Sustained Release *In Situ* Gelling Systems Of Metformin: Formulation Development

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ABSTRACT

Metformin hydrochloride has relatively short plasma half-life and low absolute bioavailability. Administration of the medication several times per day in high dose is therefore necessary to compensate the decrease in drug plasma concentration resulting poor patient compliance. Development of the sustained release oral solution of metformin can be a better alternative to overcome the problems associated with the existing solid oral dosage forms of the drug. In situ gelling systems are polymeric formulations that are in solution form before entering into the body, while change to gel form under the physiological conditions. In this study an in situ *gel-forming sustained release solution of metformin hydrochloride was prepared with sodium alginate as a gelling agent, which can get converted to gel in the presence of divalent-cations inside the body. The formulation was evaluated for* in vitro *drug release profile. The formulation showed sustained release behaviour over a period of 12h dissolution experiment. The developed* in situ *gelling systems can be a better alternative to the existing conventional oral dosage form of metformin hydrochloride.*

Keywords: Metformin hydrochloride, *In situ* gel, Sustained release solution.

INTRODUCTION

Oral liquid dosage form offers unique advantages compared to conventional tablets and capsules to majority of the patients. Liquids may provide superior patient compliance for the patients with swallowing difficulties and also better dosage control when compared to a fixed dose tablet. Irrespective of the type, oral drug delivery has been known for decades as the most widely utilized route of administration of drugs because of their low cost, accurate dosing capability, ease of administration and high patient compliance (Kaur, Gill, Kumar, & Gupta, 2011; , Kai, Kok, & Yvonne, 2013; Sudhir, Vinay & Shailesh, 2010; Jaysukh, Dhaval, & Kantilal, 2009).

Metformin hydrochloride (HCl) is a well established antidiabetic drug having glucose lowering efficacy in addition to the microvascular and macrovascular benefits. It is considered as a first-line drug for the treatment and prevention of diabetes (Ali & Fonseca, 2012; Jabbour & Ziring, 2011). Though oral metformin hydrochloride tablet is widely used, a significant percentage of type-2 diabetes patients do not prefer to consume it. The major drawback of the tablet dosage form is the difficulty in swallowing for the patient having dysphagia, especially elderly people (Kaur, Gill, Kumar, & Gupta, 2011; Mohapatra, Parikh, & Gohel, 2008). The problem is worsened by the size of the metformin tablet due to its high dose (500-1000 mg) and frequent dosing requirement (Bouchoucha, Uzzan , &Cohen, 2011).

In addition, digestive disorders (diarrhoea, vomiting) represent the most common side-effects of metformin treatment in type 2 diabetes (Bouchoucha, Uzzan , &Cohen, 2011). In general, gastrointestinal problems can be reduced by administering the drug with food and a gradual increment of dosing or providing the drug in divided doses (Jabbour & Ziring, 2011). But

gastrointestinal side effects of metformin still persist even with those strategies. Again, the divided dosing may lead to poor medication adherence. To improve the gastrointestinal absorption and tolerability of metformin, sustained release formulations can be an alternative instead of the conventional tablets (Ali & Fonseca, 2012). Additionally, the slower absorption from sustained release formulations allows decrease in dosing frequency, which can improve patient compliance, particularly in patients taking multiple medications. Moreover, existing literature supports the superior clinical efficacy and tolerability with metformin sustained release formulation compared to their immediate release products (Schwartz, Fonseca, Berner, Cramer, Chiang, & Lewin, 2006; Fujioka, Pans, & Joyal, 2003; Blonde, Dailey, Jabbour, Reasner, & Mills, 2004). Sustained release formulation that would maintain plasma level for 8-12 h might be sufficient for daily dosing of metformin.

In situ gel forming polymeric formulations are drug delivery systems that are in sol form before administration in the body, but once administered, undergo gelation to form a gel (Van, Storm, & Hennink, 2008). The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. Various polymers that are used for the formulation of *in situ* gels include gellan gum and sodium alginate (Yang, Xie, & He, 2011). The choice of solvents depends on the solubility of polymer used. Since both sodium alginate and gellan gum are hydrophilic in nature, water can be used as the main solvent for these polymers (Gombotz & Wee, 2012).

Short plasma half-life and low absolute bioavailability is the major limitation for the use of metformin hydrochloride (Kamlesh, Rajendra, & Milind, 2011). The objective of this study was to prepare a sustained released solution adopting the concept of *in situ* gelling system for oral delivery of metformin HCl.

