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Formulation development and evaluation of glyburide beads for controlled release

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ABSTRACT

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the advantages of oral route of drug administration. In certain conditions conventional drug release pattern is not suitable like Diabetes mellitus, Asthma, cardiovascular diseases Arthritis, Peptic ulcer etc. this present study an attempt was made to formulate controlled release beads of Glyburide by using Sodium alginate, HPMC K100M, Carbopol 940 and Calcium Chloride(fused).Beads were successfully prepared by Ionotropic Gelation Method .The prepared beads evaluated for various parameters lke encapsulation efficacy, swelling index, Mean particle size, flow properties and in vitro release. The yields were varies from 88-93.8% and encapsulation efficacy is up to 91.2% which encourage the investigation. The in-vitro dissolution profile of optimized formulation batch i.e., F4 is resulted up 12 hours. The various parameters of model equation of beads containing Glyburide in vitro kinetic release were thoroughly investigated and it was seen that the statistically significant confined to Zero- order, Higuchi and Korsmeyer- Peppas model. To establish the release kinetic, Korsmeyer- Peppas model shows the prominent release characteristics.

Keywords: Glyburide, Microspheres, Sodium alginate, HPMC K 100 M and Carbopol 940.

INTRODUCTON

Oral drug delivery is the most used and preferred route of administration with the obvious advantage of ease of administration and patient acceptance. To develop a drug delivery system for oral administration, it is necessary to optimize not only the release rate of an active ingredient from the system but also the residence time of the system in the gastrointestinal tract[1]. our population afflicted with diabetes specially the Type-2, which are not dependent on insulin production.The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. This goal can be achieved on the basis of proper design of the dosage regimen**.** Microspheres have potential to deliver drug in a controlled fashion. [2] Glyburide is a second-generation sulfonyl urea that is an orally bioavailable hypoglycemic agent used in the management of type 2 diabetes. Different research has reported that glyburide has a low bioavailability, which is attributed to its poor dissolution properties. It has short half life of 4-6 hours. Glyburide in oral conventional dosage form has the dosage regime of three times a day due to having short elimination half life of 5 hour. Controlled release concept and technology has received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs. When drugs are administered as conventional dosage forms such as tablets, capsules etc. usually produce wide ranging fluctuations in drug concentration in the blood stream and tissues and consequently undesirable toxicity and efficiency[3].

MATERIALS AND METHODS

Materials

S.NO	CHEMICAL NAME	SUPPLIER
1	Glyburide	Yarrow Chemicals
2	Sodium alginate	Loba Chemie
3	HPMC K100M	Central drug house
4	Carbopol 940	Qualigens
5	Calcium Chloride(fused)	Merck

Methodology

Preperation Of Standard Graph

Pure drug sample of Glyburide was taken in volumetric flask of 10ml capacity and the volume was made up with Phosphate buffer at p^H 7.4. **Stock solution** prepared by using 10 mg/10ml equivalent to 1000 µg/ml. From1000 µg/ml take 1 ml made up to 10 ml i.e., equivalent to 100 µg/ml. From 100 µg/ml take 1ml made upto 10 ml i.e., equivalent to 10 µg/ml. From 10 µg/ml take 1ml made upto 5 ml i.e., equivalent to 1µg/ml. Thus, different Concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml and 12 µg/ml were prepared and absorbance was taken at 230 nm.

Preperation

Glyburide microspheres were prepared by Ionotropic gelation method.

Preparation of polymer drug solution

Accurately weighed quantity of Sodium alginate was taken in a mortar and pestle and made into a homogenous dispersion by addition of required quantity of water. The required quantity of drug was added to form a polymer drug solution. Different combinations of polymers were used to get various proportions of beads.

Preparation of calcium chloride solution

10% Calcium chloride solution was prepared by mixing 10 g of calcium chloride (fused) in 100 ml of water.

Preparation of Beads

Polymer solutions were taken in a syringe with a 24 gauge needle and they are extruded into calcium chloride solution. Beads formed were allowed to stand for 30 min for the curling reaction. Then the beads were filtered. Washings are done with water and they are dried in the oven. Beads were dried at room temperature for 24 hrs. Repeated batches were primed to get reproducible results and all the experiments were conducted in duplicate.

