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Original Article

Formulation and In Vitro Evaluation of Floating Microspheres of Glipizide

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ABSTRACT

Objective: The aim of the present study is to develop floating microspheres of Glipizide, an oral rapid- and short-acting anti-diabetic drug from the sulfonylurea class. Glipizide is rapidly and completely absorbed from the gastrointestinal tract. Single unit dosage form of Glipizide causes gastric irritation and when converted to multiple unit dosage like microspheres causes no gastric irritation and maintains a constant drug concentration in the blood plasma for a longer period of time as glipizide is rapidly absorbed and eliminated from the body.

Methods: Preformulation studies like identification tests, solubility analysis, melting point determination, compatibility studies and evaluation of formulation blend are determined by suitable methods. Floating microspheres of Glipizide were prepared by 'emulsion solvent evaporation technique'by employing polymers like ethylcellulose, HPMC K4M, HPMC K15M and solvents like ethanol, dichloromethane and tween80. Floating microspheres are evaluated for drug entrapment efficiency, particle size by microscopic method, shape and surface morphology by scanning electron microscopy, in vitro drug release studies.

Results: The floating microspheres were evaluated for angle of repose, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy, drug release and DSC(Differential Scanning colorimetry), of microspheres. Results show that as the concentration of polymer increases, the particle size, percentage yield, in vitro buoyancy and drug release from microspheres varies. Percentage drug release at the end of 12 hrs was found to be 91%. Microspheres that are prepared by HPMC K15M exhibited excellent Micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release when compared to HPMC K4M and Ethyl Cellulose polymer.

Conclusion: Results clearly indicate that floating microspheres of Glipizide offers a suitable, practical approach to achieve a prolonged gastric residence time and continuous release of the medication over an extended period of time thus oral bioavailability of the drug and subsequent efficacy is improved.

Keywords: Glipizide, Floating Microspheres, Solvent Evaporation Technique, In-vitro Buoyancy, Percentage Drug Release

1. INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. Glipizide is used to control hyperglycemia in type II diabetes. [1] It is commercially available as conventional tablets. Drugs that are easily

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absorbed from the gastrointestinal tract (GIT) and having a short half life are eliminated quickly from the blood circulation eg. Glipizide . To avoid this problem, the oral sustained or controlled release (CR) systems have been developed as these systems release the drug slowly from the delivery systems and maintain a constant drug concentration in the blood plasma for a longer period of time. Single unit dosage form of Glipizide causes gastric irritation and when converted to multiple unit dosage like microspheres causes no gastric irritation. [2] 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.

2. MATERIALS AND METHODS

Glipizide is used to control hyperglycemia in type-II diabetes was procured from Hetero Drugs Ltd, Hyderabad ,Ethyl cellulose and Tween -80 were procured from Thomas Baker chemicals, Mumbai , HPMC K 4 M and HPMC K 15 M were purchased from Yarrow Chem Products, Mumbai, Ethanol was procured from Fine Chem industries, Chennai.

2.1 Preformulation studies

Preformulation studies were carried on obtained samples of drug, excipients and drug-excipient granules to establish the necessary physicochemical characteristics of the drug substance and to establish drug compatibility with different excipients. Preformulation studies include identification tests, solubility analysis, melting point determination, compatibility studies and evaluation of formulation blend. [3]

IR Spectroscopy

Identification of the chemicals procured is done by IR spectroscopy, in which FT-IR spectrum of the obtained sample of chemicals were compared with standard FT-IR spectra of the pure chemicals. [3, 4]

Solubility analysis

Solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used. [5]

Melting point determination

Melting point determination of the obtained sample was done by open capillary method. Drug was taken in a capillary tube whose end was sealed by means of flame. The capillary tube was placed in a melting point apparatus to measure the melting point. [5] Melting point is the first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.

Drug-Excipient compatability studies

Before producing the actual formulation, compatibility of Glipizide with different polymers was tested using FT-IR spectroscopy and differential scanning calorimeter (DSC) studies.

FT-IR Spectroscopy

In the present study Potassium bromide pellet (KBr) method was employed. The samples were thoroughly blended with dried Potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in spectrophotometer and spectra of pure drug and drug-excipient combinations were recorded. [6]

The FT-IR spectra of the samples were compared with FT-IR spectra of the pure drug and excipients.

