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Formulation and evaluation of mucoadhesive microspheres loaded with glipizide

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ABSTRACT

In the present work, microspheres of Glipizide using Sodium alginate along with Carbopol 934, HPMC as copolymers were formulated to deliver Glipizide via oral route.The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Glipizide microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used. Micromeritic studies revealed that the mean particle size of the prepared optimized microspheres was in the size range of 611µm and are suitable for microspheres for oral administration.Increase in the polymer concentration lead to increase in % Drug entrapment efficiency, Particle size, % swelling.The invitro drug release decreased with increase in the polymer and copolymer concentration.Analysis of drug release mechanism showed that the drug release from the formulations followed zero order kinetics with higuchis model of drug release.Based on the results of evaluation tests formulation coded F3 was concluded as best formulation.

Keywords: Glipizide, Sodium alginate, Carbopol 934, HPMC And Ionotropic gelation method.

INTRODUCTION

Microencapsulation

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation is arbitrarily differentiated from macro coating techniques in that the former involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size.[6]

Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental

protection, and of controlling the release characteristics or availability of coated materials.

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded or enclosed, by an intact shell. Two major classes of microencapsulation methods have evolved i.e. chemical and physical.

The first class of encapsulation method involves polymerization during the process of preparing the microcapsules. The second type involves the controlled precipitation of a polymeric solution where in physical changes usually occur.[7, 8]

MUCOADHESION / BIOADHESION

Mucoadhesive drug delivery system are the systems which utilizes the property of bio adhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time.

The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer. Bio adhesions are a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces. In biological systems, bio adhesion can be classified into 3 types:

1. Adhesion between two biological phases, for example, platelet aggregation and wound healing
2. Adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio film formation on prosthetic devices and inserts
3. Adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bio adhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion / mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. In bio adhesion, the polymer is attached to the biological membrane.

METHODOLOGY

Method of preparation

Ionotropic gelation method

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polyatomic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (50 ml) to form a homogeneous polymer mixture. The API, Glipizide were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (2% w/v) aqueous solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

Table no: 1 Formulation of microspheres

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug: polymer	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2
Muco adhesive Polymer ratio	--	1:1	1:1.5	1:2	0.5:1	0.5:1	--	2:1	1.5:1	1.5:2
Carbopol	1%	1%	1%	1%	0.5%	0.5%	1.5%	1.5%	1.5%	1.5%
HPMC K100	--	1%	1.5%	2%	--	--	--	0.75%	1%	2%

Xanthum gum	--	--	--	--	1%	--	--	--	--	--
Guar gum	--	--	--	--	--	1%	--	--	--	--
Na-Alginate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Water	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml
Calcium Chloride (2%)	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

RESULTS AND DISCUSSION

Drug excipient compatibility studies

The From the IR spectral data of ideal formulation F3, it is clearly evident that there were no interactions of the drug.

