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FORMULATION AND EVALUATION OF MICROSPHERES OF GLIPIZIDE

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ABSTRACT

Microspheres constitute an important part of drug delivery systems by virtue of their small size and reliable means to deliver the drug to the target site with specificity. However, the advantages of microspheres. The prepared microspheres were characterized for various physicochemical parameters such as particle size, percentage yield, encapsulation efficiency, scanning electron microscopy, *in-vitro* drug release and kinetics study. The i*n-vitro* drug release studies were performed in buffer media and shown the controlled release pattern of drug up to 10 hours. Drug release from the microspheres was found following zero order release kinetics with non-fickian release mechanism. The satisfactory results were obtained in all prepared formulations and based on the results F4 was best formulation when compared to other formulations

KEYWORDS: Microspheres, Glipizide, Eudragit, Invitro release, regression co-efficient.

1. INTRODUCTION

Microspheres are free flowing powders consisting of spherical particles of size ideally less than 125 microns that can be suspended in suitable aqueous vehicle and injected by an 18 or 20 no needle. Microspheres are small matrices release drug at a faster rate and thus, by using particles of different sizes, various degrees of controlled-release can be achieved. In order to overcome uptake of intravenously administered microspheres by the RES and promote drug targeting to tumours with good perfusion magnetic microspheres were developed. Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently dosage

forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact in formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems.[1-3] They have varied applications and are prepared using various polymers.[4-8] Microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption Glipizide is a second generation oral anti-diabetic drug used in type 2 diabetes (non Insulin dependent diabetes mellitus) that can acutely lower the blood glucose level in humans by stimulation the release of insulin from the pancreas. It's shot biological half life (0.3+0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg per day.[9,10,11,12]

Single unit dosage form of Glipizide causes gastric irritation and when converted to multiple unit dosage like microspheres causes no gastric irritation.[13] The gastro retentive drug delivery system of Glipizide can be prepared to improve the bioavailability and extend the release of Glipizide by retaining the system in the stomach for prolonged period of time.[14]

2. MATERIALS AND METHODS

2.1. Polymer Profile

Hpmc

Semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

Eudragit

Eudragits are biocompatible copolymers which were synthesized from acrylic and meth acrylic acid esters and have been used in the formulation of dosage forms especially matrix tablets for oral sustained release and in tablet coating. They have also been used in the microencapsulation of drugs.

Ethyl cellulose

A derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups, mainly used as a coating material and release modifier.

2.2. Expermental Procedure

Preparation of 0.1N Hydrochloric Acid (pH1.2)

8.5ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000ml.

Preparation of Standard Curve of Glipizide With 0.1 N HCL

100mg of Glipizide was weighed and dissolved in a small portion of methylene chloride (Dichloromethane) and make the volume with 0.1 N HCL in a 100 ml volumetric flask then the volume was made up to 100ml with 0.1 N HCl. This was the primary stock solution contained concentration of 1000 g/ml. From this primary stock solution 1ml was pipette out transferred in to a 100ml volumetric flask and volume was made up to 100ml with 0.1N HCL which contained the concentration of 100mg/ml. From the stock solution again 10ml was pipette out and diluted up to 100 ml with 0.1 N HCL to get concentration of 10mg/ml.

From third stock solution equivalent to 1-10mg were pipette out in to 10ml volumetric flask and volume was made up to 10 ml with 0.1N HCL. The absorbance of these solutions was measured against the 0.1 N HCl as blank at 276 nm using UV-Visible double beam spectrophotometer. Then the calibration curve was plotted taking concentration in mg/ml on X-axis and absorbance on Y-axis.

Preparation of Phosphate Buffer pH: Placed 11.45 gm of potassium di hydrogen phosphate and 28.80 gm of disodium hydrogen phosphate and made up to 1000ml with distilled water.

