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PREPARATION AND CHARACTERIZATION OF GERIATRIC-FRIENDLY PIOGLITAZONE DOSAGE FORM WITH MODULATED RELEASE RATE

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ABSTRACT

Pioglitazone hydrochloride is an antidiabetic drug used to improve glycemic control in patients with type II diabetes mellitus. According to Biopharmaceutical classification system, it is categorized as Class II with poor aqueous solubility. However, it shows a pH-dependent solubility, with high solubility in the acidic gastric condition. Accordingly, development of oral *in situ* gel forming system with gastro retentive capability could optimize the therapy by sustaining the drug release. The benefit is maximized by improving compliance by geriatric and pediatric patients due to the ease of administration of the liquid dosage form. *In situ* gelling liquids were prepared using different concentrations of sodium alginate (1, 2 and 3%w/v). To reduce drug release in acidic conditions, pioglitazone-Eudragit L100 solid dispersion microparticles were prepared by solvent evaporation technique and were incorporated in the liquid systems. The prepared *in situ* gel forming liquids were evaluated regarding viscosity, flow property, gelling capacity and *in vitro* drug release. Solid dispersions reduced drug released in the acidic conditions relative to unprocessed drug. Increasing alginate concentration increased gelling capacity, viscosity and significantly reduced drug release from the formed gel resulting in sustained drug release pattern. The study introduced oral in situ gel forming liquids for convenient administration with improved patient compliance.

KEYWORDS: Pioglitazone, in situ gelling, sodium alginate, Eudragit L100.

INTRODUCTION

Diabetes mellitus Type II is a progressive disease characterized by hyperglycemia because insufficient control of blood glucose by insulin resistance. The initial treatment consists of dietary and exercise modifications, followed by the prescription of an oral antidiabetic medication.[1]

Insulin resistance is common in type II diabetic patients, but it is also present in more than half of patients who do not have diabetes but have had an ischemic stroke or a transient ischemic stroke.[2] Insulin resistance raises the risk of vascular diseases, owing to the associated hypertension and hyperinsulinemia. Hyperglycemia, dyslipidemia, endothelial dysfunction, and increased platelet reactivity are all symptoms of diabetes.[3] Pioglitazone decreases cardiovascular events, including strokes for patients who the drug is approved to treat diabetes mellitus type II. Also, it reduces strokes in cases of insulin resistance, prediabetes and diabetes mellitus.[4] Most strokes happen in elderly people who suffer from difficulties in swallowing solid dosage forms (i.e. tablets and capsules), so there is an urge to need provide the drug market with easily swallowed formulation of many drugs, including antidiabetic ones.

Pioglitazone is a BCS class II drug with high permeability and low solubility. It is a weak base (pKa values of 5.8 and 6.8, logP of 2.3). Its solubility is highly dependent on pH value and was calculated to be 4.4 mg/mL at pH 1.2, 0.042 mg/mL at pH 3.0, 0.005 mg/mL at pH 4.0, 0.0005 mg/mL at pH 5.0, and 0.0003 mg/mL at pH 6.8).[5] This refers to easy dissolution in gastric pH and then may lead to precipitation or supersaturation upon transfer to the duodenum due to higher pH.[6-8]

It would be beneficial to formulate gastro-retentive oral liquid dosage form of pioglitazone that is converted to gel form in the stomach. The expected advantage is that for the drug to be retained in the gastric media where it is mostly in the soluble form. Meantime, oral dosage forms are convenient for geriatric as well as pediatric patients. Additionally, a sustained pattern of the drug release from the formed gel will reduce the fluctuation in the plasma concentration.

