EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 2
Issue: 2
495-509
Year: 2015

PREPARATION AND EVALUATION OF GLIBENCLAMIDE-ALGINATE MICROSPHERES

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Article Received on 01/03/2015 **Article Revised on 25/03/2015** **Article Accepted on 19/04/2015**

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ABSTRACT

Glibenclamide is an oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes. It is a weak acid and is poorly soluble in water. In the present study microspheres were prepared by ionic cross-linking technique. Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for microspheres. For slowing the rate of release from microspheres Eudragit RS100 and Xanthan gum combinations were added, so that the drug will be release constantly for 12hrs. The prepared microspheres were characterized in terms of drug-excipient compatibility study, percentage yield, micromeritics study, swelling index, particle size analysis, shape analysis, drug content, drug encapsulation efficiency and *in-vitro* drug release study. To analyze the mechanism of drug release from the tablets, the *In-vitro* dissolution data of optimized formulations were fitted to zero order, first order, higuchi release model and korsmeyer-peppas model based on regression coefficient. The n values of the optimized formulations F-8 and F-7 were 0.572 and 0.548 respectively. This indicates the release of drug followed Non Fickian or anomalous transport. Results signified the fact that, microspheres formed has sufficient good surface and size to be utilized as a dosage form responsible for slow release of drug from matrix through erosion. Among all the nine batches formed. F8 was selected as the optimized batch in terms of all parameters evaluated.

KEYWORDS: Glibenclamide, Ionic cross-linking technique, Eudragit RS100, Xanthan gum.

INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as micro particles. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug.[1] It is Needless to say that one of the most difficult problems of the new millennium is the management of vast majority of our population afflicted with diabetes specially the Type-2, which are not dependent on insulin production. It is feared that within few years India would have 50 million cases of diabetes especially among the younger generation among men and women including children will suffer from this destructive disease. Extensive work is being taken up not only to develop newer more specific molecules for Type-2 diabetes but also develop proper delivery system to maintain the activity of the drug over a prolong period of time so the proper compliance of taking the drugs regularly. The principal aim of the investigation undertaken is to develop a Multi-Particulate Drug Delivery System for non-insulin dependent diabetes mellitus drug. This type of diabetes is rising exponentially even in developing country like India due to fast life style with concomitant stressful living condition. It is expected that within coming 5 years fifty million Indian of both sexes and different age group including children will suffer from this destructive diseases, keeping above view the investigation has undertaken as the topic of national importance.[2,3] Glibenclamide (GB) is a second-generation sulfonylurea oral hypoglycaemic agent usedin the treatment of non-insulin dependent diabetes mellitus. It is administered in lowdoses (5 mg) and its active metabolites have a significant hypoglycemic effect. However, glibenclamide's low bioavailability has been attributed to its poor.[4-11] Eudragit RS 100 is the copolymers of acrylic and meth acrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make polymers permeable. The average Molecular weight is approx. 150, 000. 1g of the substances dissolves in 7g aqueous

The main objective of the present work is to develop the Glibenclamide loaded microspheres as drug delivery system. To control the release of drug by using polymers as coating materials such as sodium alginate, Xanthan gum, Eudragit RS100 to release the drug in the gastro intestinal tract.

MATERIALS

Glibenclamide was obtained as gift sample from aurabindo pharmaceuticals hyderabad. Xanthum gum, EudragitRS100,calcium chloride purchased from yarrow chem products Mumbai. Sodium alginate,sodium dihydrogen phosphate was procured from Merck Specialities Pvt, Ltd.Methanol from moly chem, Tween 80 and hydrochloric acid purchased fromS.D Fine chemicals Mumbai.

Preformulation studies

Fourier Transform Infrared Spectroscopy (FTIR)

Infra red spectroscopy is widely used in pharmaceutical research. Compatibility studies were carried out by Fourier Transformed-Infra Red and Differential Scanning Calorimeter. In this study the pure drug spectra and physical mixture of excipients spectra were compared.IR spectrum with high quality is acquired with KBr (pellet) method. The sample powder of drugs, excipients and mixture of they were prepared and placed on glass plate and apply the infra red beam to record the spectra. The mixture spectra were compared with that of the original spectra.