Preparation of Standard Curve of Glipizide with Phosphate Buffer pH 6.8

100mg of Glipizide was weighed accurately and dissolved in a small portion of Methylene chloride (Dichloromethane) and make the volume with phosphate buffer pH 6.8 in a 100 m volumetric flask. This was the primary stock solution contained concentration of 1000mg/ml. From this primary stock solution 10 ml was accurately pipette out and transferred in to 100 ml of volumetric flask and volume made up to 100 ml with phosphate buffer pH 6.8 which contained the concentration of 100 mg /ml. From second stock solution again 10 ml was pipette out and dilute up to 100ml with phosphate buffer pH6.8 to get concentration of 10 mg/ml.

From third stock solution equivalent to 1-10mg were pipette out in to a series of 10 ml volumetric flask and volume made up to 10 ml with phosphate buffer pH 6.8. The absorbance

of this solution was measured against the phosphate buffer pH 6.8 as a blank at nm using UV-Visible double beam spectrophotometer. Then a calibration curve was plotted taking concentration in mg/ml on X-axis and absorbance on Y-axis.

Preparation of Floating Microspheres of Glipizide:-Floating micro spheres containing Glipizide was prepared using emulsion solvent diffusion technique. The drug to polymer ratio used to prepare the different formulation was 1:7. The polymer content was a mixture of Eudragits RS100 (ES100).

Methodology

Preparation of Glipizide microspheres: Microspheres containing Glipizide was prepared using emulsion solvent diffusion technique. The drug to polymer ratio used to prepare the different formulations was determined. The polymer content was a mixture of Eudragit RS 100Hydroxypropylmethyl cellulose (HPMC) and Ethyl cellulose. The drug polymer mixture is dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcohol solution (200 ml). The solution was stirred with a propeller-type agitator at 40°C temperature for 1 hour at 300 rpm. The formed floating microspheres were passed through sieve no.12 and washed with water and dried at room temperature in a desiccators.

Evaluation of Microspheres

Particle size analysis: Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of floating microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles. The particle size of the microspheres was determined by using optical microscopy method.

Percentage Yield: The prepared microspheres were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres and calculated using the formula.

$$Yield\% = W/Wt \times 100$$ Where,

W=Practical Weight of prepared microspheres,

Wt=Original weight of drug+ polymer.

In-vitro Release Studies

The drug release rate from floating microspheres was carried out using the USP type II dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with 0.1 N HCI and analysed spectrophotometrically at 276 nm to determine the concentration of drug present in the dissolution medium. The dissolution studies were repeated using phosphate buffer pH 6.8 as dissolution medium.

Kinetic modelling and mechanism of drug Release: The release data obtained were fitted to zero order, first order, Higuchi, Peppas and Hixon Crowel equation to determine the corresponding release rate and mechanism of drug release from the mucoadhesive microspheres.

3. RESULTS AND DISCUSSION

3.1. Results

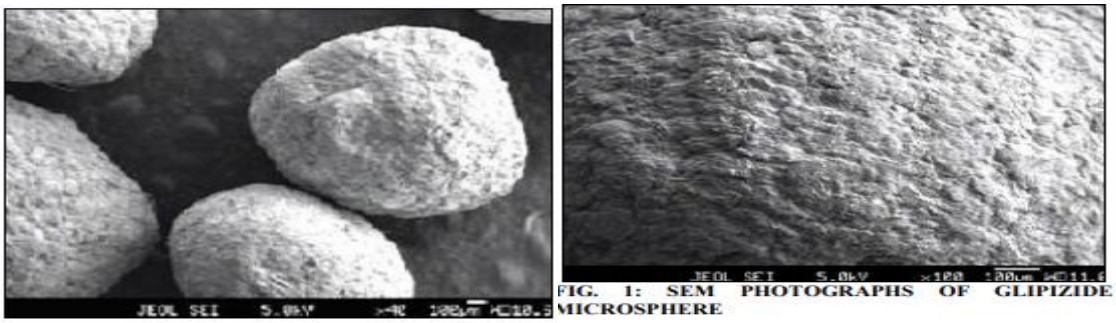

Fig 1: SEM images of Glipizide Microspheres.