Differential Scanning Calorimeter (DSC) Studies

Thermograms were obtained by using a differential scanning calorimeter at a heating rate of 10ºC/min over a temperature range of 50-300 ºC. The sample was hermetically sealed in an aluminium crucible. [6]

2.2 *Formulation and composition*

Preparation of floating microspheres of Glipizide

Floating microspheres of Glipizide were prepared by **'Emulsion Solvent Evaporation Technique'** [7, 12]

Accurately weighed drug and polymers in different ratios are dissolved in the solvents like ethanol and dichloromethane (1:1 ratio) and is given in Table No.1. The drug solution is slowly introduced in to 100ml of water containing 0.01 ml of Tween 80 and 5 ml n-hexane under continous stirring to form a homogenous solution, which is maintained at 40˚C temperature and at an agitation speed of 800 rpm for one hour to allow the volatile liquid to evaporate. The microspheres formed were filtered and air dried for 24 hours at room temperature.

Table 1: Composition of Glipizide Floating microspheres

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Glipizide	40	40	40	40	40	40	40	40
Ethyl cellulose	0.5	1	1.5	2	0.5	1	1.5	2
HPMC K4M	0.3	0.3	0.3	0.3	-----	-----	-----	-----
HPMC K15M	-----	-----	-----	-----	0.3	0.3	0.3	0.3
Ethanol: DCM (mL)	10: 10	10: 10	10: 10	10: 10	10: 10	10: 10	10: 10	10: 10
Tween80(mL)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

2.3 Evaluation and characterization of prepared microspheres

Production yield (%)

The production yield of microspheres of various batches were calculated using the weight of the final product after drying with respect to the initial weight of the drug and polymer used for the preparation of microspheres and percentage production yield was calculated as per the following formula. [8]

$$\text{Percentage yield}(\%) = \frac{\text{Practical mass (Microspheres)}}{\text{Theoritical mass (Drug + Polymer)}} \times 100$$

Particle size analysis

Many methods are available for determining the particle size, such as optical microscopy, sieving, sedimentation and particle volume measurement. Optical microscopy is most commonly used for particle size determination. [9]

The average particle size is determined by using Edmondson's equation:

$$D_{mean} = \frac{\sum nd}{\sum n}$$

Where, n - Number of microspheres observed. d - Mean size range.

Shape and surface morphology

The shape and surface characteristics of the prepared microspheres were evaluated by means of scanning electron microscopy. The scanning electron microscopy samples were prepared by lightly sprinkling the microspheres powder on a double adhesive tape, which is stucked to an aluminium stub. The stubs were then coated with gold using a sputter coater under high vacuum and high voltage to achieve a film thickness of 30nm. The samples were then imaged using a 20KV electron beam. [10]

Drug entrapment efficiency

100 mg of floating microspheres were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with ethanol. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl solution. The solution was filtered and dilutions were made and the absorbance was measured against blank solution spectrometrically at 278nm. The amount of drug entrapped in the floating microspheres was calculated by using the formula. [10, 11]

Percentage Drug entrapment = (Actual drug content/Theoretical drug content) X100

In-vitro buoyancy

100 mg of floating microspheres about 100 mg was placed in the dissolution medium of 500 ml of stimulated gastric fluid (pH1.2), which was placed in USP dissolution apparatus type II (rotating paddle). The temperature of dissolution medium was maintained at 37±0.5°C and was agitated by paddle at speed of 100 rpm for 12 hours. After agitation the microspheres that floated over the surface of the

medium and those that settled down at bottom of the flask were recovered separately and dried. The percentage buoyancy of the floating microspheres were calculated by using the formula

Buoyancy % = [W f/ (W f+ W s)] x 100

Where W f and W s are the weight of the floating and settled microspheres respectively.

In-vitro drug release studies

The *in-vitro* drug release studies of Glipizide from formulations were carried out in acid buffer pH 1.2 for 2 hours and then continued in phosphate buffer pH 6.8 for 10 hours. [13] The studies were performed in USP dissolution apparatus II, (Dissolution Test Apparatus, Model DS 8000, LAB INDIA Pvt Ltd) at 37 ± 0.5° C and 100 rpm speed. Samples were taken at hourly interval and analyzed for Glipizide content at 237 nm by using UV–visible spectrophotometer, (Mode No. UV 3000+, LAB INDIA Pvt Ltd)

Drug release kinetics

The type of release of drug Glipizide from the formulated floating microspheres was studied by curve fitting analysis of the dissolution data of the optimized formulation in following models. [14, 15] 1. Zero order 2. First order 3. Higuchi model 4. Korsemeyer and Peppas kinetic model.