As pioglitazone is highly soluble in acidic pH, the need for decreasing its solubility in stomach appears be necessary for successful delivery from the *in situ* gel forming system in mind. This was performed by enteric coating of the drug particles by Eudragit L100

employing solid dispersion technique. The latter is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state and prepared by fusion, solvent evaporation, or solvent-fusion method.[9,10] It has been widely and successfully used to improve the solubility, dissolution rates, and thus bioavailability of poorly soluble drugs when using hydrophilic polymer as matrix former.[11-13]

Due to fast release of pioglitazone HCl and its high solubility in acidic pH, a sustained release medication is required to achieve a longer effect with less fluctuation in drug plasma concentration levels.[14] This system's strategy has numerous advantages over existing conventional types, including improved efficiency, reduced toxic effect, and improved consumer conformity and ease of taking medicine.[15]

Oral in situ gel-forming liquids are new strategies for drug sustaining release. These are polymeric solutions which are liquid outside the body but undergo sol to gel transformation after administration. Different environmental stimuli; such as changes in temperature or pH values or increased electrolyte concentration is initiating in situ gelation process.[16] In-situ gelling technique is an important novel drug delivery system due to its advantages like sustained drug release, improve patient compliance and decrease frequent dosing.[15,17,18]

The mechanism of gel formation is electrolyte-triggered by using sodium alginate as gelling agent. The inclusion of calcium chloride and sodium citrate in the formulation is critical because it forms a calcium complex that ensures fluidity while in the bottle; when exposure to stomach acid, this complex immediately disintegrates, releasing free calcium ions that interact with alginate chains, resulting in spontaneous gelation via ionic crosslinking.[16,19,20] Alginate *in situ gel* forming liquid produces a gastro-retentive dosage form due to the reported mucoadhesive properties of alginate. For good mucodhesion properties, the polymer should be able to penetrate deep enough into the mucus gel layer close to the epithelium cell lining to form an anchor for the formed gel.[16,21]

The objective of this study is to prepare oral *in situ* gelling liquid dosage form of pioglitazone with gastro-retention or sustained release. The prepared liquid dosage form should have appropriate viscosity to be suitable for oral use. Combination between alginate-based *in situ* gelling system and solid dispersion formula prepared with pH-dependent polymer, Eudragit L100 which used with two different concentrations. Solid dispersion suspended in the alginate solution.

MATERIALS

Pioglitazone hydrochloride was obtained from Amounn Pharmaceutical Company, Al Qalyubia, Egypt. Eudragit L 100-55 was obtained from SIGMA Pharmaceutical Industries, Quesna, Egypt. Calcium chloride, sodium citrate, ethanol, hydrochloric acid were purchased from El Gomhoreia Co. (Egypt). Sodium alginate was a gift sample from Sigma Co. (Egypt).

METHODS

Construction of calibration curve

The stock solution of pioglitazone was prepared in ethanol at concentration of 1mg/ml. From this stock solution, aliquots were withdrawn and diluted using 0.1N HCl solution to prepare the standard concentrations of pioglitazone (20, 25, 30, 35 and 40 µg/ml). The absorbance of each concentration was recorded spectrophotometrically at 269 nm (Thermo, Evo300pc, USA). Calibration curve was constructed by plotting the concentrations (x-axis) against their corresponding absorbances (Y-axis). The obtained standard curve was linear (R^2=0.999) over the range of the tested concentrations.

Preparation of solid dispersion (SD) microparticles

The purpose of this procedure was to create SD with a polymeric carrier that has reduced solubility in the acidic environment because pioglitazone is easily soluble in acidic solutions. Since Eudragit L100 solubility is known to be pH-dependent, an alkaline media is best for its dissolution. By using the solvent evaporation approach, SDs were prepared according to the formulations shown in Table 1. Pioglitazone and Eudragit L100 were both dissolved in ethanol, which was then gently heated at 70°c to remove the organic solvent. The co-evaporates were left at room temperature overnight to ensure absence of any residual organic solvent. The resulting matrix was ground into fine powder, sieved and kept in a closed container till used.[16]

Determination of drug content

For all SD formulations, the drug concentration was calculated by dissolving 20 mg of the SD powder in 50 ml of ethanol. Drug concentration was assessed spectrophotometrically at the wavelength of 269 nm, following the appropriate dilution.

Table 1: Composition of tested SD formulations (SD1&SD2) with dissolution parameters; percentage amount released after 10 minutes (Q10), dissolution efficiency (D.E) and standard deviation (S.D).

