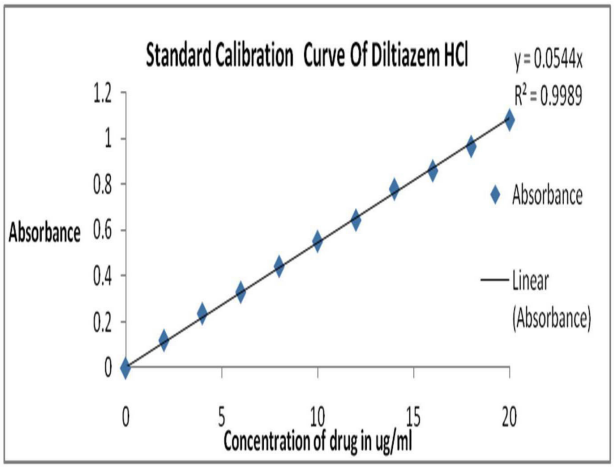


**Figure 3: Standard Calibration Curve of Diltiazem HCL in 0.1N HCL.**

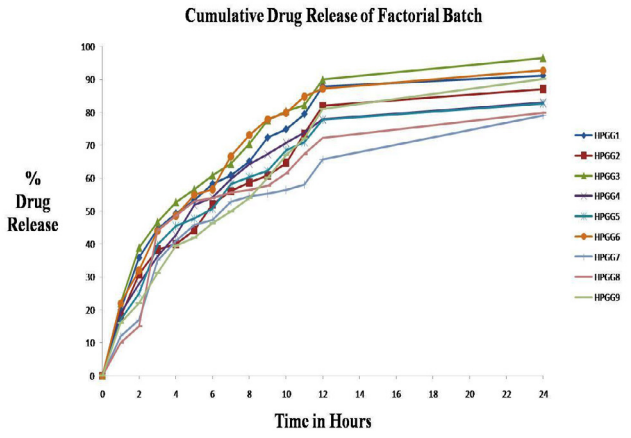


**Figure 4: Cumulative Drug Release of Factorial Batch.**

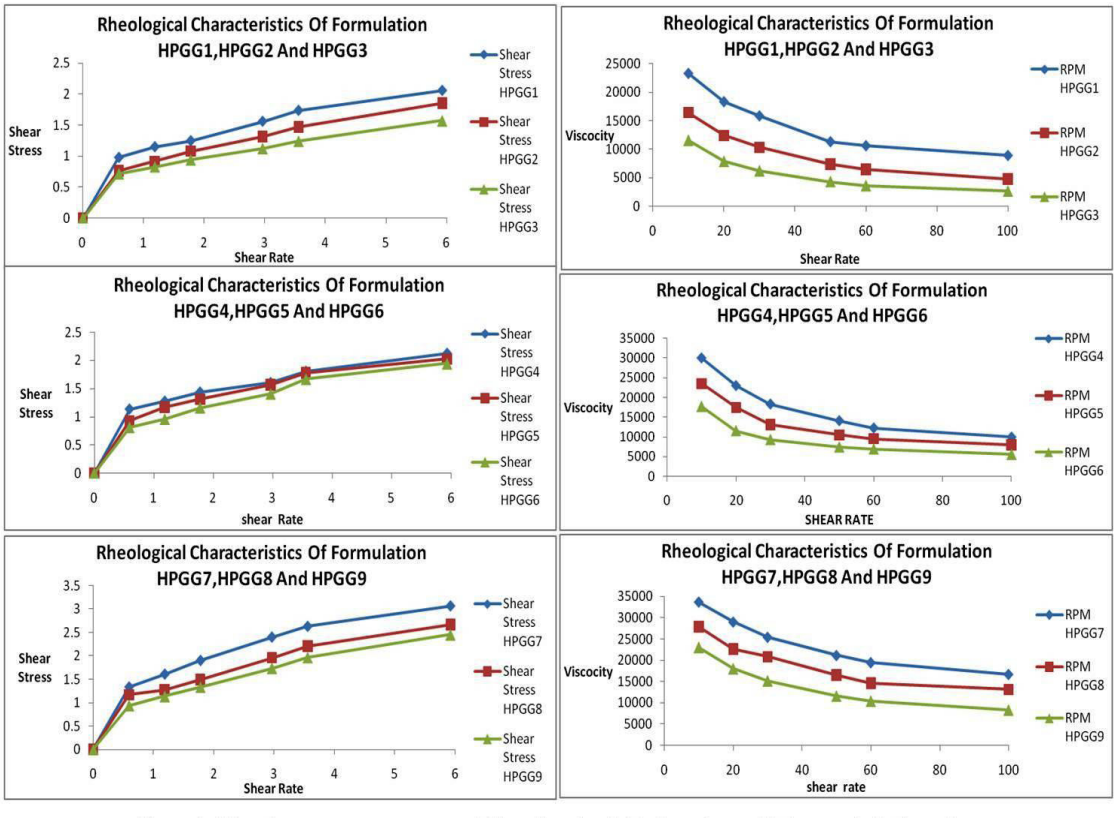


**Figure 5: Rheological Behavior of Factorial Batches.**

**Table 1: Amount of Variable in 32 Factorial Designs Batches**

| Coded Values | Actual Values | |
|---|---|---|
| | X1 | X2 |
| -1 | Sodium Alginate 0.5% | Ratio of HPMC : Gellum Gum (1:3) |
| 0 | Sodium Alginate 1% | Ratio of HPMC : Gellum Gum (2:2) |
| +1 | Sodium Alginate 1.5% | Ratio of HPMC : Gellum Gum (3:1) |

**Table 2: Experimental Designs**

| Formulation Code | Coded value | |
|---|---|---|
| | X1 | X2 |
| HPGG1 | -1 | -1 |
| HPGG2 | -1 | 0 |
| HPGG3 | -1 | +1 |
| HPGG4 | 0 | -1 |
| HPGG5 | 0 | 0 |
| HPGG6 | 0 | +1 |
| HPGG7 | +1 | -1 |
| HPGG8 | +1 | 0 |

**Table 3: Formulation of Factorial Design Batches**

| Code | Name of Ingredients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Diltiazem HCL (%)w/v | Sodium Alginate (%)w/v | HPMC K4M (%)w/v | Gellum Gum (%)w/v | Calcium Carbonate (%)w/v | Tri-sodium Citrate (%)w/v | Sodium Methyl Paraben (%)w/v | Deionised Water |
| **HPGG1** | 1.8 | 0.5 | 0.50 | 1.5 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG2** | 1.8 | 0.5 | 1 | 1 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG3** | 1.8 | 0.5 | 1.5 | 0.50 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG4** | 1.8 | 1 | 0.50 | 1.5 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG5** | 1.8 | 1 | 1 | 1 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG6** | 1.8 | 1 | 1.5 | 0.50 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG7** | 1.8 | 1.5 | 0.50 | 1.5 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG8** | 1.8 | 1.5 | 1 | 1 | 1 | 0.3 | 1.8 | qs to 100 ml |
| **HPGG9** | 1.8 | 1.5 | 1.5 | 0.50 | 1 | 0.3 | 1.8 | qs to 100 ml |