Evaluation

The primed glyburide- loaded beads was evaluated by studying the following parameters[6-12].

Percentage yield

Beads dried at room temperature were then weighed and individual weights of all the prepared beads were measured and the percentage yield was calculated using the formula

$$\% \, yield = \frac{weight \; of \; \text{the} \; beads}{\text{weight of the total raw materials taken}} * 100$$

From the calculations it was found that Formulation 4 i.e., sodium alginate in combinaticon with carbapol and HPMC K 100 M highest %yield .The results shown in Table.3.

Size Distribution of Beads

Beads were separated into different size fractions by sieving for 10 minutes using mechanical sieve shaker containing standard sieves having apertures of 1000, 710, 500, 355, 250 & 180 µm. The particle size distribution of the microspheres for all the formulations was determined and mean particle size of beads was calculated by using the following formula[4-5].

$$\text{Mean Particle size} = \frac{\text{(Mean particle size of the fraction X weight fraction)}}{\square\square\square\square\square\square\square\square\text{Weight fraction}}$$

Determination of flow properties
Flow properties were determined by determining by bulk density, tapped density, Compressibility index and Packing Factor .

The Bulk denisity was determind as the ratio of mass of the beads to the bulk volume
.
Bulk Density = W/VB;

where W= Mass of the beads ; V_f = Bulk volume

The tapped density was determind as the ratio of mass of the beads to the tapped volume.

Tapped density=W/V_f ;

where W= Mass of the blend; V_f = Tapped volume

The compressibility index was determind as

% Compressibility = [(Tapped density – Bulk density) / Tapped density] X 100

Packing factor was determind as the ratio of tapped density to the bulk density .

Packing factor = Tapped density / Bulk density

Swelling index
Beads were soaked in 0.1N Hcl , 7.4 Phosphate buffer and water. After 24 hrs, the beads were removed from their media's, excess water is removed and their weights are measured again. Swelling index was calculated using the formula:

$$swelling\ index = \frac{\text{weight of wet beads} - \text{weight of dry beads}}{\text{weight of dry beads}} * 100$$

Swelling index studies were performed for all the formulations in different medias i.e., 0.1N Hcl, pH 7.4 phosphate buffer and water.It was found the all the formulations have shown increase in swelling capacity by observing for 24 hrs.The results shown in Table.6.

Drug entrapment efficiency
Microspheres equivalent to 10 mg of Glyburide were crushed in a glass mortar and pestle and the powdered beads were suspended in 100 ml of phosphate buffer pH 7.4. The resulting mixture was kept shaking on mechanical shaker for 24 h. After 24 hours, the solution was filtered, 1ml of the filtrate was pipette out and diluted to 10 ml using of phosphate buffer pH 7.4 and analyzed for the drug content using UV Visible spectrophotometer at 230 nm.

$$Drug\ entrapment\ efficiency = \frac{drug\ recovered\ in\ beads}{\text{drug taken}} * 100$$

From the experiment it was found that Formulation 4 i.e, sodium alginate with combination of polymers has highest drug encapsulation efficiency when compared to the other formulations. It has the encapsulation efficiency of 91.2% i.e, of maximum efficiency to entrap drug molecule in it. The results shown in Table.7

In vitro release studies
In vitro dissolution studies for all the prepared dried beads after weighing were carried out in 900 ml of alkaline phosphate buffer of pH 7.4 using USP XXIV type-I (Basket) dissolution rate test apparatus (Model L6, M/S Electrolab). A speed of 50 rpm and a temperature of 37±1°C were used in each test. A 5 ml aliquot was withdrawn at different time intervals , filtered and replaced with 5 ml of fresh dissolution medium. The volume of each sample was replaced with the same volume of phosphate buffer (pH 7.4) to maintain the sink conditions. The amount of glyburide released from the beads was analyzed using a UV spectrophotometer at 230 nm. All the dissolution experiments were conducted in triplicate and the mean values are reported. The results are given in Table 8 .

Preparation of pH 7.4 phosphate buffer
6.804 gm of KH_2PO_4 and 1.288 gm NaOH ,volume made up to 1000 ml with water.

Analysis of dissolution data

The analysis of the mechanism of drug release from pharmaceutical dosage form is an important but complicated problem .The dissolution data obtained was fitted to zero order, first order, Higuchi, erosion and exponential equation to understand the order and mechanism of drug release from the beads.