Differential Scanning Calorimeter (DSC) Studies

The pure drug and optimized formulation were subjected to differential scanning calorimeter equipped with an intra cooler (NETZSCH, Japan.). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample were sealed in aluminum pans and heated at a constant rate 10°C/min over a temperature range of 50-400°C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

Determination of Derived properties of Glibenclamide alginate microspheres

Angle of repose

The angle of repose of was determined by the funnel method. The accurately weight microspheres were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the microspheres. The microspheres were allowed to flow through the funnel freely on to the surface. The diameter of the microspheres cone was measured and angle of repose was calculated using the following equation.[20]

$$\tan\theta = \frac{h}{r}$$

Where, h and r are the height and radius of the powder cone.

Apparent bulk density:[13] Apparent bulk density (ρ_b) was determined by pouring the microspheres into a graduated cylinder. The bulk volume (V_b) and weight of the microsphere (m) was determined. The bulk density was calculated by using the following formula:

$$\text{Apparent bulk density } (\rho_b) = \left(\frac{m}{V_b}\right)$$

Where, ρ_b = Bulk density11

m = Weight of sample in gm

V_b = Final volume of blend in cm^3

Tapped density

It is the ratio of total mass of the Microsphere to the tapped volume of microsphere. The volume was measured by tapping the Microspheres for 100 times. The tapped density was calculated by using the following formula.

$$\text{Tapped density } (\rho_t) = \left(\frac{m}{V_t}\right)$$

Where, ρ_t = Tapped density

m = Weight of the sample in gm

V_t = Tapped volume of blend in cm^3

Hausner's ratio

The ratio of tapped density to the bulk density of the microspheres is called the Hausner's ratio.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Carr's index (% Compressibility)

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula. Results are shown in Table 25.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Formulation of Glibenclamide microspheres

Sodium alginate and xanthium gum were dissolved in purified water (80 mL) to form a homogeneous polymer solution. Glibenclamide is dissolved in methanol to form 5 mg/mL solution. To this soluton add calculated amount of Eudragit RS100. From this add 20ml of Glibenclamide solution in to the above formulation and mixed thoroughly with a magnetic

stirrer to form viscous dispersion. The resulting dispersion was then added drop by drop with the help of syringe and needle (0.55*25 mm) to the calcium chloride (10%w/v) solution. The addition was done with continuous stirring. The added droplets were retained in the calcium chloride solution for 1hr to complete the curing reaction and to produce spherical rigid microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with water to remove excess calcium impurity and air dried[16]

Table.1. Formulation of Glibenclamide microspheres

Form. code	Glibenclamide (mg)	Sodium Alginate (mg)	Eudragit RS 100(mg)	Xanthan gum(mg)	Total weight (mg)
F1	100	2	50	50	2.2
F2	100	2	50	100	2.25
F3	100	2	50	150	2.3
F4	100	2	100	50	2.25
F5	100	2	100	100	2.3
F6	100	2	100	150	2.35
F7	100	2	150	50	2.3
F8	100	2	150	100	2.35
F9	100	2	150	150	2.4

Characterization of Glibenclamide microspheres

Percentage yield

The practical percentage yield was calculated from the weight of dried microspheres recovered from each batch in relation to the sum of the initial weight of starting materials.

$$\text{Percentage yield} = \frac{\text{practical mass(microspheres)}}{\text{Theoritical mass(Drug + polymer)}}$$

Drug entrapment efficiency:[14]

Microspheres equivalent to 10mg of Glibenclamide was weighed and crushed in a glass mortar and pestle and the powdered microspheres were suspended in 100ml of phosphate buffer pH 7.4. After 24hours, the solution was filtered, 1ml of the filtrate was pipette out and diluted to 10ml **.**

$$\text{Percentage entrapment efficiency} = \frac{\text{practical drug content}}{\text{Theoritical Drug content}} \times 100$$

Swelling studies:[15]

The swellability of microspheres in physiological media was determined by swelling them in the phosphate buffer saline pH 7.4and analyzed for the drug content using Elico SL- 164 UV Visible spectropphotometer at 229nm.