**Table 4: Characterization of *in situ* gel**

| Formulation Code | pH | Lag Time (Sec) | Total Floating (Time) | Drug Content (%) | Viscosity Before Gel (cp) | Viscosity After Gel (cp) |
|---|---|---|---|---|---|---|
| **HPGG1** | 7.2 ± 0.20 | 80 ± 1.15 | >24 | 98.57 ± 0.82 | 23265 ± 2.88 | 23843 ± 1.73 |
| **HPGG2** | 7.2 ± 0.20 | 74 ± 1.15 | >24 | 98.23 ± 1.02 | 16430 ± 2.30 | 17693 ± 2.88 |
| **HPGG3** | 7.2 ± 0.20 | 72 ± 1.15 | >24 | 98.14 ± 1.073 | 9595 ± 1.15 | 11253 ± 1.73 |
| **HPGG4** | 7.3 ± 0.20 | 84 ± 2.30 | >24 | 98.94 ± 0.611 | 27315 ± 2.88 | 29535 ± 2.30 |
| **HPGG5** | 7.3 ± 0.20 | 77 ± 1.15 | >24 | 98.74 ± 0.72 | 21480 ± 5.19 | 25480 ± 2.30 |
| **HPGG6** | 7.3 ± 0.20 | 74 ± 2.30 | >24 | 98.48 ± 0.87 | 14645 ± 2.30 | 18320 ± 4.61 |
| **HPGG7** | 7.4 ± 0.20 | 98 ± 0.57 | >24 | 99.92 ± 0.04 | 32715 ± 1.15 | 39850 ± 1.73 |
| **HPGG8** | 7.4 ± 0.20 | 87 ± 0.57 | >24 | 99.49 ± 0.29 | 26880 ± 5.19 | 29530 ± 5.19 |
| **HPGG9** | 7.4 ± 0.20 | 82 ± 3.46 | >24 | 99.30 ± 0.40 | 22045 ± 1.15 | 29440 ± 1.73 |

proportion and the arrangement of the blocks along the polymer chain much depend on the algal source. The aqueous alginate solutions could form firm gels in presence of di-and tri-valent metal ions by a cooperative process involving consecutive guluronic residues in the G blocks of the alginate chain. This property has been widely used for preparation of vehicles for sustained delivery of the bioactive molecules. Alginates show characteristic ion binding for multivalent cations and this forms the basis for their gelling properties. The alginate binding leads to the formation of covalent bonds leading to the perception of the insoluble hydrogel. Cross-linking processes stiffen and roughen the polymer and reduce the swelling in solvents. This generally leads to a reduction in the permeability of different solutes hindering the release of embodied drugs in alginate matrices, allowing these systems to be used in controlling the drug release. Matrices containing sodium alginate and sodium-calcium alginate have been investigated for their sustained release effects. To achieve repeatability in gelation we used a source of $Ca^{++}$ ions in the solution itself. Due to the free calcium ions being complexes with sodium citrate, gelation was delayed until the administered solution reached the acidic environment of the stomach. Gelation was then occurred as the complex broke down and the $Ca^{++}$ ions were released. The calcium carbonate present in the gelling formulation released carbon dioxide in gastric environment thereby making the formulation porous and buoyant and prolonging the residence time. This floating in stomach provides the potential to sustain the drug release over a long period of time. Gelation of sodium alginate will occur in the presence of $H^{+}$ ions, the soft alginic acid gels that are formed are generally suitable as vehicles for drug delivery. In this study $Ca^{++}$ ions were included in the formulation for induc-