Zero order release kinetics

It defines a linear relationship between the fraction of drug released versus time.

$Q = k_o t$

where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process, suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics. The equation used to describe first order kinetics is

$\ln (1-Q) = -k_1 t$

where, Q is the fraction of drug released at time, (t) and k_1 is the first order release rate constant.Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equaiton

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$Q = k_2 t^{½}$

where, k_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation[11].

Erosion equation

This equation defines the drug release based on erosion alone.

$Q = 1-(1-k_3 t)^3$

where, Q is the fraction of drug released at time t, k_3 is the release rate constant. Thus, a plot between $[1-(1-Q)^{1/3}]$ against time will be linear if the release obeys erosion equation.

Dissolution studies were performed in pH 7.4 phosphate buffer, 900 mL for 12 hrs and at regular intervals of time samples were collected and absorbance were measured and % drug release were calculated. From the studies, it was found that the drug release was high till 2 hrs and from then, the release is slow and sustained till the 12th hour. Formulation 4 has attained 99.42% of drug release.

RESULTS

TABLE 1: Formulations of Glyburide beads

Composition of various formulations of glyburide beads			
	Drug: Polymer ratio	calcium chloride	Purified water
F1	1:0.5	10%w/v	q.s
F2	1:1	10%w/v	q.s
F3	1:2	10%w/v	q.s
F4	1:3	10%w/v	q.s

TABLE 2: Standard Graph of Glyburide

Sl. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.101
3	4	0.184
4	6	0.277
5	8	0.37
6	10	0.46
7	12	0.567

TABLE 3 Percentage Yield of the different formulations

Beads Formulations	% Yield
F1	88
F2	90.4
F3	91.4
F4	93.8

TABLE 4 Mean Particle Size and Particle Size Distributions Of Various Formulations

Formulation	% Weight retained on each sieve				Mean Particle Size (µm)
	710 µm	500µm	355 µm	250 µm	
F1	31.51	45.20	22.35	0	502.63
F2	16.24	55.00	26.32	0	526.65
F3	18.32	40.11	31.22	10.11	492.23
F4	57.32	29.89	12.12	0	629.23

TABLE 5: Flow Properties Of Glyburide Beads

Formulation	Bulk Density	Tapped Density	Compressibility Index	Packing factor
F1	0.572	0.623	8.1	1.089160839
F2	0.612	0.634	3.4	1.035947712
F3	0.518	0.627	1.7	1.21042471
F4	0.565	0.612	7.6	1.083185841

TABLE 6 : Swelling index of the formulation

Formulation	0.1NHCl			Phosphate Buffer			Water		
	W_O gm	W_S gm	α	W_O gm	W_S gm	α	W_O gm	W_S gm	α
F1	0.10	0.20	100	0.10	0.49	390	0.10	0.14	40
F2	0.10	0.26	160	0.10	0.59	490	0.10	0.18	80
F3	0.10	0.34	240	0.10	1.24	1140	0.10	0.32	220
F4	0.10	0.31	210	0.10	1.21	1110	0.10	0.25	150

TABLE 7 : Drug Encapsulation Efficiency

S. NO	Formulations	Drug Recovered In Beads(mg)	Total Drug Taken(mg)	Encapsulation Efficiency(%)
1	F1	8.27	10	82.7
2	F2	8.01	10	80.1
3	F3	9.06	10	90.6
4	F4	9.12	10	91.2

TABLE 8 : In vitro release studies

TIME (h)	cummulative%Drug release			
	F_1	F_2	F_3	F_4
0	0	0	0	0
0.5	8.53	10.21	12.78	14.35
1	20.36	22.35	24.56	26.13
2	40.23	42.39	44.36	48.49
3	53.24	58.34	60.19	62.28
4	69.32	71.56	73.12	75.91
6	79.32	81.93	85.14	87.34
8	88.67	90.49	92.56	94.29
12	93.84	95.54	97.13	99.42

TABLE 9 :In vitro release studies-r^2 values

Formulation	Zero order	First order	Higuchi	Korsemeyer-Peppas
F1	0.971	0.9691	0.9891	0.9834
F2	0.9719	0.9687	0.9907	0.9822
F3	0.9712	0.9689	0.9893	0.9831
F4	0.9772	0.9676	0.9809	0.9835

