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Formulation and Optimization of Gliclazide Alginate Microspheres by Plackett Burman's Factorial Design

Samir Chaudhary[1]*, Pankaj Gangurde[1]

1.Bhupal Nobels' College of Pharmacy, Udaipur, Rajasthan, India

ABSTRACT

The main aim of present study is to formulation & optimize Gliclazide alginate microspheres by plackett burman's factorial design. Which offers a flexible and easily controllable process for the manipulating the characteristics of the beads which is important in controlling the release rate and consequently the absorption of Gliclazide from the GIT, variation in polymer, concentration, time of gelation in the external phase were examined systemically for their effects on rate release and entrapment efficiency by Plackett Burman's factorial design. The swelling behavior strongly depends on the polymer concentration. The result of the study will depends on the release profile of the drug from the formulation. The formulations follows zero order kinetics for the drug release. The *in vitro* release study indicates that the swelling is the main parameter in controlling the release rate from microcapsules.

Keywords: Ionic gelation, Gliclazide, Plackett Burman's.

*Corresponding Author Email: samirchaudhary06@yahoo.com

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INTRODUCTION

Microsphere:

Microspheres are the polymer particle produced on micron scale capable of releasing a preloaded drug that has been incorporated into a central reservoir. These spheres can release a drug via the surface on bulk degradation of the polymer used and its properties.

In polymerization bridging formed between linear polymer chains, leading to 3-dimensional network structure known as cross linking.

Alginates are naturally occurring polysaccharides obtained from marine brown algae, consisting of two monomeric unit, B-D mannurinic unit, B-D Mannuronic acid (M) and a-L-glucoronic acid (G). The residue are arranged in homopolymeric alginate shows gelling properties in the presence of the divalent cations such as Ca^{2+}, Sr^{2+} or Br^{2+}. The gelation phenomenon can be explained by the egg-box model in which divalent cations binds to two carboxyl groups on adjacent alginate molecules. Gel beads of calcium alginate can be produced by extruding sodium alginate solution as droplets into calcium chloride solution.[1,2]

Plackett Burman Design:

The design is very useful for the economically detecting large main effects assuming all interaction are negligible when compared with the few interaction are negligible when compared with the few important main effects. The main effect may be aliased by two way interaction. It consist two level fractional designs.[3]

Main effect:

$$\text{Effect A} = \frac{(y_2+y_4+y_6+y_8)}{4} - \frac{(y_1+y_3+y_5+y_7)}{4}$$

$$\text{Effect B} = \frac{(y_3+y_4+y_7+y_8)}{4} - \frac{(y_1+y_2+y_5+y_6)}{4}$$

$$\text{Effect C} = \frac{(y_5+y_6+y_7+y_8)}{4} - \frac{(y_1+y_2+y_3+y_4)}{4}$$

Table 1: Plackett Burman (2^3) Factorial Model

Sr. No.	A	B	C	
1.	-	-	-	Y_1
2.	+	-	-	Y_2
3.	-	+	-	Y_3
4.	+	+	-	Y_4
5.	-	-	+	Y_5
6.	+	-	+	Y_6
7.	-	+	+	Y_7
8.	+	+	+	Y_8

The present study involves the ionic gelation of alginate molecules which offers a flexible and easily controllable process for the manipulating the characteristics of the beads which is important in controlling the release rate and consequently the absorption of Gliclazide from the GIT, variation in polymer, concentration, time of gelation in the external phase were examined systemically for their effects on rate release and entrapment efficiency by Plackett Burman's factorial design. The swelling behavior strongly depends on the polymer concentration.[4,5]

Gliclazide is one of the sulfonylurease in the treatment of type II diabetes. The conventional formulation required twice daily administration. A new once daily Gliclazide modified release formulation has been recently introduced. In a large randomized study on type II diabetic patients, once daily Gliclazide modified release 30- 120 mg was found as effective as twice daily Gliclazide 80-320 mg in reducing glycosylated hemoglobin (HbA1C), with fewer side effects and less risk of hypoglycemia. Thus in this study an attempt was made to prepare oral controlled release coated chitosan microcapsules of gliclazide. The microcapsules were characterized by *in vitro* tests to optimize the variables.[6,7,8]

MATERIALS AND METHODS

Materials Used:

Gliclazide was Gift sample from Aurochem Pvt Ltd

Software Used:

- QI Macros for all versions of excel 2000-2010.

Formulation of Gliclazide loaded Calcium alginate beads

Formulation of Gliclazide loaded calcium alginate beads prepared by Plackett Burman's fractional design (2^3 factorial design) are shown in Table 2.

Alginate is used in the controlled release of medicinal drugs and other chemicals. In this study the active ingredient is placed in a calcium alginate bead and slowly released as the bead is exposed in the appropriate environment. More recently, oral controlled-release systems involving alginate microspheres, sometimes coated with chitosan to improve the mechanical strength, have been tested as a way of delivering various drugs. Gliclazide loaded alginate beads were prepared using ionotropic gelation method. Gliclazide API was added to solution of Sodium Alginate and dispersed homogeneously. The bubble free suspension was forced through needles into 150ml of a stirred (0.1 M) $CaCl_2$ solution at flow rate 10-12 drops/min.