Formulation	Drug	Eudragit L100	Q10 (%)	D.E. (%)
Pure drug	-	-	102.44	103.55
SD1	1	2	45.9 ±5.9	79.23
SD2	1	3	40.0±2.9	80.73

Characterization of solid dispersion formulas

Differential scanning calorimetry (DSC)

Thermal characterization of unprocessed pioglitazone, Eudragit L100 and their solid dispersion microparticles was detected using differential scanning calorimeter (Setaram, Themys one/one+, France). Samples of approximately 5-7 mg were individually loaded into the aluminum pans that were crimped using Shimadzu crimper. The pans were then heated in a temperature range from 25°C to 300°C, the rate of temperature rising was 10°C per min.

Fourier transform infrared spectrophotometry (FTIR)

FTIR spectra of unprocessed pioglitazone, Eudragit L100 and their SDs was recorded using FTIR spectrophotometer (Bruker Vertex 80 type, Germany). Samples were ground and mixed with KBr, compressed with disks then scanned from 4000 to 400 cm^{-1}.

***In vitro* release studies of solid dispersion microparticles**

To establish a baseline for comparison, the rate of pioglitazone release from the prepared SD microparticles was examined. The study used a Copley, NG 42 JY dissolution apparatus USP type II (paddle method) (Nottingham, UK). The dissolution medium consisted of 900 ml of 0.1N HCL, maintained at 37.0 ±0.5°C. Rotation at 75 rpm was set as the paddle speed. After loading 30 mg of the drug or its equivalent from various SD microparticles in each dissolution vessel, aliquots of 5 ml each were withdrawn and replaced with fresh dissolution medium. The samples were filtered via a 0.45 mm Whatman membrane filter, and the drug concentration was detected at 269 nm using spectrophotometry. To determine the dissolution profiles, the cumulative amount of drug released expressed as a proportion of the total amount of loaded drug was plotted as a function of time.[16] The similarity factor assessment was used to compare between the dissolution profiles of the two microparticle formulations employing the following equation.

$$F2=50\times\log\left\{\left[1+\frac{1}{n}\sum_{t-1}^{n}(Rt-Tt)^2\right]^{-5}\right\}\times 100$$

Where n is the data points numbers, Rt is amount of the control dissolved (%) at time t and Tt is amount (%) dissolved from the test at the same time.[22] Value of *F*2 less than 50 indicates significant difference, while *F*2 more than 50 indicates nonsignificant differences.

Preparation of *in situ* gelling systems

In situ gelling liquid systems containing sodium alginate, sodium citrate and calcium chloride were prepared according to formulations shown in Table 2. The preparation method was adopted from the previously published method[23,24], Two-third of the required volume of distilled water was used to dissolve sodium alginate while heating at 60°C with continuous stirring using magnetic stirrer. Sodium citrate (0.45% w/v) and calcium chloride (0.15% w/v) were dissolved in the remaining volume of water and added to the alginate solution with continuous stirring until homogeneity. After cooling down, accurately weighed amount of the selected SD microparticle formulation (SD2), enough to produce a concentration of 30mg/10 ml liquid, were to alginate solution while stirring till homogenous dispersion was obtained.

Evaluation of the prepared *in situ* gel liquid systems

Gel forming capacity

The goal of this study was to identify the formulations' ability to form a gel structure when placed in the suitable conditions. Three liquid formulations were prepared containing increasing concentration of sodium alginate (Table 2). Exactly measured 10 ml of each system were placed in a cellulose bag, previously hydrated overnight in distilled water, and submerged in 100 ml of 0.1 N HCl at 37°C. After 24 hours, each bag was opened. The weight of the formed gel mass was obtained after separating any liquid content in each cellulose bag. The gel was examined visually for consistency, and the relative weight of the formed gels was used to calculate the gel forming capacity.[16,25]

Viscosity of *in situ* gelling systems

The viscosity and flow properties of the prepared liquid systems were examined using HAAKE Rheometer (HAAKE Viscotester IQ Thermo Fisher, Germany).