| Table 5: Cumulative Drug Release of Factorial Batches | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (Hours) | % Cumulative Drug Release | | | | | | | | |
| | HPGG1 | HPGG2 | HPGG3 | HPGG4 | HPGG5 | HPGG6 | HPGG7 | HPGG8 | HPGG9 |
| 0 | 00 ± 00 | 00 ± 00 | 00 ± 00 | 00 ± 00 | 00 ± 00 | 00 ± 00 | 00 ± 00 | 00 ± 00 | 00 ± 00 |
| 1 | 20 ± 0.64 | 18 ± 0.014 | 22 ± 0.01 | 19 ± 0.01 | 17 ± 0.69 | 22 ± 0.68 | 12 ± 0.69 | 10 ± 0.69 | 16 ± 0.12 |
| 2 | 35.87 ± 0.38 | 30.91 ± 0.66 | 38.93 ± 0.68 | 28 ± 0.02 | 25 ± 0.68 | 32 ± 0.68 | 17 ± 0.69 | 15 ± 0.69 | 22 ± 0.68 |
| 3 | 44.5 ± 0.25 | 38.35 ± 0.27 | 46.68 ± 0.51 | 36.22 ± 0.18 | 39.78 ± 0.12 | 44 ± 0.67 | 34.98 ± 0.69 | 44.23 ± 0.50 | 31.19 ± 0.54 |
| 4 | 49.3 ± 0.27 | 40.02 ± 0.04 | 52.77 ± 0.58 | 42.79 ± 0.59 | 45.57 ± 0.26 | 48.62 ± 0.23 | 40.93 ± 0.17 | 48.59 ± 0.25 | 39.58 ± 0.26 |
| 5 | 53.33 ± 0.26 | 44.19 ± 0.16 | 56.65 ± 0.50 | 51.93 ± 0.69 | 47.76 ± 0.13 | 54.94 ± 0.70 | 45.94 ± 0.63 | 53.01 ± 0.65 | 41.92 ± 0.23 |
| 6 | 58.31 ± 0.69 | 52.08 ± 0.09 | 60.87 ± 0.66 | 54.19 ± 0.17 | 50.79 ± 0.10 | 56.65 ± 0.20 | 47.3 ± 0.45 | 53.94 ± 0.70 | 46.32 ± 0.44 |
| 7 | 60.92 ± 0.12 | 56.07 ± 0.09 | 64.38 ± 0.31 | 59.74 ± 0.57 | 58.21 ± 0.51 | 66.66 ± 0.18 | 52.86 ± 0.57 | 55.57 ± 0.96 | 49.87 ± 0.52 |
| 8 | 65.1 ± 0.31 | 58.73 ± 0.56 | 70.47 ± 0.38 | 64.36 ± 0.30 | 60.43 ± 0.35 | 73.14 ± 0.55 | 54.5 ± 0.31 | 56.39 ± 0.38 | 53.96 ± 0.69 |
| 9 | 72.36 ± 0.65 | 60.84 ± 0.64 | 77.68 ± 0.54 | 67.32 ± 0.27 | 62.26 ± 0.47 | 77.91 ± 0.24 | 55.32 ± 0.43 | 57.83 ± 3.61 | 60.22 ± 1.21 |
| 10 | 74.84 ± 0.41 | 64.68 ± 0.53 | 80.47 ± 0.39 | 70.85 ± 0.65 | 68.56 ± 0.25 | 79.96 ± 0.67 | 56.48 ± 0.32 | 61.54 ± 0.27 | 67.01 ± 0.05 |
| 11 | 79.5 ± 0.06 | 73.5 ± 0.41 | 82.27 ± 0.25 | 73.83 ± 0.64 | 70.98 ± 0.66 | 84.8 ± 0.74 | 58.08 ± 0.60 | 67.32 ± 0.42 | 72.14 ± 0.15 |

| Table 6: Kinetics of Drug Release of Factorial Batches | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Formulation Code | HPGG1 | HPGG2 | HPGG3 | HPGG4 | HPGG5 | HPGG6 | HPGG7 | HPGG8 | HPGG9 |
| Zero order | 0.400 | 0.596 | 0.362 | 0.443 | 0.495 | 0.425 | 0.621 | 0.486 | 0.764 |
| T-test | 1.515 | 2.573 | 1.347 | 1.713 | 1.974 | 1.629 | 2.750 | 1.930 | 4.114 |
| 1st order | 0.925 | 0.936 | 0.984 | 0.870 | 0.888 | 0.936 | 0.922 | 0.855 | 0.977 |
| T-test | 8.448 | 9.275 | 19.31 | 6.115 | 6.717 | 9.233 | 8.265 | 5.711 | 16.04 |
| Matrix | 0.965 | 0.976 | 0.967 | 0.964 | 0.968 | 0.961 | 0.973 | 0.940 | 0.977 |
| T-test | 12.90 | 15.79 | 13.23 | 12.63 | 13.45 | 12.14 | 14.84 | 9.583 | 16.05 |
| Peppas | 0.974 | 0.982 | 0.976 | 0.978 | 0.972 | 0.977 | 0.953 | 0.906 | 0.987 |
| T-test | 14.94 | 18.14 | 15.80 | 16.38 | 14.35 | 16.15 | 10.90 | 7.444 | 21.97 |
| Hix.Crow. | 0.840 | 0.875 | 0.906 | 0.779 | 0.805 | 0.846 | 0.850 | 0.763 | 0.944 |
| T-test | 5.374 | 6.267 | 7.417 | 4.314 | 4.702 | 5.501 | 5.604 | 4.101 | 9.993 |
| n = | 0.501 | 0.528 | 0.486 | 0.531 | 0.550 | 0.516 | 0.639 | 0.700 | 0.619 |
| k = | 23.11 | 19.38 | 25.23 | 19.93 | 18.57 | 23.14 | 13.48 | 12.90 | 15.17 |
| best model | Pepps | Peppas | 1st order | Peppas | Peppas | Peppas | Matrix | Matrix | Matrix |