The analysis of drug release mechanism from the pharmaceutical dosage form is an important but complicated process and it is practically evident in case of matrix systems. As model-dependent approach, the dissolution data are fitted to four popular release models such as a zero-order, first order, Higuchi and Peppas equations (Higuchi, 1963; Peppas, 1985; Ritger, 1987). The order of drug release from matrix systems was studied by using Higuchi equation and Erosion equation. The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates fickian diffusion and values of n between 0.5 and 1.0 or n=1.0 indicate non-fickian mechanism. In case of a cylinder n=0.45 instead of 0.5, and 0.89 instead of 1.0. This model was used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon being involved.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies

Identification studies

IR Spectroscopy

Functional group frequencies of Glipizide were in the reported range which indicates that the obtained sample was of Glipizide and was pure. [16]

Table 2: Reported and observed IR frequencies of Glipizide

Functional group	Reported frequencies (in cm^{-1})	Observed frequencies (in cm^{-1})
N-Methyl piperazine ring vibrations		
C-N stretching		1222.91cm^{-1}
Symmetrical stretching of CH_3	2960-2850 cm^{-1}	2925.15cm^{-1}
Benzamide ring vibrations		
N-H stretching	3400-3100 cm^{-1}	3337.93cm^{-1}
In plane C-C stretching	1315 cm^{-1}	1313.57cm^{-1}
Out plane C-H Vibration	830-800 cm^{-1}	808.20 cm^{-1}
Methyl benzene ring vibrations		
C-H stretching	3050-3000 cm^{-1}	3009.05cm^{-1}
Amino pyridine ring vibrations		
C-N stretching	1360-1180 cm^{-1}	1279.81cm^{-1}
Out plane C-H deformation	830-800 cm^{-1}	808.20cm^{-1}
In plane C-H deformation	1500-1300 cm^{-1}	1418.69cm^{-1}
Pyridine ring vibrations		
C=N stretching	1700-1600 cm^{-1}	1600.41cm^{-1}
Peptide group vibrations		
N-H stretching	3400-3100 cm^{-1}	3337.93cm^{-1}
Out plane N-H deformation	555 cm^{-1}	551.66cm^{-1}
C=O stretching	1900-1600 cm^{-1}	1655.94cm^{-1}
Mesylate group vibrations		
S=O stretching	830-880 cm^{-1}	855.46 cm^{-1}
Asymmetric C-H deformation	1470-1430 cm^{-1}	1476.56 cm^{-1}

Solubility analysis

Sample of Glipizide was found to be soluble in water, chloroform, methanol, dimethylsulphoxide. [17]

Melting point determination

The melting point of obtained sample was found to be 170°C which is within the reported range of 169-171°C. It complies with the standards thus indicating

that, the sample was pure [18] without any impurities as presence of impurities widen the melting point range.

3.2 Drug-excipient compatability studies

FT-IR Spectroscopy

The FT-IR spectra of pure drug alone and along with the polymers are shown in the figures 1 to 3 which indicate no interaction between the drug and the polymers when compared with the FT-IR spectrum of pure drug as there are no prominent changes in peaks of FT-IR spectrum.