***In vitro* drug release studies for the liquid systems**

The USP apparatus (Type II) was used to evaluate the *in vitro* release of pioglitazone from the prepared systems (Copley, UK). The dissolution medium was 500 ml simulated gastric fluid without enzymes (0.1N HCL, pH 1.2) kept at 37.0 ±0.5°C. Exactly measured 10 ml of each liquid formulation was loaded into a petri dish having internal diameter of 2.7cm^2. The loaded petri dish was carefully placed at the bottom of dissolution vessel, loaded with the release medium, without much disturbance. The paddle speed was set at 50 rpm. Drug release was monitored by withdrawing samples (5 ml each) at pre-scheduled time interval for 6 hrs. Drug concentration was determined spectrophotometrically, after filtration using 0.45-mm Millipore filter. Dissolution parameters were calculated, and the release profiles were fitted to zero order, first order as well as Higuchi system release kinetics. The similarity factor test (see above) was also used to compare between the release profiles of different liquid formulations.[16]

Statistical Analysis

All experiments were performed in triplicates and statistically analyzed by student *t*-test. Results were cited as significant where $p < 0.05$. Similarity factor test was employed to compare between the release profiles for different formulations (solid dispersions and in situ gel forming liquids).

RESULTS AND DISCUSSION

Evaluation of pioglitazone-Eudragit L100 microparticles

The preliminary studies showed a rapid release of pioglitazone from the prepared in situ gel forming system. As a weak basic compound with pK_a of 5.8 and 6.8, the solubility of pioglitazone HCL shows a strong dependency on the pH value with maximum solubility in the acidic media.[5] As the main aim of this work was to prepare a gastro-retentive oral *in situ* gel forming liquid of pioglitazone with a sustained release profile, it was necessary to reduce its solubility in the gastric conditions. Therefore, the drug was dispersed in a polymeric matrix using polymer with limited solubility in the acidic medium. Eudragit L100 was selected for this purpose. Eudragit L100 was previously used to reduce Losartan potassium release in simulated gastric condition.[23]

Eudragit L100 is anionic co-polymer based on methacrylic acid/methyl methacrylate backbone structure. It has a pH-dependent solubility, with limited solubility in the acidic condition.[26] Solid dispersion was prepared employing solvent evaporation strategy and the obtained microparticles were evaluated regarding their physical properties as well as *in vitro* dissolution.

Differential scanning calorimetry (DSC)

The thermograms of unprocessed pioglitazone HCL, Eudragit L100, and solid dispersion formulations are shown in Figure 1A.

Pioglitazone thermogram showed a melting transition (Tm) at 185.7°C with onset of 171.5°C and endset of 197.5°C. This thermogram reflects the crystalline nature of pioglitazone. Other investigators reported a similar thermal transition for the same drug.[27]

Thermogram of Eudragit L100 reflected two endothermic peaks. The first peak was a broad one started at 43.8°c with endset at 91.5°C. This transition is most probably due to the evaporation of the absorbed moisture.[23] The second peak appeared at higher temperature, the transition started at 190.4°C with endset of 217.8°C and Tm of 205.7°C. This thermogram correlates well to the reported thermogram for the same drug.[23,28]

For solid dispersion formulations SD1 and SD2, the characteristic melting transition of pioglitazone disappeared indicating reduced drug crystallinity and its presence as molecular dispersion in the polymeric matrix.

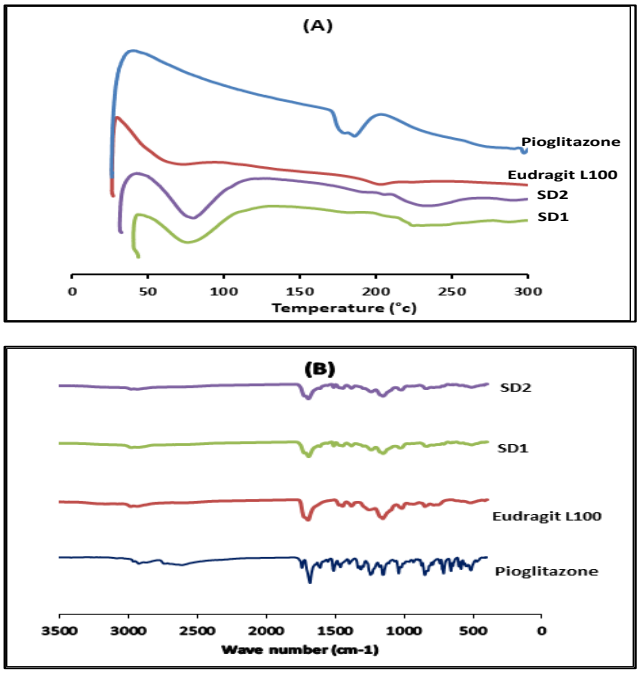

Figure 1: Differential Scanning Calorimetry (A) and Fourier Transform Infrared (B) of pioglitazone, Eudragit L100 and solid dispersion formulations. Detailed formulations are in Table 1.