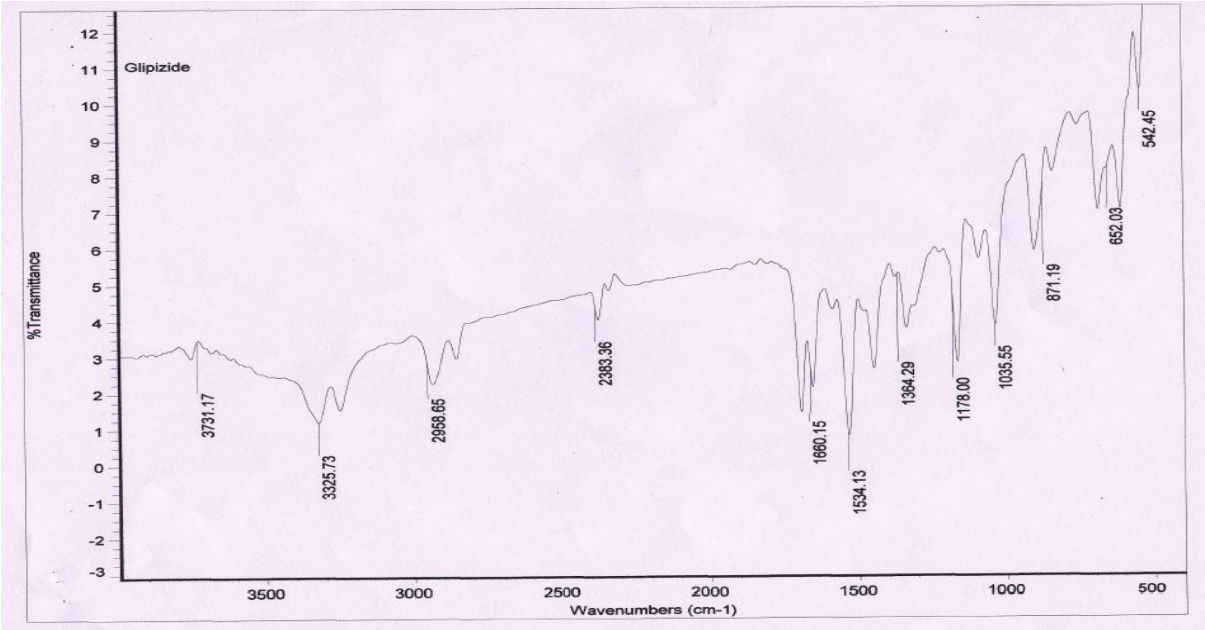


Figure No 2:FTIR Spectra of Glipizide pure drug

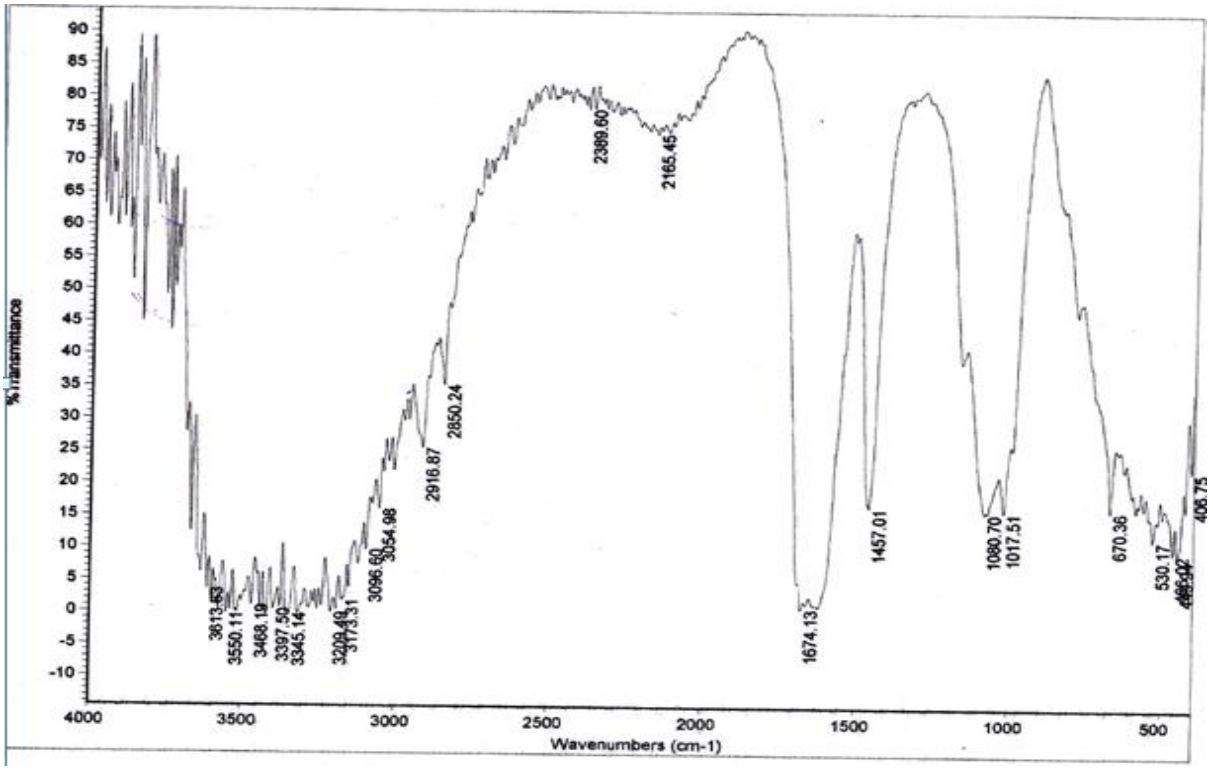


Figure No 3:FTIR Spectra of Glipizide optimized formulation

EVALUATIONAND CHARACTERISATION OF MICROSPHERES

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 87.6 to 96% for microspheres containing sodium alginate along with carbopol 940 and HPMC as copolymers, around 90.1% for microspheres containing sodium alginate along with Xanthum gum as copolymer and 