**Table 7: Stability Studies of optimum formulation (HPGG7) at various temperature condition.**

| **10 $^0$C ± 2 $^0$C , 75 % ± 5 % RH** | | | | |
|---|---|---|---|---|
| **Evaluation Parameter** | **0 Month** | **2 Month** | **3 Month** | **6 Month** |
| Drug Content (%) | 99.92 ± 0.04 | 99.62 ± 0.58 | 99.52 ± 0.35 | 99.11 ± 0.25 |
| pH | 7.4 ± 0.20 | 7.4 ± 0.20 | 7.4 ± 0.20 | 7.4 ± 0.20 |
| Lag Time(Sec) | 98 ± 0.57 | 98 ± 0.11 | 98 ± 0.65 | 98 ± 0.85 |
| Floating Time (Hours) | 24 | 24 | 24 | 24 |
| Viscosity Before Gel (cp) | 32715 ± 1.15 | 32711±1.45 | 32719 ± 1.89 | 32721 ± 1.87 |
| Viscosity After Gel (cp) | 39850 ± 0.73 | 39852 ± 0.73 | 39853 ± 0.73 | 398553 ± 0 .73 |
| Cumulative Drug Release (%) | 79.2 ± 0.50 | 79.45 ± 0.22 | 79.82 ± 0.55 | 79.52 ± 0.57 |
| **25 $^0$C ± 2 $^0$C ,75 % ± 5 % RH** | | | | |
| Evaluation Parameter | 0 Month | 2 Month | 3 Month | 6 Month |
| Drug Content (%) | 99.92 ± 0.04 | 99.62 ± 0.78 | 99.55 ± 0.12 | 99.53 ± 0.56 |
| pH | 7.4 ± 0.20 | 7.4 ± 0.22 | 7.4 ± 0.01 | 7.4 ± 0.01 |
| Lag Time(Sec) | 98 ± 0.57 | 98 ± 0.65 | 98 ± 0.75 | 98 ± 0.82 |
| Floating Time (Hours) | 24 | 24 | 24 | 24 |
| Viscosity Before Gel (cp) | 32715 ± 1.15 | 32715 ± 1.23 | 32715 ±1.10 | 32715 ± 1.25 |
| Viscosity After Gel (cp) | 39850 ± 0.73 | 39852 ± 0 .15 | 39850 ± 0.87 | 39859 ± 0.02 |
| Cumulative Drug Release (%) | 79.2 ± 0.50 | 79.26 ± 0.50 | 79.24 ± 0.50 | 79.29 ± 0.50 |
| **40 $^0$C ± 2 $^0$C, 75 % ± 5 % RH** | | | | |
| Evaluation Parameter | 0 Month | 2 Month | 3 Month | 6 Month |
| Drug Content (%) | 99.92 ± 0.04 | 99.92 ± 0.57 | 99.92 ± 0.22 | 99.92 ± 0.22 |
| pH | 7.4 ± 0.20 | 7.4 ± 0.28 | 7.4 ± 0.23 | 7.4 ± 0.24 |
| Lag Time(Sec) | 98 ± 0.57 | 98 ± 0.59 | 98 ± 0.65 | 98 ± 0.87 |
| Floating Time (Hours) | 24 | 24 | 24 | 24 |
| Viscocity Before Gel (cp) | 32715 ±1.45 | 32715 ± 1.32 | 32715 ± 1.02 | 32715 ± 1.89 |
| Viscocity After Gel (cp) | 39850 ± 0.73 | 39852 ± 0.73 | 39859 ± 0.73 | 39850 ± 0.73 |
| Cumulative Drug Release (%) | 79.2 ± 0.50 | 79.45 ± 0.43 | 79.89 ± 0.12 | 79.78 ± 0.12 |