Fourier transform infrared spectroscopy (FTIR)

The FTIR study was carried out to investigate any potential interactions between the pure drug and Eudragit L100. The FTIR spectra of unprocessed pioglitazone, Eudragit L100, and solid dispersion formulations are shown in Figure 1B.

FTIR spectrum of pioglitazone showed peaks at 2920.23 cm^{-1} correspond to amide group, 1683.86 cm^{-1} for C=O, 2964.38 cm^{-1} and 2737.37 cm^{-1} for aliphatic C-H group. A peak at 1510.82 cm^{-1} demonstrates C=N group and peak at 1608.89 cm^{-1} for aromatic ring. This spectrum is in agreement with the reported data.[29,30]

Spectrum of Eudragit L100 showed bands of vibrations of carboxyl group at 1697.5 cm^{-1}. Esterified carboxyl group at 1555.07 cm^{-1} and ester vibrations at 1156.03 and 1256.21 cm^{-1}. OH bands appeared between 2588.98

and 3500 cm^{-1} and CH vibrations between 2933.65 and 2981.61 cm^{-1}. This spectrum is related to monograph and supplied data.[23,28]

FTIR spectra of SD formulations shows that characteristic peaks of drug are not changed; this represents no interaction between drug and Eudragit L100.

***In vitro* release of pioglitazone from solid dispersion formulations**

The dissolution profiles of pioglitazone and solid dispersion microparticles are shown in Figure 2A. For comparative purpose, the dissolution parameters were taken as the amount of drug released after 10 min (Q10) and the dissolution efficiency (DE%). The later was computed according to Khan.[31]

Unprocessed pioglitazone showed a prompt dissolution pattern with 100% released in the first10 min. This can be accredited to salt form of drug.[5]

Preparation of solid dispersion greatly reduced pioglitazone dissolution. The amount released after 10 min (Q10) was 40% and 43% for SD1 and SD2, respectively. The dissolution efficiency was similarly reduced (Table 1). The results could be accredited to the anionic nature of Eudragit L100 that resists its solubility in the acidic environment imparting, thus, enteric effect. Eudragit L100 copolymers backbone structure based on methacrylic acid and methyl methacrylic acid. In the acidic media, the copolymer chains are coiled entrapping the drug particles and hinder, to some extent, its exposure to the release media. Interestingly, increasing Eudragit L100 concentration slightly reduced dissolution behavior of pioglitazone ($P > 0.05$). Similarity factor showed significant difference between solid dispersion microparticles and unprocessed pioglitazone ($F2<50$). This indicates that solid dispersion using Eudragit L100 successively reduced dissolution of the drug in the acidic medium. Though SD1 and SD2 showed similar dissolution behavior ($F2 >50$), SD2 was used to prepare *in situ* gel forming liquids due to the noticed trend in reducing pioglitazone release.

Characterization of the gel-forming systems

Development of liquid oral *in situ* gelling liquids necessitate good fluidity while in the package container, for ease of dose measuring and administration, with the ability of forming firm gel mass after ingestion. Accordingly, viscosity and gel-forming capacity were used to evaluate the physical properties of the *in situ* gelling systems. Data are shown in Table 2.

The viscosity of the formulation depended on the concentration of sodium alginate, where the viscosity increases with increasing concentration of alginate. This can be attributed to greater chance for chain entanglement in presence of high polymer concentration.[32] The flow behavior of the systems followed the shear thinning non-Newtonian flow characteristics. This flow type is advantageous as it indicates that the formulations will become more fluid upon shaking of the container to allow convenient withdrawal of the required volume. Similar flow patterns were reported for the similar system.[16,24,33] The gel-forming property of the formulation is another important factor that can determine the rate of drug release from the developed systems. This parameter was previously used as a prediction for the ability of the liquid system to convert to gel form when at the appropriate condition.[16,24]