Table 1: Flow properties of Different Formulations.

Formulation Batch	Bulk density (g/cc)	Tapped Density (g/cc)	Carrs Index (%)	Hausners Ratio	Angle of Repose (Degrees)
F1	0.416	0.5	16.8	1.20	7.28
F2	0.38	0.7	45.12	1.85	19.2
F3	0.384	0.71	45.91	1.84	16.42
F4	0.25	0.384	34.0	1.5	17.2
F5	0.45	0.55	18.18	1.2	18.8
F6	0.5	0.714	29.97	1.4	15.3
F7	0.416	0.5	16.8	1.20	11.29
F8	0.5	0.55	9.09	1.1	13.37
F9	0.38	0.5	24.0	1.3	20.11

Table 2: Drug Entrapment for Different Formulations.

Formulation	Drug entrapment(%w/w)
F1	86.51
F2	83.35
F3	81.18
F4	80.50
F5	76.12
F6	71.34
F7	68.52
F8	65.15

Table-3: IN-vitro dissolution characteristics of F1-F5 formulations of Glipizide Microspheres.

S.No	Time (hrs)	F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	01.0	43.70±1.06	22.79±1.24	23.59±1.14	26.41±1.19	20.77±0.32
3	02.0	45.84±1.11	27.33±1.29	28.35±1.13	34.17±1.24	24.84±1.26
4	03.0	48.12±1.16	33.25±0.27	34.80±1.32	44.28±1.03	26.15±1.34
5	04.0	50.38±1.28	44.22±1.34	40.88±1.26	56.40±1.17	35.68±0.37
6	05.0	53.12±1.23	54.45±1.08	50.45±1.24	71.05±1.06	48.03±1.44
7	06.0	55.69±1.39	61.88±0.37	59.88±1.19	74.57±1.07	55.08±0.46
8	07.0	58.06±1.42	65.69±1.05	68.32±1.05	78.54±1.14	58.14±1.55
9	08.0	61.48±1.29	67.96±0.53	73.23±0.59	81.73±1.12	60.61±1.60
10	09.0	64.59±1.52	71.54±0.094	76.45±0.57	86.11±1.24	63.37±0.61
11	10.0	67.82±1.34	74.40±1.02	79.87±0.65	89.82±1.28	66.81±1.08
12	11.0	71.99±1.03	78.66±1.16	83.59±1.34	93.77±1.34	69.77±0.06
13	12.0	80.57±1.25	82.30±1.25	87.84±1.27	99.63±0.45	72.82±0.18

Table 4: IN -vitro dissolution characteristics of F6-F8 formulations of Glipizide Microspheres.

s.no	Time (hrs)	F6	F7	F8
1	0	0	0	0
2	01.0	38.14±0.24	28.28±0.52	17.79±1.12
3	02.0	40.04±0.36	29.68±0.78	20.69±1.14
4	03.0	41.85±0.38	31.06±1.13	21.43±1.32
5	04.0	43.91±0.19	32.59±1.27	22.57±0.48
6	05.0	45.81±1.07	34.12±0.24	23.88±0.67
7	06.0	48.38±1.42	35.71±0.39	24.60±1.06
8	07.0	50.18±1.05	37.26±0.57	25.90±1.54
9	08.0	52.67±0.57	39.19±1.05	26.97±1.16
10	09.0	56.04±0.34	40.79±0.38	28.43±1.24
11	10.0	57.87±0.78	42.83±1.59	29.75±1.03
12	11.0	60.63±1.15	44.76±1.76	31.34±0.26
13	12.0	71.24±1.26	51.27±1.81	32.99±0.48

Fourier Transform Infra-red Spectroscopy (FT-IR) Analysis

The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during microencapsulation process. Fourier transform infra-red spectrum of pure Glipizide, Eudragit, HPMC, EC, Physical mixture and floating microspheres (formulation) were recorded.