95.1% for microspheres containing sodium alginate along with Guar gum as copolymer.

Drug entrapment efficiency

The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 3, and displayed in Figure 5.

In vitro Mucoadhesion Studies

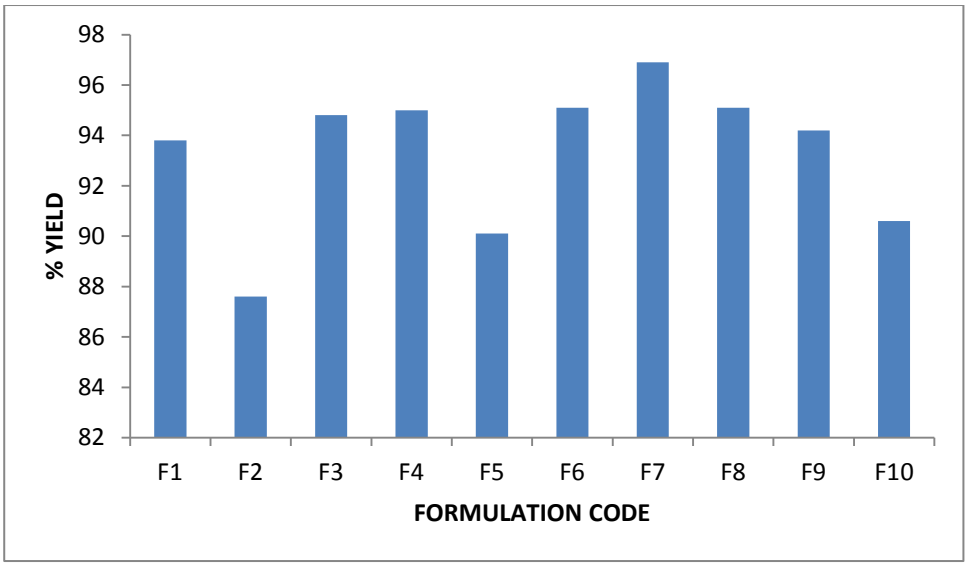
Percentage mucoadhesion of the formulations were carried out and were found to be within the range between 68.6 to 96.4%.

Table no: 3. Percentage yield and percentage drug entrapment efficiency of the prepared Microspheres