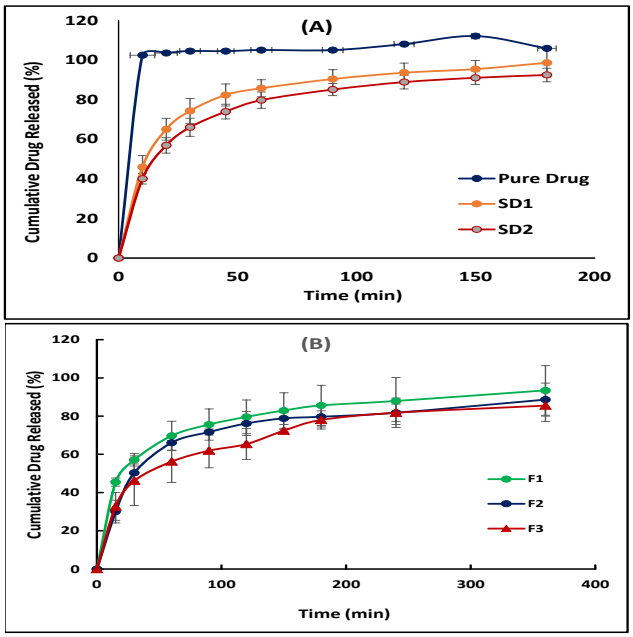

Figure 2: Dissolution profile of pioglitazone from solid dispersion formulations (A) and in situ gelling liquid systems (B). Detailed formulations are in Tables 1 for solid dispersions and Table 2 for in situ gel forming liquids.

Table 2: Composition of tested sodium alginate formulations (1%,2%,3%) with viscosity and release parameters represented as percentage amount liberated after 15 minutes (Q15) and release efficiency (RE%).

Formulations	Drug	Alginate (%w/v)	Viscosity (cP)	Gelling capacity	Q15 (%)	R.E (%)	R^2		
							Zero-order	First-order	Higuchi-order
F1	0.3	1	5.3	4.8	45.5±2.1	79.6	0.589	0.664	0.853
F2	0.3	2	15.9	5.8	30.1±5.9	73.9	0.578	0.560	0.844
F3	0.3	3	44.5	6.1	29.7±7.2	70.0	0.626	0.681	0.876

-Each formulation contains 4.5 and 1.5% (w/v) of sodium citrate and calcium chloride, respectively.

The gel-forming property was investigated by packing the liquid formulation into cellulose bag and incubation in 0.1 N HCl at 37 ºC for 24 hr, after which the bag was opened. Gel formation was visually inspected and the weight of the obtained gel phase, after separation of liquid content, was recorded and used to compare between different formulations having different alginate concentrations. Larger weight is usually taken as an indication for the strength of the gel.[24,25,33] Figure 3 shows photographs of the formed gels. The photographs demonstrate the dependence of the gel forming capacity on the composition of the system, mainly the concentration of sodium alginate. Liquid comprising 1% w/v alginate produced soft gel mass that became relatively firm on increasing alginate concentration to 2% and 3%. w/v (Table 2).

***In vitro* drug release of pioglitazone from in situ gelling systems**

The release profiles of pioglitazone from the tested in situ gel forming liquids are presented as cumulative amount drug released, expressed as percentage versus time plots in Figure 2B. The release parameters are shown in Table 2 and comprises the percentage

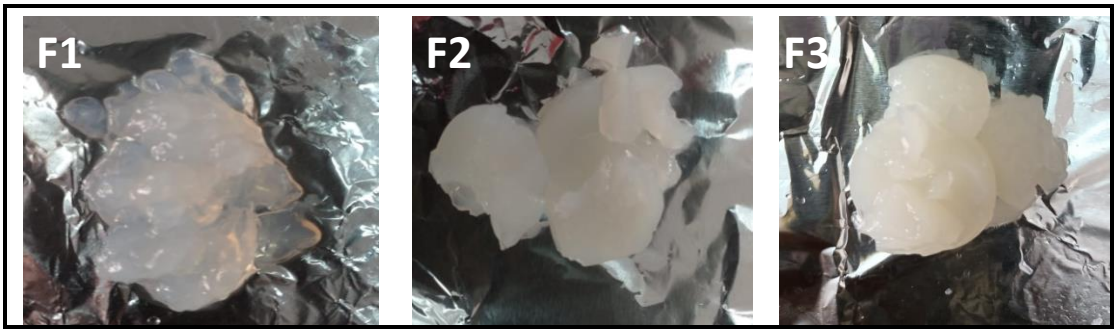

Figure 3: Photographs of gel formed after incubation in 0.1N HCL. Detailed formulations are in Table 2.