tion of alginate gelation. However, for ease of administration we required the formulation to be in the fluid (sol) state. This was achieved by addition of sufficient sodium citrate to the formulation to form a complex with all of the $Ca^{++}$ ions present in the formulation and hence to effectively remove them from solution. In the acidic environment of the stomach the complex is broken down and the $Ca^{++}$ ions released cause gelation to occur. HPMC K4M was selected for formulations to maintain viscosity and releases behaviour from the formulations. The viscosity is an important variable because it effects the gelation of the solutions, flow of the formulation and time required for the gelation. The viscosity is dependent on the concentration of the polymers. Methyl-paraben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone or in combination with other parabens or with other antimicrobial agents. Owing to the poor solubility of the parabens, paraben salts (particularly the sodium salt) are more frequently used in formulations. However, this raises the pH of poorly buffered formulations.

Drug excipients interaction study by FTIR was carried out as per standard procedure. FTIR spectra of Diltiazem hydrochloride, HPMC K4M, sodium alginate, gellum gum and FTIR spectrum for physical mixture of Drug and polymers is shown in Figure 1. It was observed that principle peaks of drug were found to be in FTIR spectra of a drug as well as FTIR spectra of physical mixture of drug and excipients. It was suggested that there was no physical and chemical interaction between drug and polymers.

Drug excipient study was carried out by DSC spectra graph of a drug Diltiazem Hydrochloride and DSC spectra of drug and excipient was shown in Figure 2. It was observed that peak onset temperature and peak of

temperature in DSC spectra of physical mixture of drug and polymers was compiled with DSC spectra behaviour as noted in DSC spectra of pure drug. Thus there was no physical and chemical interaction between drug and polymers.

Standard calibration of Diltiazem HCL was carried out in 0.1N HCl and result showed in Figure 3. From the standard curve, it was observed that the drug obeys Beer's law in concentration range of 2.0-20 μg/ml in 0.1 N HCL. Drug shown good linearity with regression of coefficient ($r^2$=0.998) and equation for this line obtained was found to be y = 0.046x + 0.005 which is used for the calculation of amount of drug and dissolution study.

*In situ* gel of formulation were characterized for various evaluation parameter such as pH, lag time, total floating time, % drug content, viscosity before gel and viscosity after gel. The result of characterization of factorial batches was show in Table 4.

It was observed that pH of *in situ* gel of formulations (HPGG1 to HPGG9 ) were found to be range 7.2 to 7.4. Viscosity before gel and after gel of *in situ* gel of formulation (HPGG1 to HPGG9) was found to be range (9595 ± 1.15) to (32715 ± 1.15) cp and (11253 ± 1.73) to (39850 ± 1.73) cp respectively. It was observed that viscosity of *in situ* gels was dependent on concentration of Sodium alginate and ratio of polymer Gellum Gum and HPMC K4M. For Formulation, (HPGG1 to HPGG9), as concentration of sodium alginate was increased (0.5%, 1%, 1.5%) w/v, viscosity before gel and after gel was found to be also increased. For formulation, (HPGG1 TO HPGG3), as concentration gellum gum was decreases, and concentration of HPMC K4M increases, viscosity before gel and after gel was decreases. Similar observation was found for (HPGG4 to HPGG6) and (HPGG7 to HPGG9). *In situ* gel of formulation HPGG7 was shows highest viscosity i.e (32715 ± 1.15) cp which contain Sodium alginate (1.5%) HPMC K4M (0.5%) and Gellum gum (1.5%) and HPGG3 was show lowest viscosity i.e. (9595 ± 1.15) cp which contain sodium alginate (0.5%), HPMC K4M (1.5 %) and gellum gum (0.5 %). Hence, it was concluded that viscosity of *In situ* gel formulation (HPGG1 to HPGG9) was contribute due to sodium alginate and ratio of Gellum Gum and HPMC K4M.