Stirring of mixture was continued using mechanical stirrer at 400 RPM for 30 mins. The beads were separated by filtration on filter paper.

X_1= Concentration of Sodium Alginate

X_2= Concentration of Calcium Chloride

X_3= Time of Gelation

Table 2: Gliclazide formulation table according to placket burman's model.

Sr. No.	X_1	X_2	X_3
1.	-1	-1	-1
2.	+1	-1	-1
3.	-1	+1	-1
4.	+1	+1	-1
5.	-1	-1	+1
6.	+1	-1	+1
7.	-1	+1	+1
8.	+1	+1	+1

Note: In the table +1= 5% and -1= 3%.

Procedure:

Weigh equal quantity of sodium alginate and calcium chloride as given Plackett Burman's factorial design (2^3 factorial design). 80 mg constant Gliclazide API is weighed and solution of sodium alginate and calcium chloride is made separately. Drug is added to solution of calcium chloride with 21G syringe drop by drop with specified time of gelation. The microspheres were filtered and dried in hot-air oven. The dried beads were washed with ether and dried. Then the microspheres were evaluated to measure.[9,10]

- Drug content
- Swelling Measurement
- *In*-vitro Dissolution Studies

X_1= Sodium Alginate -1= 3gm, 10mins

X_2= Calcium Chloride +1= 5gm, 30mins

X_3= time of Gelation

Table 3: Table showing the Quantity of excipients.

Formulation	X_1	X_2	X_3	X_1 (gm)	X_2(gm)	X_3(gm)
F_1	-1	-1	-1	3	3	3
F_2	+1	-1	-1	5	3	3
F_3	-1	+1	-1	3	5	3
F_4	+1	+1	-1	5	5	3
F_5	-1	-1	+1	3	3	5
F_6	+1	-1	+1	5	3	5
F_7	-1	+1	+1	3	5	5
F_8	+1	+1	+1	5	5	5

Test for Drug Content:

Amount of beads containing theoretical wt of 8 mg Gliclazide was accurately weighed and broken down in mortar and pestle. The grounded beads were placed in 100 ml phosphate buffer pH 7.4 and shaken at $37^0C \pm 0.5^0C$ then the sample was filtered and analyzed for drug content Spectrophotometrically at 228nm and entrapment efficiency was calculated[10]

$$\text{Drug Entrapment Efficiency} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Swelling Measurement:

The extent of swelling was determined by suspending the beads in 0.1 N Hcl at 37^0C. The beads were then removed and weighed after drying the excess water. The extent of swelling was calculated by:

$$\% \text{ Water Uptake} = 100 \times \left(\frac{\text{Wt of Wet microsphere}}{\text{Wt of Dry microsphere}} \right)$$

***In*-vitro Dissolution Studies:**

Weighed quantity of bead equivalent to 80mg of Gliclazide were placed in basket which were lowered into 900ml of test solution (Phosphate Buffer pH 7.4) and (0.1N Hcl pH 1.2). The solution was previously warmed and maintained at $37^0C \pm 0.5^0C$ and the baskets were rotated at 100 RPM. Samples were collected at specific interval of time. 5ml of sample was collected then filtered and these samples were analyzed for drug content at 228 nm.[11]

Drug Release Kinetics:

Data from *In*-vitro Drug Dissolution studies can be used to determine the Kinetic release model of the drug. In this study the drug release from the dosage form were examined under 3 kinetic models Zero order kinetics, First order kinetics and Higuchi Model.[12]

RESULT AND DISCUSSION

Entrapment Efficiency of Gliclazide

Figure 1 demonstrates the effect of processing conditions on the entrapment efficiency of gliclazide loaded calcium alginate beads. The loading capacity of majority of system investigated was between 30-70% owing to low solubility of Gliclazide in water and minimum loss of drug during preparation of beads. However slight reduction in the entrapment efficiency was observed by increasing in internal phase volume due to reduction in viscosity which resulted increase in partitioning of drug into external in the drug content.

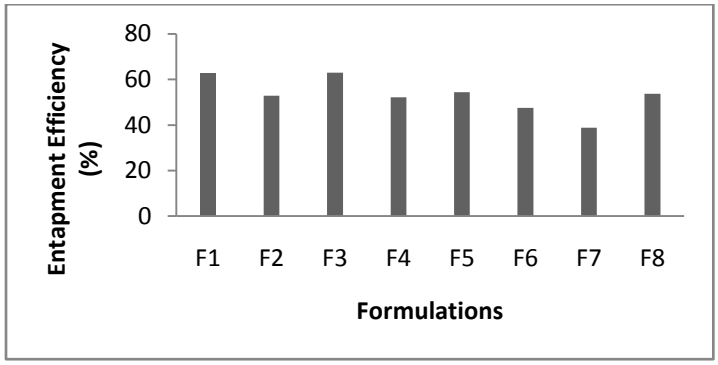

Figure 1: Graph representing entrapment efficiency of formulations.