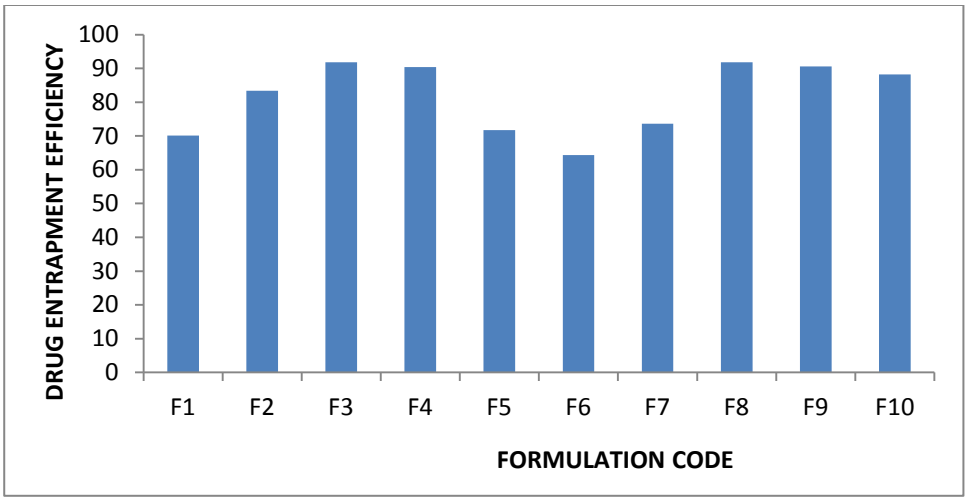
S.No.	Formulation code	% yield	%Drug entrapment efficiency	% Muco adhesion
1	F1	93.8	70.1	68.6
2	F2	87.6	83.4	88.1
3	F3	94.8	91.8	90.6
4	F4	95.0	90.4	92.4
5	F5	90.1	71.7	80.5
6	F6	95.1	64.3	74.8
7	F7	96.9	73.6	83.5
8	F8	95.1	91.3	90.2
9	F9	94.2	90.6	93.6
10	F10	90.6	88.2	96.4

DISCUSSION

Formulation F3 containing blend of carbapol and HPMC K100maximum percentage of drug loading about 91.8%.Formulation F1 contianing carbapol percentage of drug loading about 70% because these microspheres are small in size which results more loss of drug from surface during washing of microspheres.



FigureNo4: Graphical representation of percentage yield of formulations F1-F10



FigureNo5: Graphical representation of percentage drug entrapment efficiency of formulations F1-F10

Scanning electron microscopy

The SEM photography revealed that the drug loaded microsphere are spherical .Microspheres prepared containing higher amount of polymer exhibited smoother surface than those prepared with a low amount of polymer Irregular surfaces and large sizes of microspheres were observed for those prepared with the lower amount of polymer >This has greatly affected the Morphological Characteristics of the microspheres. As the drug – to-polymer ratio was increased, more spherical microspheres with smooth surfaces were obtained.

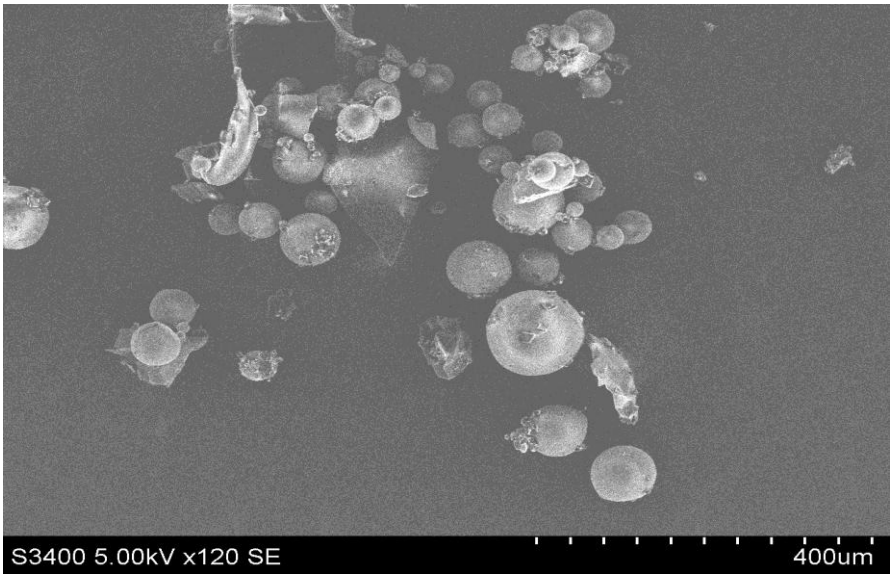


Figure No6: SEM of Glipizide

Particle size analysis

The mean particle size and size distribution of the mucoadhesive microspheres of Glipizide with different drug/polymer ratio were studied and found to be in the range of 642µm -834 µm. The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. . The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Table no 4: Average Particle Size analysis for formulation F1-F10