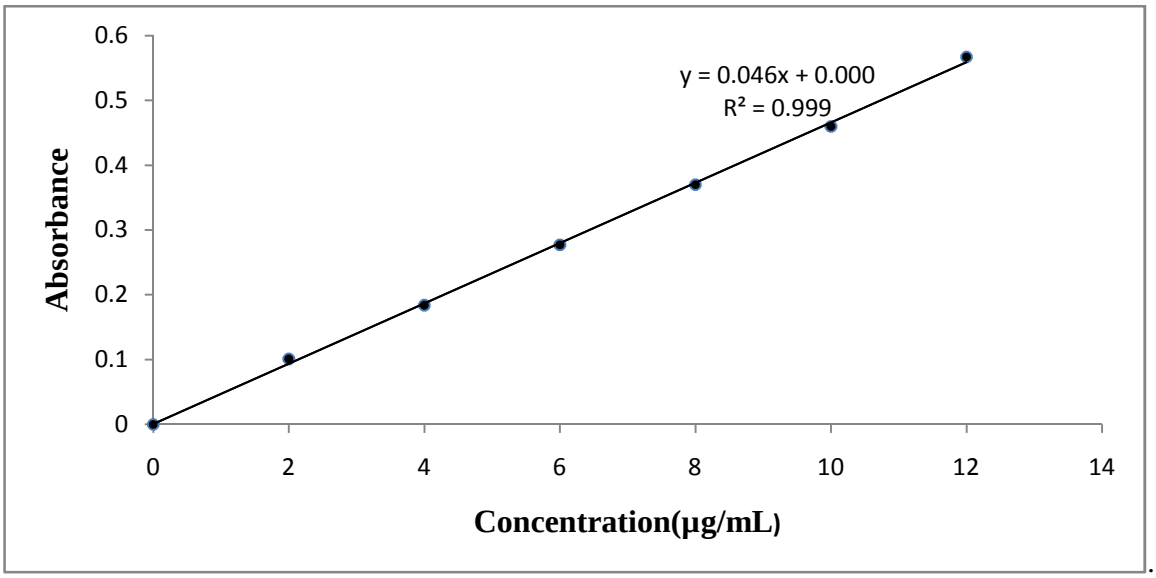

Figure 1 :Standard Graph of Glyburide Percentage yield

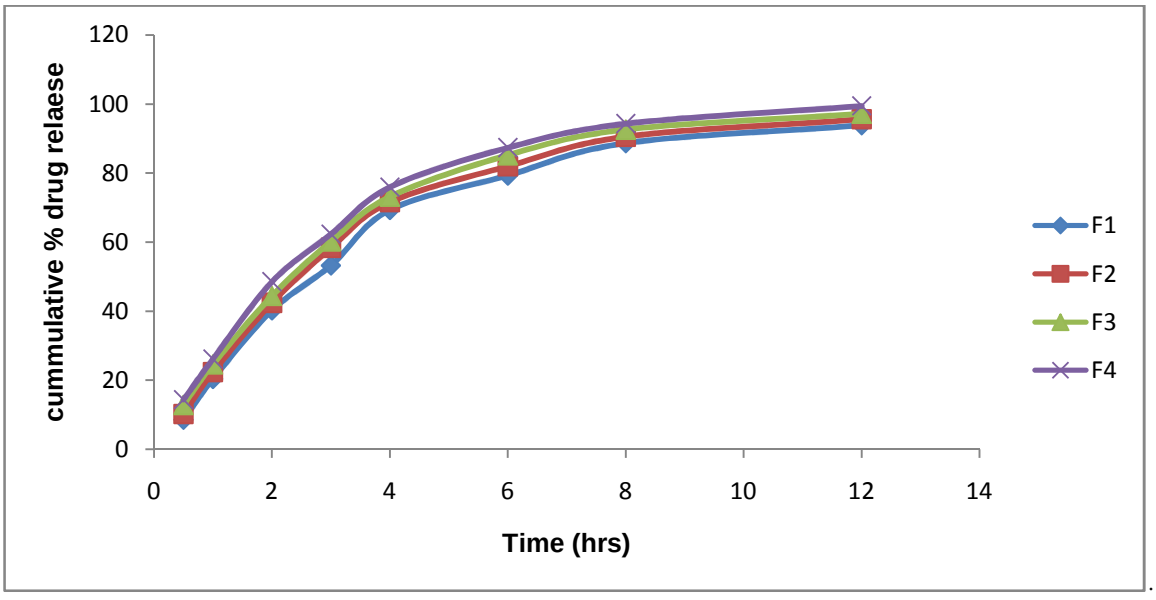

Figure 2: Comparative Dissolution Plots of various formulations (F1-F4)