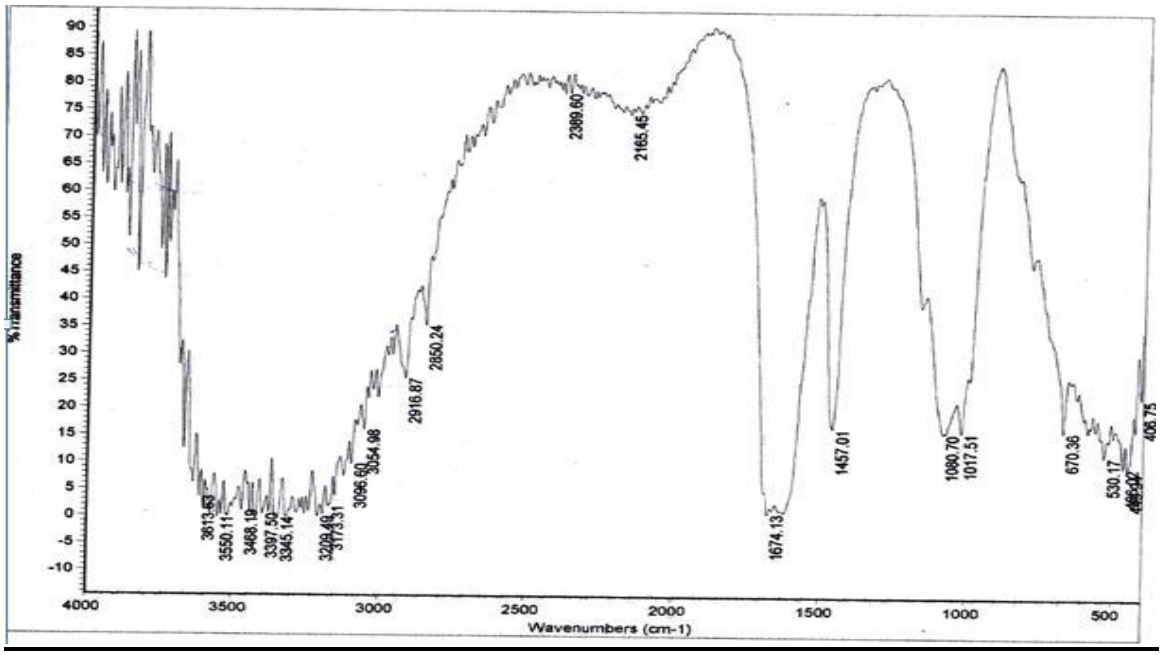

Fig-2-FTIR Spectra of Glipizide pure drug.