MATERIALS AND METHODS

Chemicals And Reagents

Metformin hydrochloride, gellan gum and sodium alginate were purchased from Apollo Healthcare Ltd, China. Calcium chloride, sodium citrate, hydrochloric acid and sodium hydroxide were purchased from Fisher Scientific (M) Sdn. Bhd. Malaysia.

Calibration Curve

The concentration of metformin in the drug solution was measured by UV-visible spectrophotometer. A standard stock solution of metformin was prepared by dissolving 200 mg metformin in 100 mL of water. The solution (2000 µg/mL) was then diluted successively with water to get the different standard working concentrations ranging from 0.5 to 20 µg/mL of metformin. The absorbance of each working concentration was recorded. A six point calibration curve was prepared by taking the absorbance in Y-axis and concentration of the analyte (0.5, 1, 2, 5, 10 and 20 µg/mL) in X-axis.

Preparation of Sustained Released Solution Using Gellan Gum

Optimization Of Gelling Point And Salt Content

Different concentration of gellan gum solutions (0.3-6.0%, w/v) were prepared by adding the gum in water with continuous stirring and heating up to 90^0C. Different amounts of sodium citrate and calcium chloride was dissolved separately in water and added to the gellan gum solution after cooling below 40^oC.

The appropriate amount of sodium citrate needed was calculated according to the calcium chloride used based on the molar concentration required to complete their chemical reaction.

$2Na_3C_6H_5O_7 + 3CaCl_2 \rightarrow 6NaCl + Ca_3(C_6H_5O_7)_2$

A fixed concentration of sodium citrate was added into distilled water together with variable amount of calcium chloride. The resulting solution was mixed with the gellan gum solution with continuous stirring until homogenous solution was achieved. The final volume was then made up to 100mL with water. Procedure was repeated with different amount of the gum and calcium chloride to optimize the gelling point of the formulation.

Formulation of Sustained Released Solution

Gellan gum was dissolved in water with stirring on a hot plate stirrer below 90^{O}C. Separately, calcium chloride was dissolved in water together with sodium citrate. After the temperature drop below 40^{o}C, two solutions were mixed together with continuous stirring. The metformin HCl solution was prepared by dissolving the drug in water. The metformin HCl solution was then added into the gum solution and the volume was made up to 100mL by using distilled water.

Preparation of Sustained Released Solution Using Sodium Alginate

The sustained release solution using sodium alginate as gelling agent was optimized for the amount of sodium alginate, calcium chloride and sodium citrate in similar way as discussed for gellan gum. The optimized amount of sodium alginate was added in water while stirring on the hot plate below 90^{o}C. When the temperature became below 40^{o}C, the solution containing sodium citrate and calcium chloride was added into it. Metformin HCl solution was prepared and added into the former solution. The final volume was made up to 100 mL with water.

In-Vitro Drug Release Study Using UV Spectroscopy

A solution of 250mL acidic buffer (0.1M HCl) was poured into the dissolution apparatus (USP type II) and the temperature was set to 37° C. The rotation of the paddle was set to 50rpm. At a predetermined time interval of 0.5 to 12 h, 0.5mL solution was withdrawn each time from the acidic sink, diluted up to 10mL and subjected to UV spectroscopy for determining the absorbance of metformin at 232nm wavelength.

RESULTS AND DISCUSSION

Calibration Curve

The calibration curve was constructed using calibration standards of 0.5 - 20.0 µg/mL. The response observed for metformin absorbance over the calibration range (Table-1) was linear and the correlation coefficient of the calibration curve was 0.9999 (Figure 1).

Table 1: Absorbance of metformin HCl

Concentration (µg/mL)	Absorbance
0.5	0.043
1.0	0.086
2.0	0.162
5.0	0.413
10.0	0.807
20.0	1.604