pioglitazone released after 15 minutes (Q15) as well as release efficiency (RE%). The release profiles reflected the dependence of drug release on sodium alginate concentration. Considering liquid system F1 (contains 1% w/v sodium alginate), there was a liberation of 45±2.1% of the loaded dose after 15 min, with a total release of 93.4±12.9% at the end of the experiment (i.e. 6 hr.). When compared to dissolution parameters of solid dispersion SD2 microparticles, there was insignificant difference ($P>0.05$) in the release pattern. This indicates that the consistency of the formed gel was not strong enough to slow down the drug release. This result contradicts the previously published work where *in situ* gel system containing 1% w/v alginate significantly reduced drug release.[16] Such discrepancy could be explained based on the physicochemical properties of the drug. This published work was conducted to control the release of pioglitazone; that is a poorly water-soluble drug, where pioglitazone has high solubility in the gastric acidity. Increasing alginate concentration to 2% w/v resulted in reduction in drug release with the liberation of 30.1±5.9 after 15 min, release efficiency was also reduced (Table 2). However, a similarity factor value of 57 (i.e. similarity in release is >50%) between F1 and F2 indicates comparable results. Meanwhile, increasing alginate concentration to 3%w/v further reduced percentage pioglitazone released especially at the early time of the experiment. Similarity factor value of 47 (i.e. similarity is <50%) indicates significant difference in the release pattern between F1 and F3. This could be accredited to the gel consistency as increasing alginate concentration increased the gel forming capacity producing, thus, a firm gel strong enough to reduce drug release.

Gelation of sodium alginate (a polyanionic polymer) is triggered by presence of ions (especially cations) in the media. Alginate is a family of linear and un-branched copolymers. Its backbone structure consists of Mannuronic (M) acid and Guluronic (G) acid. They are arranged as different block copolymers forms of either GG, MM, or alternating G and M residues (m/g).[34] In absence of cations, alginate chains present at its linear form. The presence of cations in the media is the trigger for gelation by crosslinking the linear chains via ionic interaction with carboxylic groups all over the chains.

Incorporation of sodium citrate and calcium chloride in each liquid system is important as it forms calcium citrate complex, thus calcium ions are in a complex form and not free to cross-link the alginate chains to form the gel network. This is advantageous as it ensures fluidity of the system while in the bottle (i.e., prior to administration). However, in the acidic condition of the stomach, calcium complex dissociates with the liberation of divalent calcium ions that is now available to interact with the polyanionic alginate chains forming a network structure with spontaneous gelation.[16,20] The similarity factor indicates similar release pattern for liquids F1 and F2 (*F*2 equals57).

The release kinetics for liquid systems were calculated by fitting the release profiles to various release kinetic models namely, zero order, first order and Higuchi diffusion. The R^2 values were used to compare between different models. According to R^2 values, drug release from the three liquid systems complied to Higuchi model (Table 2). Therefore, it can be concluded that the primary mechanism of drug release is diffusion-controlled release. The same release kinetic was reported for similar in situ gel forming systems.[15]

CONCLUSION

The study tested *in situ* gel forming system as a liquid oral dosage form for the sustained delivery of pioglitazone hydrochloride for convenient administration by geriatric patients. The pH dependent solubility of the drug, that led to high solubility in the acidic gastric media, was overcome by coating of the drug particles with Eudragit L100 polymer via solid dispersion technique. The poor solubility of Eudragit L100 in the acidic media reduced pioglitazone release, make it more suitable for incorporation in the in *situ* gelling liquids composed of sodium alginate and calcium citrate complex. The freed calcium cations in the acidic medium initiated ionic crosslinking of the polyanionic alginate chains forming, thus, a network structure. The gel firmness, and consequently its ability to reduce drug liberation was directly proportion to the percentage alginate in the liquid system. The study offers the range of formulations in which the rate of drug release can be controlled by modulating the composition of the *in situ* gelling system.

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