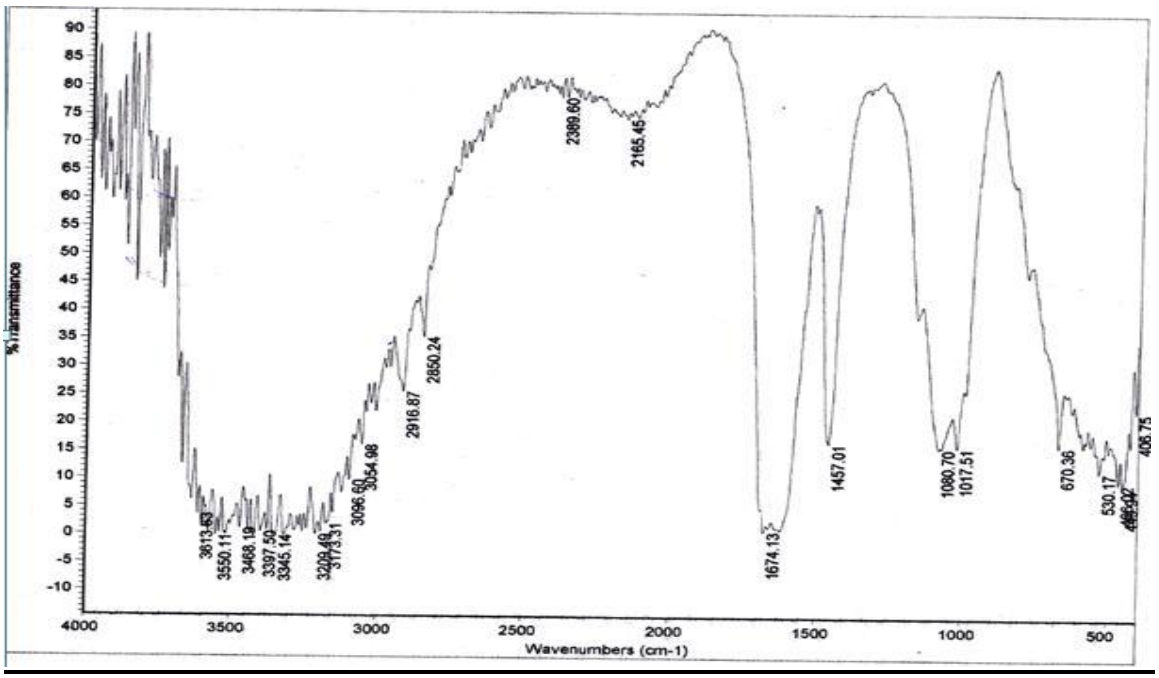

Fig-3-FTIR Spectra of Glipizide optimized formulation.

Table-5-Regression co-efficient (R^2) values, of Glipizide microspheres according to different kinetics models.

s.no	Formulation code	zero order (R^2)	First order (R^2)	Higuchi (R^2)	Peppas (n)
01	F1	0.9959	0.9905	0.9840	0.1882
02	F2	0.9124	0.9950	0.9756	0.1864
03	F3	0.9306	0.9750	0.9786	0.1888
04	F4	0.8919	0.9581	0.9627	0.1996
05	F5	0.9369	0.9975	0.9815	0.4817
06	F6	0.9257	0.9685	0.9535	0.4855
07	F7	0.9307	0.9833	0.9706	0.4900
08	F8	0.9828	0.9876	0.9722	0.5092

3.2. DISCUSSION

The present study was an attempt to develop and evaluate Microspheres drug delivery system. All microspheres formulations were found spherical shape and having particle size in the range of 498- 520 µm. The microspheres showed some porous structure. Release of the active constituents is an important consideration in case of mucoadhesive microspheres. Scanning electron microscopy was performed to characterize the surface morphology of the formed microspheres. The in-vitro release studies of glipizide from prepared microspheres were carried in the buffers for a period of 10 hrs. The overall cumulative % releases for F1 to F8 were found to be about 90 % at the end of 10 hrs. Basing on the release characteristic F4 is found to be the optimized formula. Kinetic and mechanism of drug release from all formulation was evaluated on the basis of zero order Higuchi equation and peppas model.

4. CONCLUSION

Floating hollow microspheres are prepared with enteric coated polymer (Eudragit RS 100) successfully by the solvent evaporation technique. In-vitro data obtained from floating microspheres of Glipizide showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion (Anamolous transport diffusion) was found to be the main release mechanism. Thus the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intra gastric condition. It increases the bioavailability of dosage form with prolong effect, hence improves the patients compliances. Mean particle size for all formulations were varied, due to change in drug and polymer ratio. Drug release pattern was evaluated in 0.1 N HCl. Release rate of F1, F2, F3 formulations were found to be slow and incomplete in both dissolution medium. F4

formulation showed best appropriate balance between buoyancy and drug release rate, which can be considered as a best fit for floating microspheres. Zero order plots for F4 formulation was found to be linear in dissolution medium, that indicates it may follow zero order mechanism. The design system F4 floats in the stomach and prolongs the gastric residence time (GRT) consequently, providing sustained action.

5. ACKNOWLEDGEMENT

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