Formulation code	Average particle size(µm)
F1	642
F2	617
F3	611
F4	717
F5	642
F6	792
F7	834
F8	664
F9	702
F10	740

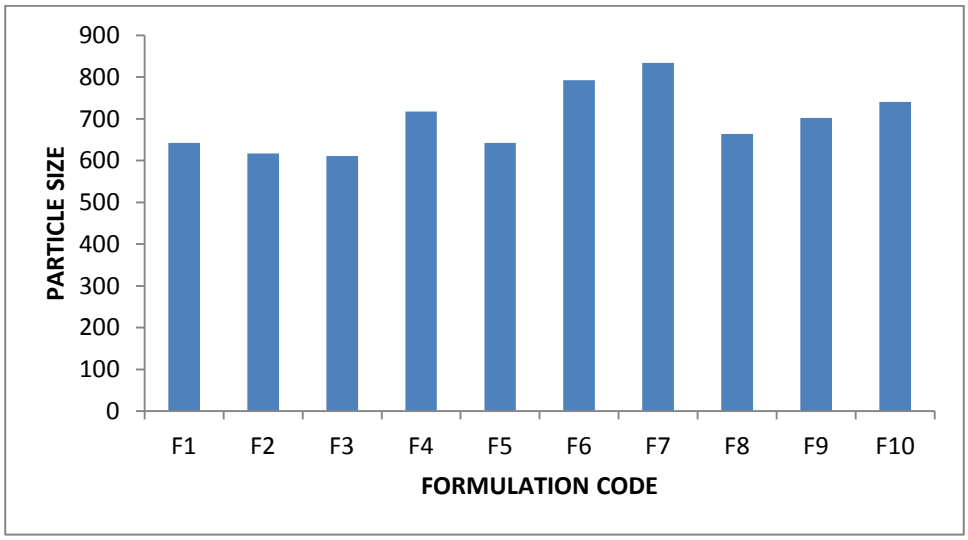


Figure No7: Graphical representation of average particle size for formulations F1-F10.

Swelling study

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swell ability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swell ability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swell ability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table that with an increase in polymer concentration, the percentage of swelling also increases. Thus we can say that amount of polymer directly affects the swelling ratio..The percentage swelling of the prepared microspheres is displayed in Fig.8. The effect of drug to polymer ratio on percentage swelling is displayed in Figure 8.Table no 5: Percentage Swelling of the Prepared Microspheres.

S.NO.	FORMULATION CODE	PERCENTAGE SWELLING
1	F1	90.3
2	F2	105.8
3	F3	106.4
4	F4	91.8
5	F5	93.1
6	F6	94.6
7	F7	95.1
8	F8	101.4
9	F9	116.8
10	F10	120.3

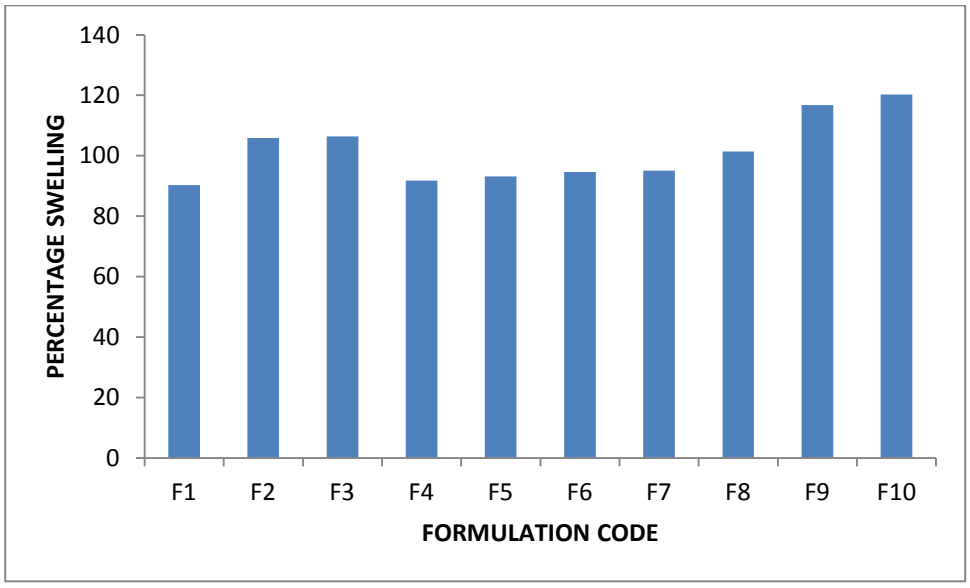


Figure No 8: Graphical representation of Percentage swelling index of formulations F1-F10