Particle size analysis

Many methods are available for determining particle size, such as optical microscopy, sieving, sedimentation and particle volume measurement. Optical microscopy is most commonly used for the particle size determination.[16]

Shape and surface morphology[17]

The shape and surface characteristics of the prepared microspheres were evaluated by means of scanning electron microscopy (JEOL – JSM - 840A, Japan). The samples for scanning electron microscopy were prepared by gently sprinkling the microspheres powder on a double adhesive tape, which is stuck to an aluminum stub. The stubs were then coated with gold using a sputter coater (JEOL Fine coat JFC 1100E, ion sputtering device) under high vacuum and high voltage to achieve a film thickness of 30nm. The samples were then imaged using a 20KV electron beam.

***In-Vitro* Drug release studies**

Procedure

In-vitro release profile of the microspheres was evaluated using USP XXVI dissolution test apparatus. Phosphate buffer (pH7.4) is used as dissolution medium and maintained at 37±0.5 0C with speed of agitation at 100 rpm. Accurately weighed amount of microspheres equivalent to 10 mg of drug were placed and dissolution is done in pH 7.4 phosphate buffer solution. At prefixed time (every 1 hour), 5 ml of solution were withdrawn. It is replaced with same quantity of pH 7.4 phosphate buffer .After suitable dilution, samples were assayed spectrophotometrically for the drug content at 229 nm using UV-Visible spectrophotometer.

***In-vitro* release mechanism[18,19]**

Depending upon R and k values obtained from different models, the best-fit model was selected.

Zero order release

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented as

$$Q = Q_0 + K_0 t$$

Where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero), and

K_0 is the zero order release constant. The plot made: cumulative % drug release Vs time (zero order kinetic model).

First order release

To study the first order release rate kinetics the release rate data were fitted into the following equation,

$$LogC = LogC_o - kt / 2.303$$

Where C is the amount of drug released at time t, C_o is the initial amount of drug in the solution and K_1 is the first order release constant.

Higuchi model

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion

$$Q = K_t^{1/2}$$

Where, K is the constant reflecting the design variables of the system.

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

Korsmeyer-peppas model

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t/M_\infty = Kt^n$$

Where M_t / M_∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in following table for cylindrical shaped matrices.