Lag Time of *In situ* gel of formulations (HPGG1 to HPGG9) were found to be range (72 ± 1.15) to (98 ± 0.57) sec. Here, it was observed that lag time of *in situ* gel depends on concentration of sodium alginate and ratio of Gellum gum and HPMC K4M. For Formulations (HPGG1 to HPGG9), as concentration of sodium alginate were increases (0.5%, 1%, 1.5%) w/v respectively, Lag time of formulations were also increases. For formulations, (HPGG1 to HPGG3), as concentration gellum gum was decreases, and Concentration of HPMC K4M was Increases, lag time of formulations were decreases. Similar observation was found for (HPGG4 to HPGG6) and (HPGG7 to HPGG9). *In situ* gel of formulation HPGG7 was showed prolong lag time i.e. (98 ± 0.57) sec which contain sodium alginate (1.5%), HPMC K4M (0.5%) and gellum gum (1.5%) and also HPGG3 was showed minimum lag time i.e. (72 ± 1.15) sec which contain sodium alginate (0.5%), HPMC K4M (1.5%) and gellum gum (0.5%). Hence, it was concluded that viscosity of *in situ* gel formulations (HPGG1 to HPGG9) were contribute due to Sodium alginate and ratio of gellum gum and HPMC K4M. Here, an increase in the polymer concentration resulted in increases floating lag time of the prepared systems.

Total floating times of *in situ* gel of formulations (HPGG1 to HPGG9) were found to be more than 24 hours. All these formulation show good floating behaviour as dissolution media 0.1 N HCL came in contact with formulation, it become instantly gel due to reaction between sodium alginate and calcium alginate in presence of acidic medium. Simultaneously, gas generation was form due to reaction between tri sodium citrate and calcium carbonate. These gases was trapped in rigid structure of gel which has buoyant behaviour in dissolution media for prolong time sufficiently for up to 24 hours or more than 24 hours.

% Drug content of *in situ* gel of formulations (HPGG1 to HPGG9) was found to be range (98.14 ± 1.073) to (99.92 ± 0.04) %. Here, it was observed that drug content of *in situ* gel depends on concentration of Sodium alginate and ratio of gellum gum and HPMC K4M. For Formulations (HPGG1 to HPGG9), as concentration of sodium alginate (0.5%, 1%, 1.5%) was increased, drug content of formulations were also increases. For formulations (HPGG1 to HPGG3) as concentration gellum gum was decreased and concentration of HPMC K4M was increases, drug content of formulations was decreases. Similar observations were found for (HPGG4 to HPGG6) and (HPGG7 to HPGG9). *In situ* gel of formulation HPGG7 was showed maximum drug content i.e. (99.92 ± 0.04) % which contain sodium alginate (1.5%) HPMC K4M (0.5%) and gellum gum (1.5%) and HPGG3 show minimum drug content i.e. (98.14 ± 1.073)% which contain sodium alginate (0.5%), HPMC K4M (1.5%) and gellum gum (0.5%).

The rheological properties of the solutions are of importance in view of their proposed oral administration. Result rheological behaviour of *in situ* gel formulations (HPGG1 to HPGG9) is shown in Figure 5. It was

observed that shear rate was directly proportional to shear stress for both upward and downward curve. As evident from Figure 5 formulations (HPGG1 to HPGG9) shows slight decrease in viscosity with increase in rpm due to the shear thinning behaviour. Though there was a shear thinning pattern observed, there was a fair resistance to flow as far as pour ability of the sol was concerned. This is mainly attributed to high polymer concentration. These formulations show better flow and good sol properties. Hence, *in situ* gels formulations (HPGG1 to HPGG9) shows peudoplastic Flow.