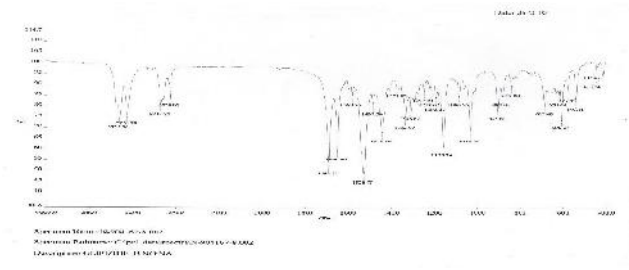

Fig 1: FT-IR Spectra of Glipizide

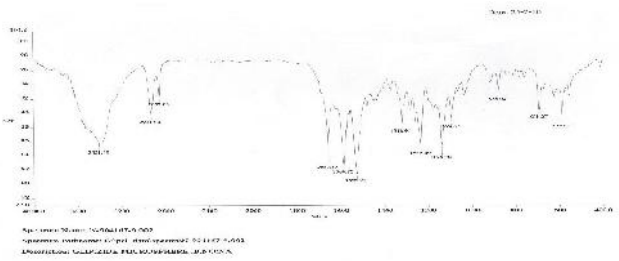

Fig 2: FT-IR spectra of HPMC K4M

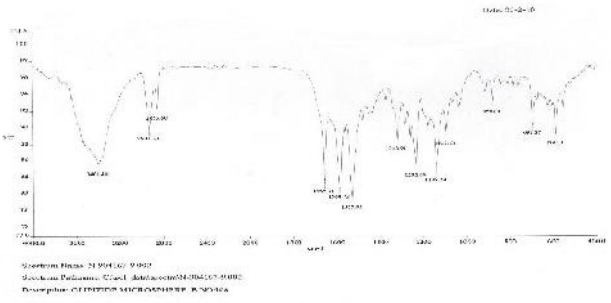

Fig 3: FT-IR spectra of Glipizide With HPMC K15M

DSC Studies

The thermo gram of Glipizide exhibited an endothermic peak at 204 ºC corresponding to its melting point range. [19, 20] The thermo grams of formulation does not show profound shift in peaks, suggesting that drug has almost same melting point in its formulation. Hence it was concluded that drug had not interacted with the polymer, which indicates compatibility

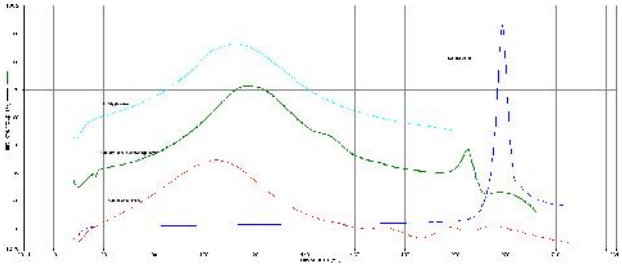

Fig 4: DSC Thermogram of Drug, Polymer, Physical mixture and Formulation

3.3 Characterization of floating microspheres of Glipizide

The Floating microspheres of Glipizide were characterized for flow properties like angle of repose, bulk density, tapped density, Carr's index, and drug content. [21] Angle of repose was less than 35° and Carr's index values were less than 12 for the raw material of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content was more than 90 % for all the granules of different formulations.

Table 3: Physical Properties of Glipizide (API)

Formula Code	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
API	30	0.44	0.49	11.60	1.13

Standard Calibration curve of Glipizide

Table 4: Calibration curve data for Glipizide in 0.1N Hydrochloric acid.

S. No.	Concentration	Absorbance
1	0	0
2	1	0.100
3	2	0.235
4	3	0.320
5	4	0.432
6	5	0.534
7	6	0.662
8	7	0.745
9	8	0.874

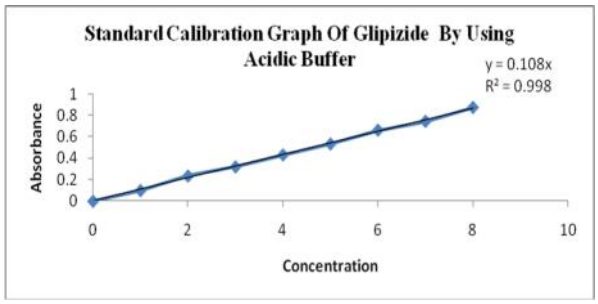

Fig 5: Standard calibration curve of Glipizide in 0.1N HCl

Table 5: Calibration curve data for Glipizide in phosphate buffer.

S. No.	Concentration	Absorbance
1	0	0
2	1	0.101
3	2	0.233
4	3	0.342
5	4	0.417
6	5	0.513
7	6	0.633
8	7	0.742
9	8	0.831

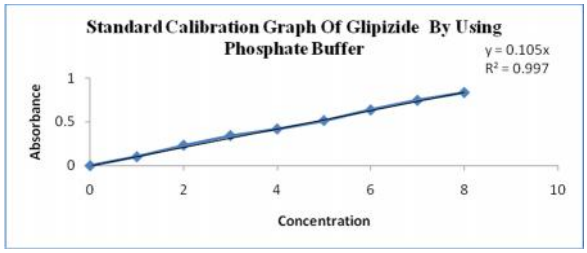

Fig 6: Standard calibration curve of Glipizide in phosphate buffer

From the standard curve of 0.1 N HCl and Phosphate buffer pH 6.8 it was observed that the drug obeys Beer – Lambert's law in concentration range of 0 – 30µg / ml in the medium.

3.4 Characterization of formulated floating microspheres of glipizide [22]

Percentage yield

The production yield of Floating microspheres prepared by Solvent evaporation method was found to be between 80.46 to 87.12%. It was observed that as the polymer ratio in the formulation increases, the product yield slightly decreases. The probable reason behind this may be the high viscosity of the solution which decreased its syringe ability resulting in blocking of needle and wastage of the drug- polymer solution which ultimately decreased the production yields of microspheres.