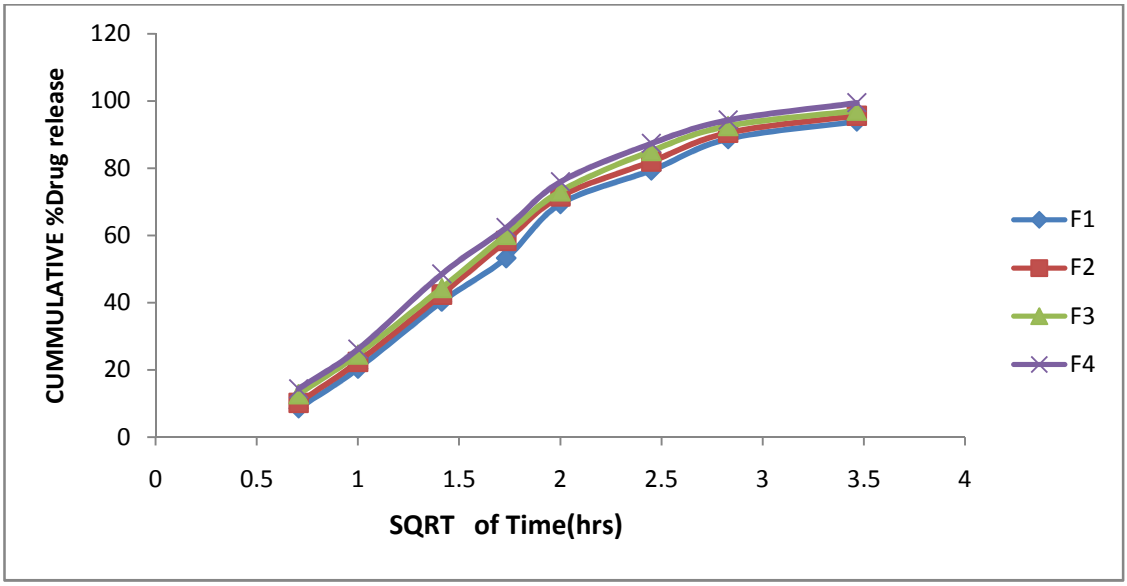

Figure.3:Comparative Higuchi Order Release of Glyburide Beads (F1-F4)