Results

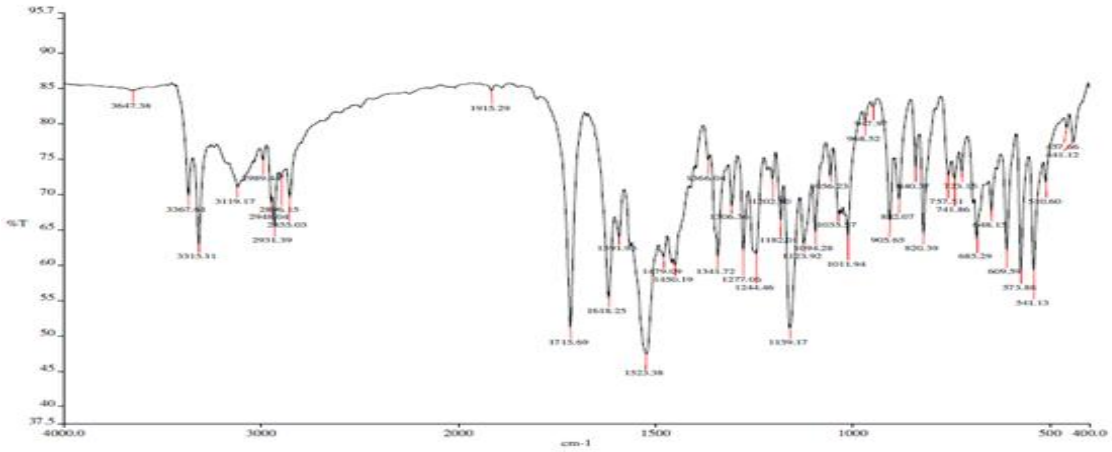


Fig: 1FTIR Spectra of Glibenclamide pure drug

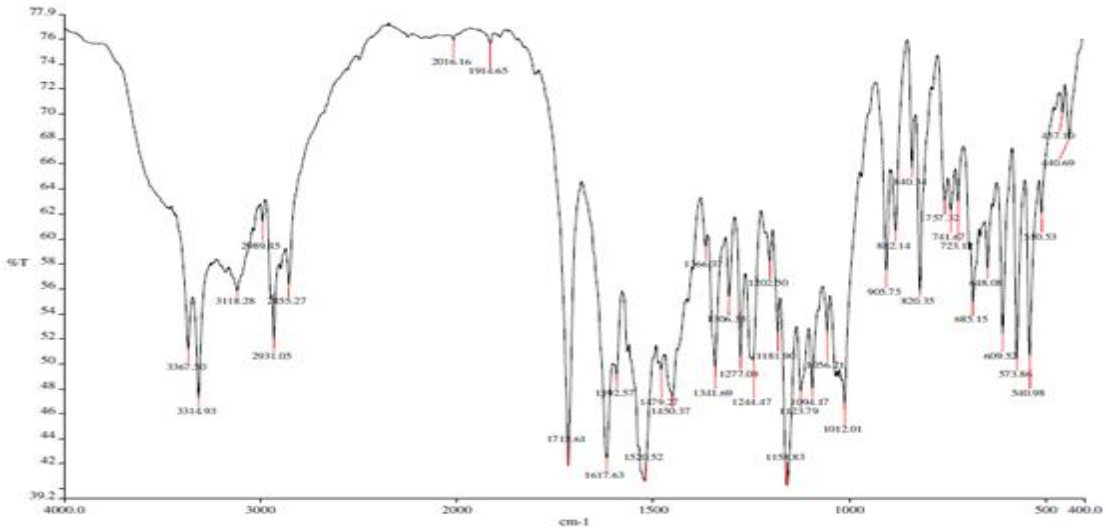


Fig: 2 FTIR spectra of Glibenclamide+ Xanthan gum

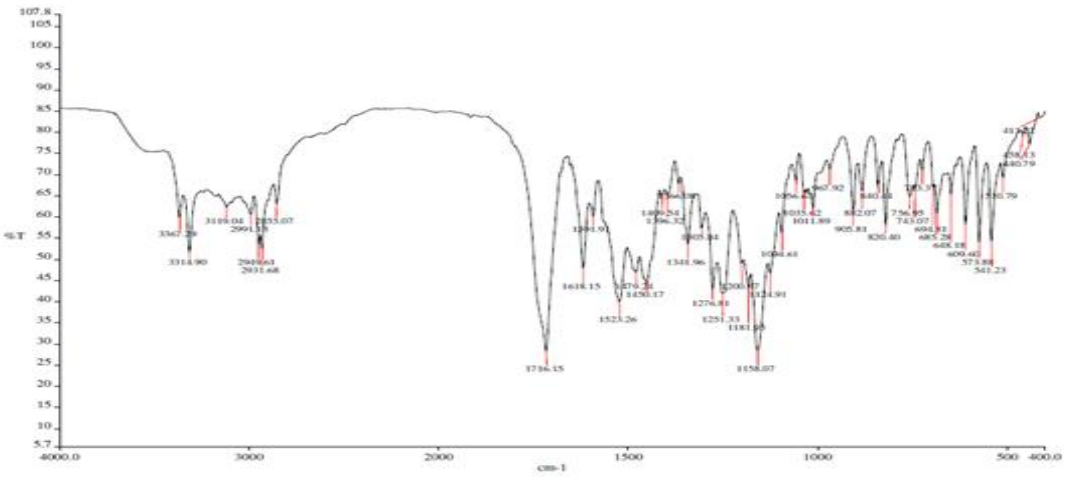


Fig: 3FTIR spectra of Glibenclamide and Eudragit RS 100

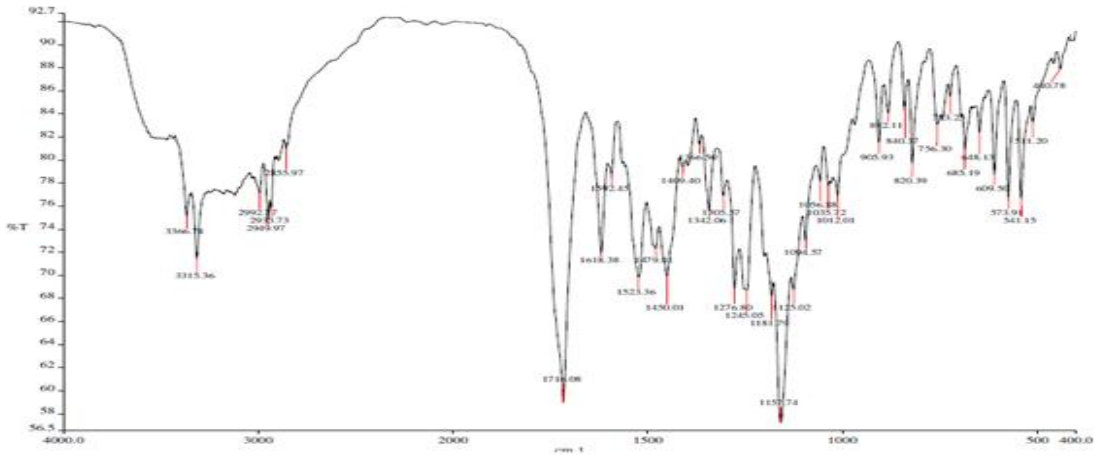


Fig: 4 FTIR spectra of Glibenclamide, Xantham gum and Eudragit RS100

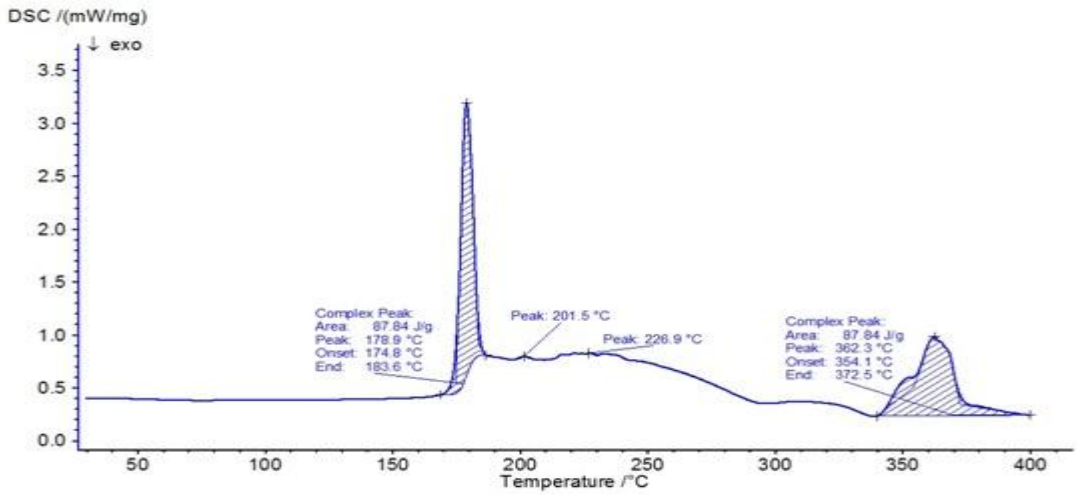