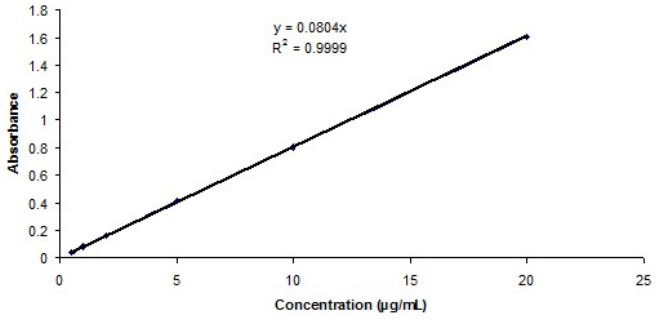

Figure 1: Calibration Curve For Metformin

Preparation Of Sustained Released Solution Using Gellan Gum

Different concentrations of gellan gum solution (0.3- 6% w/v) and calcium chloride solution were used to optimize their concentration in formulating the sustained release solution of metformin. In case of high concentration of gellan gum (more than 4% w/v), gel was formed instantaneously even before adding calcium chloride. Again, when the gellan gum concentration used between 1 to 2% w/v, the solution was too thick even though the gel was formed after addition of calcium chloride. However the solution was thin and suitable for oral intake when it was formulated with 0.5% gellan gum. But upon aaddition of metformin solution, the content turned to gel instantaneously. Initially, it was suspected that the water used was not pure and may contain cation. However, after addition of the water only with gellan gum solution, it did not transform into gel. Thereafter, pH adjustment of the metformin hydrochloride solution was made in order to determine the pH effect of the solution. But, after the pH adjustment ranging from acidic, neutral and alkaline (pH 3.00, pH 7.06, pH 9.52, pH 13.0) the solution still transformed into gel form instead of remaining as a solution. Thus, it was assumed that, the metformin itself may not be compatible to be formulated with gellan gum for this particular type of formulation, and changing of the polymer to other suitable compatible one was triggered.

Preparation Of Sustained Released Solution Using Sodium Alginate

A similar approach was adopted to optimize the sodium alginate and salt concentration required to formulate the oral solution of metformin hydrochloride as discussed for gellan gum. The mechanism of *in situ* gelation for both gellan gum and sodium alginate is mainly contributed by the existence of divalent or trivalent cations (Lee & Mooney, 2012; Dhanaraju, Sundar, NandhaKumar, & Bhaskar, 2009). The calcium ions were included in the formulation in the form of calcium chloride for induction of gelation. But the calcium ion kept inactivated by complex formation with required quantity of sodium citrate, to maintain the fluidity. Theoretically, the complex should be broken down in the acidic environment of stomach to convert into a sustained release gel form. The sustained released solutions containing different quantity of sodium alginate, calcium chloride and sodium citrate prepared for final optimization of the gelling agent are tabulated in Table 2.

Table 2: Composition of sodium alginate formulations

Formulation code	Sodium Alginate (mg)	Sodium Citrate (mg)	Calcium Chloride (mg)	Metformin HCl (mg)	Water (mL)
S1	500	300	150	500	100
S2	1	300	150	500	100
S3	3	300	150	500	100
S4	5.0	300	150	500	100
S5	7.5	300	150	500	100

Amongst the above formulations, S3 was found optimum in terms of consistency and gelling capacity. Other formulations were either thick gel or not having required gelling capability.

In-Vitro Drug Release Study Using UV Spectroscopy

The *in vitro* release of metformin from formulation S3 was studied by carrying out their dissolution in USP type II dissolution apparatus. The total in vitro drug release was calculated using the equation of standard calibration curve of metformin HCl. It was observed that the release of drug from the formulation after 8h was just above 82%. About 95% of the drug released after 12h during the dissolution test (Table 3). Figure 2 illustrated the

release profile of metformin from the sustained release metformin HCl solution.

Table 3: *In-vitro* drug release

Time (minutes)	Metformin release (%)
15	9.56
30	11.22
60	15.57
90	19.88
120	24.4
180	35.73
240	48.22
300	62.54
360	73.59
480	82.36
720	94.48

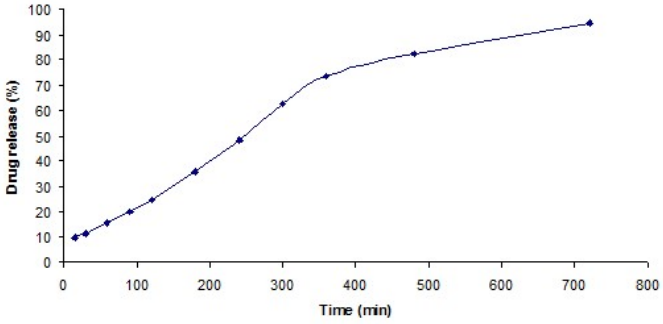

Figure 2: Release profile of metformin

CONCLUSION

An *in situ* gel-forming sustain released metformin hydrochloride solution was prepared as an alternative dosage form to the existing oral drug delivery options of metformin. The developed formulation is a solution which can get converted into gel form when in the physiological system. Initially, the formulation was tried to develop with gellan gum as a gelling agent. But it was not found suitable for this formulation, particularly to be used with metformin hydrochloride. Finally, the formulation has been developed using sodium alginate which showed to have desired gel forming and sustained release capability for metformin. Due to the sustained release capacity, the developed formulation will help in reducing the frequency of administration of the drug leading to improved patient compliance and subsequently improved efficacy of the therapy in a cost effective manner.

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