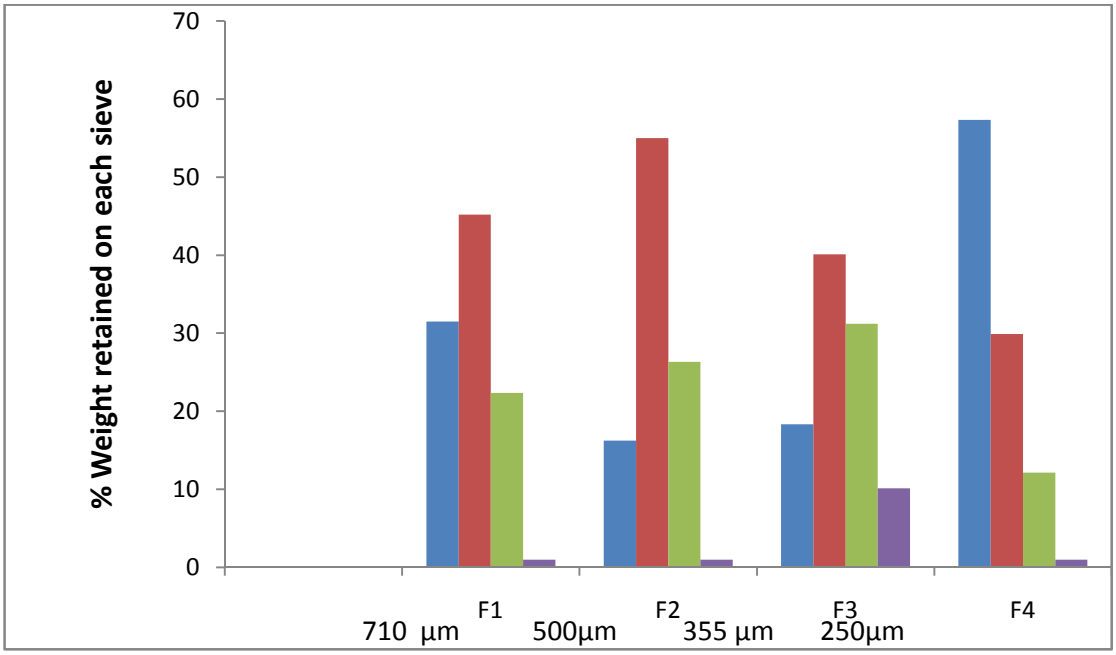

Figure.4: Particle Size Distribution Curve of Various Formulations (F1-F4)

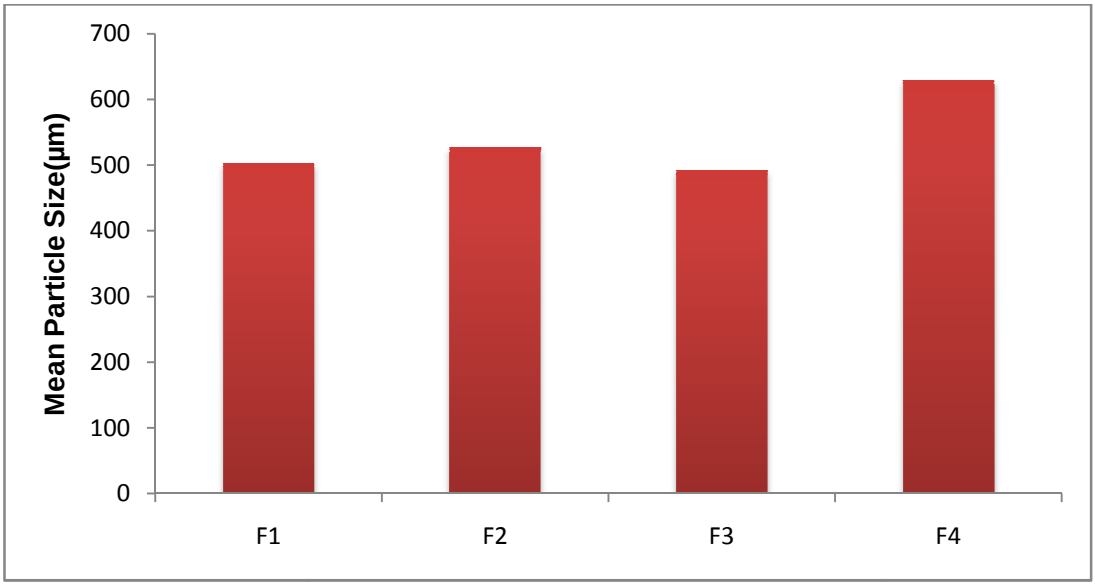

Figure.5: Mean Particle Size of Various Formulations (F1-F4)

CONCLUSION

The Glyburide beads were prepared by ionotropic gelation method using sodium alginate, carbopol 940, HPMC K 100 M as polymers. As Glyburide has short half life of 4-6 hrs, this can be increased by using combination of polymers for a sustained release of drug. This method is performed by using $CaCl_2$ solution as cross linking agent for hardening of alginate beads.After preparation the obtained beads were evaluated for % yield, drug entrapment efficiency, swelling index, in vitro drug release studies and results were tabulated. The obtained microspheres were found to be free flowing, discrete and the %yield was found to be 88 to 93.8%, drug entrapment efficiency was found to be 82.7 to 91.2 %,and swelling index of beads were satisfactory. The dissolution was performed for 12 hrs and the drug release was found to be 99.42% for formulation with combination of polymers (F_4) and found to be significant optimized batch, which may be the ideal batch .Therefore usage of combination of polymers gave significant results and satisfactory when compared to single use of polymers.

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