In-vitro drug release studies

The invitro release studies of all the extended release microspheres formulated (F_1-F_{10}) were performed using USP II dissolution apparatus at 37.5±0.5 in 0.1N HCL and samples were withdrawn and analyzed by using UV spectrophotometry at 274nm. The results were shown in table

Release studies of Glipizide mucoadhesive microspheres formulations F_1-F_{10}

The release profile of formulations F_1-F_{10} comprising various polymers like Carbopol, HPMC K 100, Xanthum gum ,sodium alginate with different l concentrations were shown in **table**. Formulations F_1, F_2, F_3 and F_4 exhibits release rates of 88.7%, 85.4%, 91.0% , 90.0%,86.0% ,69.1%,87.6%,88.0%,85.1%,72.6%.

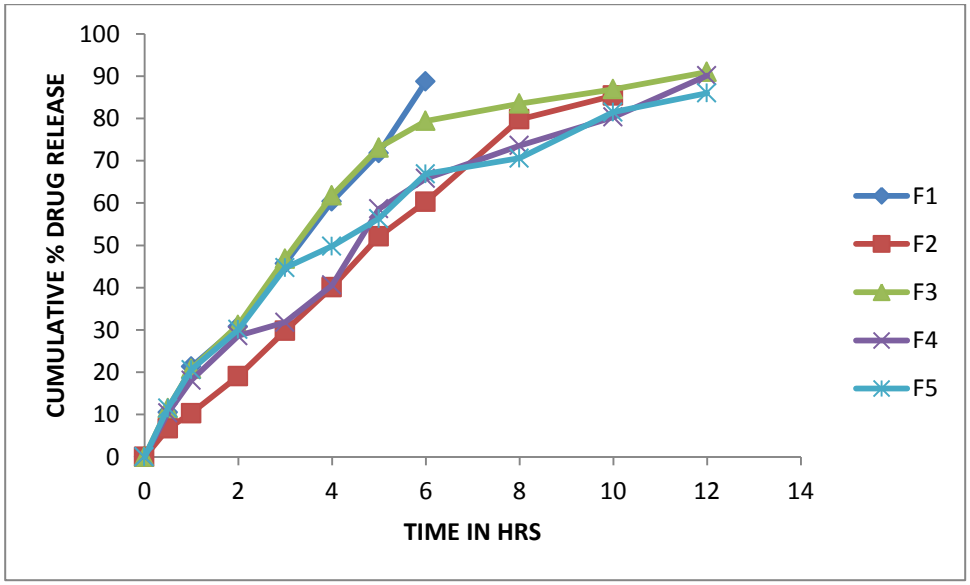
The results of the in-vitro dissolution studies of formulations F_1 to F_{10} and shown in table .The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations F_1 to F_{10}.

TABLE NO: 6 In-Vitro drug release data of Glipizide microspheres

TIME (h)	Cumulative Percent Of Drug Released				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	10.5	6.7	11.5	10.4	11.5
1	21.3	10.3	20.8	18.1	20.6
2	30.8	19.1	31.2	28.6	30.1
3	45.7	29.8	46.8	31.8	44.7
4	60.4	40.1	61.8	40.6	49.8
5	71.8	52.1	73.1	58.6	56.3
6	88.7	60.3	79.4	65.8	66.9
8	--	79.8	83.5	73.6	70.6
10	--	85.4	86.9	80.3	81.5
12	--	--	91.0	90.1	86.0