Fig: 5 DSC thermogram of Glibenclamide pure drug

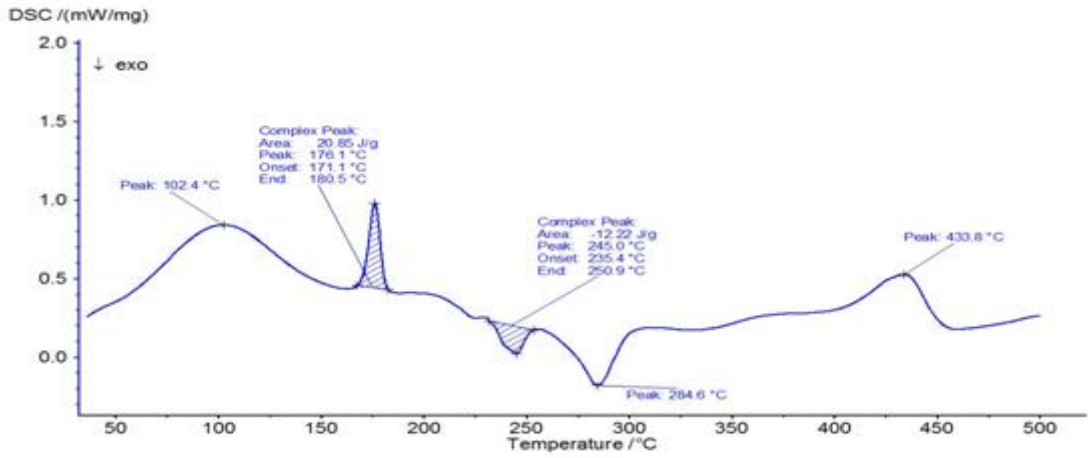


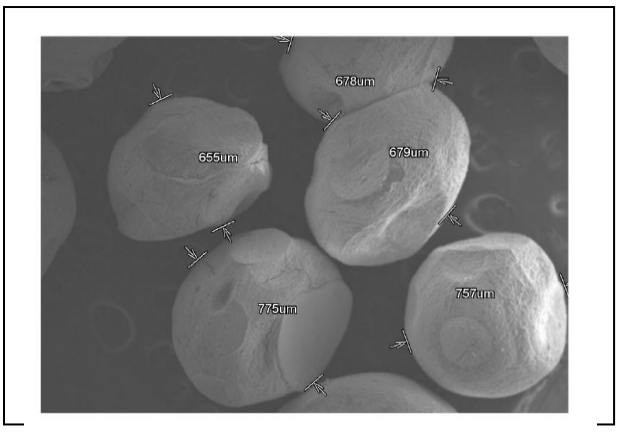
Fig: 6 DSC thermogram of Glibenclamide mixture

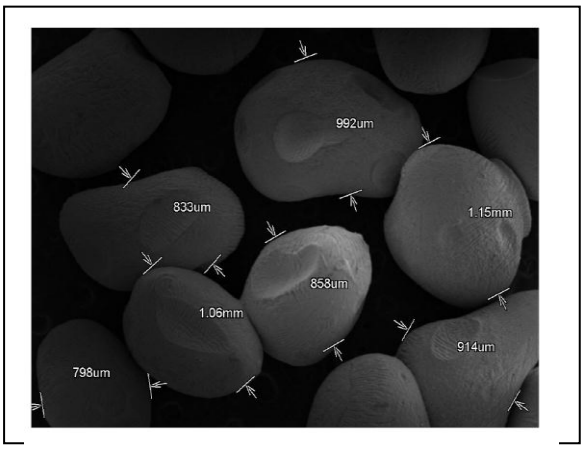
Table: 2Derived properties of Glibenclamide microspheres of formulations (F1-F9)

Form. code	Bulk density (g/cc) Avg±SD (n=3)	Tapped density (g/cc) Avg±SD (n=3)	Compressibility index (%) Avg±SD (n=3)	Hausner's ratio Avg±SD (n=3)
F-1	0.487±0.018	0.526±0.006	7.26±0.55	1.078±0.021
F-2	0.506±0.026	0.587±0.039	13.74±0.190	1.159±0.003
F-3	0.615±0.029	0.645±0.037	4.651±0.157	1.048±0.013
F-4	0.634±0.020	0.720±0.041	11.94±0.41	1.135±0.024
F-5	0.547±0.022	0.579±0.030	5.52±0.327	1.058±0.016
F-6	0.533±0.025	0.571±0.040	9.81±0.597	1.108±0.028
F-7	0.531±0.010	0.625±0.026	15.04±0.565	1.177±0.018
F-8	0.588±0.025	0.634±0.035	6.34±0.395	1.078±0.011
F-9	0.605±0.016	0.660±0.015	8.33±0.30	1.09±0.020