Cumulative drug release of factorial batches of *in situ* gels was shown in Table 5 and Figure 4. *In vitro* drug release of *in situ* gels of formulations (HPGG1 to HPGG9) was found to be range (79.2 ± 0.50)% to (96.61 ± 0.50)% up to 24 hr. Here, it was observed that cumulative drug release of *in situ* gels depends on concentration of sodium alginate and ratio of gellum gum and HPMC K4M. For formulations (HPGG1 to HPGG9), as concentration of sodium alginate (0.5%, 1%, 1.5%) was increased, cumulative drug release of formulations decreases. For formulations, (HPGG1 to HPGG3), as concentration gellum gum decreases, and concentration of HPMC K4M increases, cumulative drug release of formulations were increases. Similar observations were found for (HPGG4 to HPGG6) and (HPGG7 to HPGG9). *In situ* gels of formulation HPGG7 was show prolong and controlled cumulative drug release i.e. (79.2 ± 0.50)% up to 24 hr which contain sodium alginate (1.5%), HPMC K4M (0.5%) and gellum gum (1.5%); HPGG3 was show % cumulative drug release i.e. (96.61 ± 0.50)% up to 24 hr which contain sodium alginate (0.5%), HPMC K4M (1.5%) and gellum gum (0.5%).

Hence, it was concluded that % cumulative drug release of *in situ* gels formulations (HPGG1 to HPGG9) were contribute due to sodium alginate and ratio of gellum gum and HPMC K4M.

The release kinetic of drug release was shown in Table 6. It was observed that *in situ* gels formulations (HPGG1, HPGG2, HPGG4, HPGG5, and HPGG6) were best fitted to peppas model. *In situ* gels formulation HPGG2 were $r^2$ value (0.9823) and n value (0.5283). *In situ* gels formulation HPGG3 was best fitted to first order release with $r^2$ value (0.9843), n value (0.4866). *In situ* gels formulations (HPGG7, HPGG8, and HPGG9) were best fitted to matrix model. Formulation HPGG7 has $r^2$ value 0.9738 and n value (0.6397). From evaluation of *in situ* gels formulation for factorial batches, formulation HPGG7 has show good gel strength, lag time (98 ± 0.57) sec, ph value (7.4 ± 0.20), % drug release (99.92 ± 0.04)%, viscosity before and after gel (32715 ± 1.15) and (39850 ± 1.73) cp respectively, total floating time more than 24 hours and also have good controlled release behaviour as it retard drug release up to (79.2 ± 0.50)%. Hence, from above it was concluded that formulation, *in situ* gels formulation HPPGG7 containing sodium alginate (1.5%), HPMC K4M (0.5%), gellum gum (1.5%),which could be most promising gastro-retentive *in situ* gel formulation.

The stability studies of optimum formulation HPGG7 revealed that there is slightly reduction in drug content was observed over period of 3 month. No significant change was observed on % drug content, pH , lag time, total floating time, viscosity before and after gel, % cumulative drug release (after 24 hours) at various storing condition $10^0$C ± $2^0$C, 75% ± 5% RH, $25^o$C ± $2^o$C ,75% ± 5% RH and $40^o$C ± $2^o$C, 75% ± 5% RH. Hence formulation, HPGG7 was found to be stable for 3 month. The results are shown in Table 7.

## CONCLUSION

It was concluded that *In situ* gel formulation HPPGG7 containing sodium alginate (1.5%), HPMC K4M (0.5%), Gellum gum (1.5%), which could be most promising gastro-retentive *in situ* gel formulation. *In situ* gel will remain stomach for prolong time up to 24 hours and during time it release in controlled manner. *In situ* gel will be promising pharmaceutical formulation for development of gastro-retentive drug delivery system for Diltiazem HCL.

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## CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

## ABBREVIATION USED

**HPMC:** Hydroxyl Propyl Methyl Cellulose;
**DSC:** Differential Scanning Calorimeter.

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## SUMMARY

- Drug and Polymer Compatibility Studies was revealed that there is no physicochemical interaction between drug and polymer under study.
- Floating lag time and floating time was dependent on concentration of sodium alginate and polymer ratio (gellum gum/HPMC K4M).
- From cumulative drug release of drug, it was concluded that high concentration gellum gum, sodium alginate was responsible for controlled release behavior.
- Viscosity of formulation was dependent on all polymers under study. It was also noted that polymer HPMC K4M maintain flow-ability of formulation.
- All formulations were showed pseudo-plastic behaviour.
- Kinetic data of release study was concluded that high polymer concentration formulation shows matrix release pattern of drug release.
- Stability data of optimized formulation was remark that that is no significant change in drug for short turn and also there are no changes was found in floating and rheological behaviours of study.