DISCUSSION

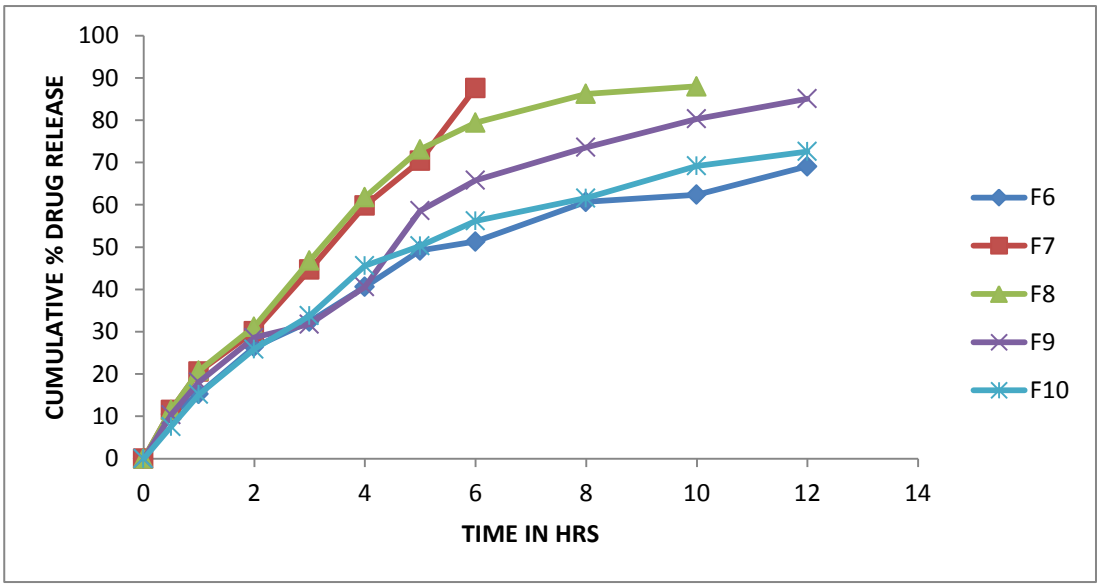
Among all the formulations F3 Containing carbopol, HPMC and sodium alginate showed maximum release at 12 hours.This shows that more sustained release was observed with the increase in percentage of polymers.As the polymer to drug ratio was increased the extent of drug release decreased.A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.



FigureNo9: **Comparison of In-Vitro drug release profile of Glipizide microspheres (F1 – F5)**

TABLE NO:7 In-Vitro drug release data of Glipizide microspheres

TIME (h)	Cumulative Percent Of Drug Released				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
0.5	10.5	11.5	11.5	10.4	7.6
1	15.3	20.6	20.8	18.1	15.2
2	26.4	30.1	31.2	28.6	25.9
3	32.4	44.7	46.8	31.8	33.8
4	40.6	59.8	61.8	40.6	45.6
5	49.2	70.4	73.1	58.6	50.3
6	51.3	87.6	79.4	65.8	56.2
8	60.7	--	86.2	73.6	61.6
10	62.4	--	88.0	80.3	69.2
12	69.1	--	--	85.1	72.6



FigureNO10: Comparison of In-Vitro drug release profile of Glipizide Microspheres (F5-F10).

In-vitro drug release kinetics

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.274488491	-0.14046354	31.43943102	1.37238628
Intercept	9.643606138	2.20149929	-12.2709975	0.703967511
Correlation	0.950160504	-0.92487055	0.966554763	0.876716503
R 2	0.902804983	0.855385541	0.93422811	0.768631826

CONCLUSION

Micromeritic studies revealed that the mean particle size of the prepared optimized microspheres was in the size range of 611µm and are suitable for microspheres for oral administration.Increase in the polymer concentration lead to increase in % Drug entrapment efficiency, Particle size, % swelling.The invitro drug release decreased with increase in the polymer and copolymer concentration.Analysis of drug release mechanism showed that the drug release from the formulations followed zero order kinetics with higuchis model of drug release.Based on the results of evaluation tests form ulation coded F_3 was concluded as best formulation.

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