When concentration of sodium alginate, calcium chloride and time of gelation is high there is significant decrease in entrapment efficiency but when concentration of both sodium choride and calcium chloride is low there is significant increse in entarpment efficiency but is less than when all the three factors were in combination.

Swelling Measurment

The swelling behaviour of Gliclazide loaded calcium alginate beads were determined in 0.1N Hcl pH 1.2 as shown in figure the lowest swelling rate was noticed at pH 1.2.

The extent of swelling of beads prepared using different concentration of alginate polymers was followed in 0.1N Hcl pH 1.2 and the result showedthat swelling was related to polymer concentration with swellingbeing more significant for beads containing high polymer content.

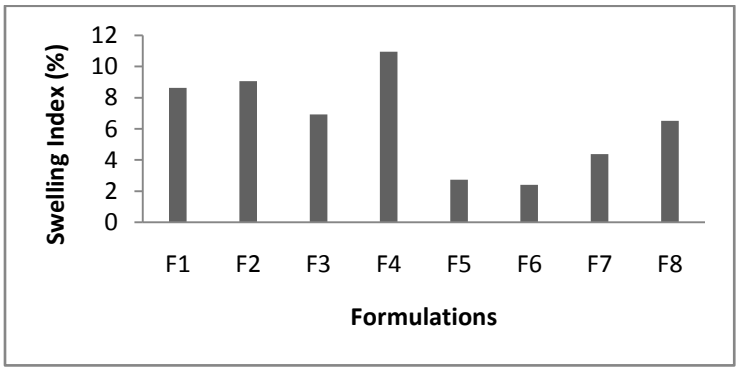

Figure 2: Graph representing Swelling index of formulations.

***In*-vitro Dissolution studies**

When concentration of sodium alginate, calcium chloride and time of gelation is high there is significant decrease in release rate but when sodium alginate, calcium chloride and time of gelation is low there is significant increase in release rate of drug.

Drug Release Kinetics

Zero order Kinetics:

The dosage form follows zero order kinetics the release pattern is shown in the figure below.

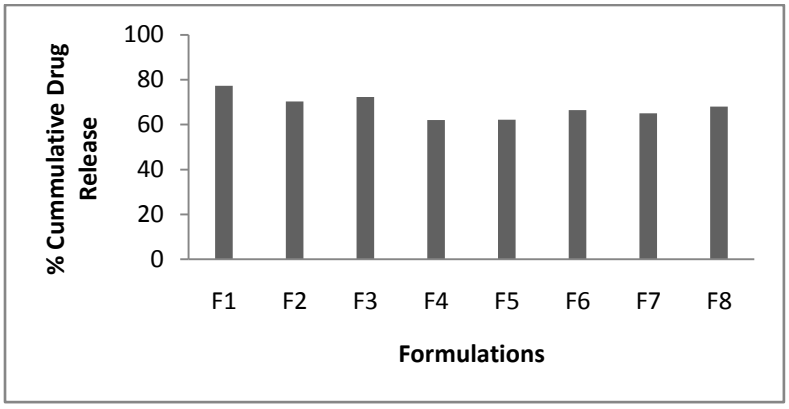

Figure 3: Graph representing Drug release from formulations.

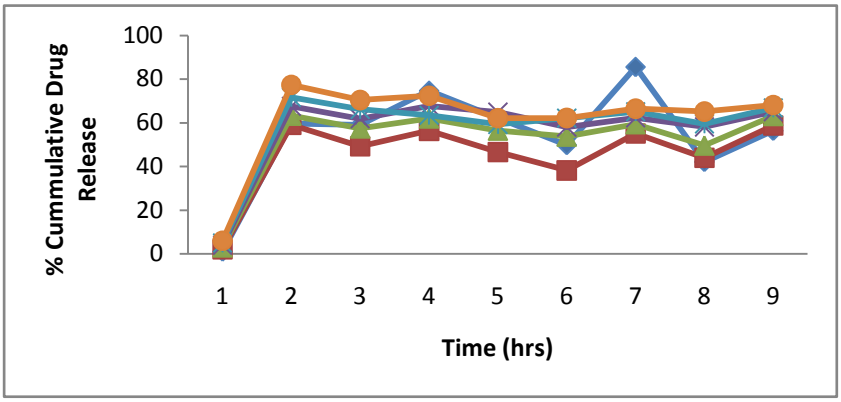

Figure 4: Graph representing zero order drug release from formulations.

Figure 4 shows zero release kinetics of F_1 to F_8. The graph is plotted for % cummulative drug release versus time. The % cummulative drug release is derived from the *in vitro* drug release profile of the drug. The graph shows that Formulations F_1 & F_3 shows proper zero order release.

CONCLUSION

Entrapment and controlling the release of an antidiabetic agent gliclazide has been studied. The gel matrix consists of calcium alginate beads obtained by ionotropic gelation method. The ability of system to incorporate and control the release of gliclazide has been investigated through variation in process condition such as polymer concentration and time of gelation. Alginate beads can control, improve and prolong the systemic absorption of the gliclazide through their mucoadhesive properties. The % cummulative drug release derived from the *in vitro* drug release profile of the drug showed that Formulations F_1 & F_3 shows proper zero order drug release.

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