Table: 3 Characterisation of glibenclamide microspheres

Form. code	Percentage Yield (%)	Entrapment efficiency (%)	Swelling index (%)
F1	88.6	66.38	81
F2	88.8	74.68	86.5
F3	91.7	78.51	89.6
F4	86.6	81.7	93
F5	93.4	86.59	99
F6	85.1	89.57	114.6
F7	891	78.51	90.1
F8	89.3	81.06	96.5
F9	91.6	82.79	107.4





(a) SEM image of microspheres without drug formulation **(b) SEM image of F8**

Fig: 7 Shape and surface morphology

Table: *4 in vitro* dissolution profile ofglibenclamide microspheres

Time (hrs)	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1	34.92	33.94	35.108	30.03	29.68	28.72	23.81	25.10	20.87
2	48.28	44.70	46.49	37.04	36.88	36.06	29.53	30.03	24.16
3	58.43	50.12	53.54	46.50	45.53	44.71	33.95	34.77	28.40
4	65.47	56.65	59.43	52.57	51.59	48.66	40.64	41.46	33.46
5	72.66	63.02	65.64	60.73	61.37	55.18	46.85	48.48	40.64
6	84.56	71.99	72.82	69.38	66.79	61.23	55.17	53.23	44.25
7	96.16	80.49	78.22	79.83	75.43	66.14	64.80	61.70	48.66
8		91.91	86.21	84.60	81.81	70.55	72.17	65.65	53.23
9			96.17	90.15	85.26	76.75	80.17	76.88	60.73
10				95.70	91.78	84.74	86.87	82.47	67.76
11						93.72	95.36	91.60	76.41
12								95.39	85.39

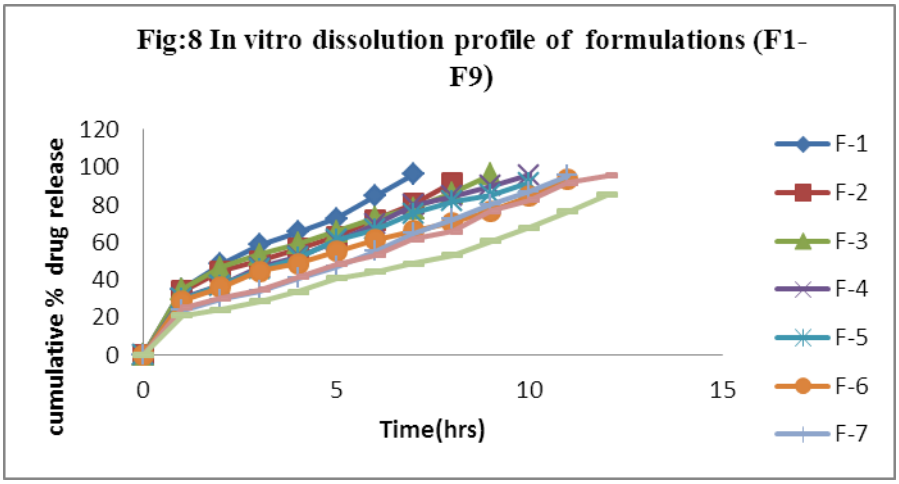


Table: 5 In vitro drug release kinetics of all formulations (F1- F9)

Form. Code	Zero order		First order		Higuchi		Korsmeyer-peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
F-1	0.929	11.92	0.826	-0.175	0.991	34.67	0.987	0.499	Fickian transport
F-2	0.922	9.22	0.861	-0.112	0.982	30.13	0.965	0.456	Fickian transport
F-3	0.909	8.763	0.822	-0.125	0.990	29.87	0.939	0.389	Fickian transport
F-4	0.953	8.591	0.915	-0.124	0.988	30.39	0.978	0.497	Fickian transport
F-5	0.944	8.102	0.951	-0.097	0.992	28.86	0.978	0.460	Fickian transport
F-6	0.941	7.014	0.852	-0.086	0.985	26.35	0.964	0.429	Fickian transport
F-7	0.982	7.842	0.845	-0.103	0.951	28.35	0.962	0.548	Non-fickian transport

F-8	0.977	7.156	0.856	-0.098	0.959	27.39	0.952	0.572	Non-fickian transport
F-9	0.974	6.093	0.874	-0.057	0.937	23.09	0.958	0.525	Non-fickian transport

DISCUSSION

In the present study controlled delivery system of microspheres of Glibenclamide was prepared by using Ionic gelation method with different polymers like Xanthan gum, Eudragit RS100 and Sodium alginate.

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymers were studied. The characteristic absorption peaks of Glibenclamide were obtained at wave numbers 3315 cm^{-1},3367cm^{-1}, 2989cm^{-1}, 2931cm^{-1}, 2848cm^{-1}, 1715cm^{-1}, 1618cm^{-1}, 1523cm^{-1},1450cm^{-1}, 1341cm^{-1}, 1306cm^{-1}, 1244cm^{-1},1159cm^{-1}, 1035cm^{-1},685cm^{-1}. The peaks obtained in the spectra's of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

The DSC thermo gram study for drug and its formulations is also utilized for establishing physical characteristics. The DSC thermo gram of pure drug gave endothermic peak corresponding to the temperature 178.9^{0}C, which indicates its sharp melting point. The DSC thermo gram of Xanthan gum shows exothermic peak at 285.8^{0}C. EudragitRS100 shows endothermic peak at 412^{0}C. Sodium alginate shows exothermic peak at 242.5^{0}C.

The DSC thermo gram of the best formulation shows drug peak at 176.1^{0}C.Even though slightly differs in the nature and appearance this endothermic peak is almost all near to 178.9^{0}C.The comparative study of these two thermo grams, i.e. drug and its best formulation F8 shows the endothermic peak corresponding to the melting point of the drug. Hence it follows that there was no interaction of the drug with polymer and other excipients in best formulation.

Drug solution concentrations from 2-20 µg/ml in 7.4 pH were prepared. The samples were analyzed by using UV Visible spectrophotometer at 229nm. A linear plot of drug absorbance and solution concentration was obtained with r^2 = 0.999 in 7.4 pH with slope of 0.055. The percentage of drug entrapment is calculated for all the formulations. F6 shown high entrapment efficiency of 89%. F8 formulation showed 81% of drug entrapment efficiency.

The swelling index of all the formulation is calculated F6 shown highest degree of swelling followed by F9. The particle size analysis of the microspheres shows average particle size in the range of 679-1035 µm. The SEM analysis of the formulations shows almost spherical in shape with rough surface and slight elevations and depressions.

The *In-vitro* dissolution studies of formulations F_1 to F_9 were carried out in phosphate buffer (pH 7.4) and the percentage of drug release was calculated. All formulations were carried out for maximum 12hrs.It was found that for F1 (96.16%) in 7hrs, F2 (91.91%) in 8 hrs, F3 (96.17%)in 9 hrs, F4(95.7%) and F5(91.78%) in 10 hrs, F6 (95.72% & F7 95.36%) within 11 hrs, F8 (95.39%) & F9 (85.39%) in 12 hrs. Finally we conclude that F9 formulation shows complete drug release with in 12 hrs. As the concentration of polymer increases drug entrapment efficiency increases and then shows the sustain drug action & maximum drug release, the following results are shown in the table no (3).

When the data was plotted as per zero order kinetics, plots were obtained with high correlation coefficient values ranging from 0.909-0.982. First order plots showed lower correlation coefficient values ranging from 0.826- 0.951. . The Diffusion exponent (n) values of first 6 formulations are obtained below 0.5, hence they follow fickian transport and F7, F8 and F9 formulations show n value above 0.5 indicating non-fickian type transport mechanism. Hence above observations let us to conclude that, all the microspheres followed diffusion controlled zero order kinetics.

CONCLUSION

Novel dosage form of Glibenclamide microspheres was found to be more effective as it promotes the sustained release of Glibenclamide. And it is more effective in terms of reducing dose frequency.

Journal Articles

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