Table 6: Evaluation and characterization of prepared Floating microspheres

S No	Formulation Code	Percentage Yield	Drug entrapment efficiency	Mean particle size (µm)	In-vitro buoyancy
1	F1	87.12	62.15±1.13	110±2.10	73.12±1.32
2	F2	85.56	72.11±1.20	135±8.23	85.14±2.25
3	F3	82.20	83.61±2.33	205±2.35	91.05±1.75
4	F4	86.02	86.12±1.24	207±1.02	90.91±2.75
5	F5	84.23	67.63±0.68	145.3±2.32	66.62±1.12
6	F6	80.62	77.91±2.26	115±3.21	74.47±0.63
7	F7	86.46	84.55±1.32	168±1.02	82.25±1.2
8	F8	83.54	85.63±1.08	226±2.35	88.05±1.54

Particle size analysis

The mean particle size of microspheres as determined by optical microscopy by using stage micrometer and ocular micrometer is shown in table 7. With the increase in the EC concentration the particle size increased from F1 to F4, F5 to F8. This is because the viscosity of the polymer increases with increasing polymer concentration, which in turn decrease the stirring efficiency. The polymer rapidly precipitates leading to hardening and avoiding further particle size reduction during solvent evaporation.

Table 7: Particle Size Analysis Glipizide floating microspheres

S No	Formulation code	Mean particle size (µm)
1	F1	110±2.10
2	F2	135±8.23
3	F3	205±2.35
4	F4	207±1.02
5	F5	145.3±2.32
6	F6	115±3.21
7	F7	168±1.02
8	F8	226±2.35

Shape and surface morphology

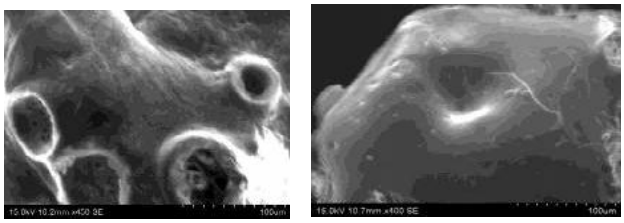

Fig 8, 9: Scanning electron microscopy of Glipizide floatingmicrospheres of optimized formulation F8

In-vitro buoyancy

The microspheres floated over the surface of dissolution media for prolonged period of time without any apparent gelation. The pores on the microspheres surface also helps in the floating which was confirmed by SEM. So as the concentration of EC increased from F1-F5 and F5-F8 the number of pores increased because of which buoyancy percentage also increased. Buoyancy percentage of the microspheres for formulations F1-F4 was in the range of 74.31% to 91.02% and for formulations F5-F8 was 66.62% to 89.01% for 12 hours as shown in the table 4:

Table 8 : In-vitro buoyancy Glipizide floating microspheres

S.No	Formulation code	In-vitro buoyancy
1	F1	73.12±1.32
2	F2	85.14±2.25
3	F3	91.05±1.75
4	F4	90.91±2.75
5	F5	66.62±1.12
6	F6	74.47±0.63
7	F7	82.25±1.2
8	F8	88.05±1.54

In-vitro drug release studies

The results of the *in-vitro* dissolution studies data of all the formulations were shown in table 9. The plots of Cumulative percentage drug release Vs Time were plotted. [23] Figure 16 shows the comparison of cumulative percentage drug release for all the formulations.

The formulation F8 containing HPMC K 15 M has showen better drug release (90.82%).

Table 9: In-vitro drug release data of Glipizide floating microspheres using HPMC K 4M , HPMC K15 as polymer.

Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8
2	20±1.2	23±2.1	25±0.3	25±1.6	24±0.2	28±1.1	30±1.4	29±1.2
4	36±1.8	36±0.6	39±1.8	41±0.4	44±0.6	45±0.6	50±1.2	51±0.4
6	44±1.3	44±0.2	45±1.2	46±1.2	46±1.8	48±0.8	55±0.6	58±0.1
8	58±1.5	53±1.2	55±0.5	65±0.7	65±1.2	67±0.2	70±0.8	71±1.4
10	64±1.1	65±0.8	65±0.2	69±0.9	69±0.9	71±1.7	84±0.2	86±0.8
12	71±1.8	72±0.4	74±1.8	76±1.5	78±1.1	80±1.3	89±0.4	91±0.3

Based on the results of evaluation tests , formulation F8 (combination of ethyl cellulose, HPMC K -15 M) was found to be the best for the oral delivery of Glipizide that complied with all the parameters and was found to have better in- vitro buoyancy and better drug release of 91% at the end of 12 hrs.

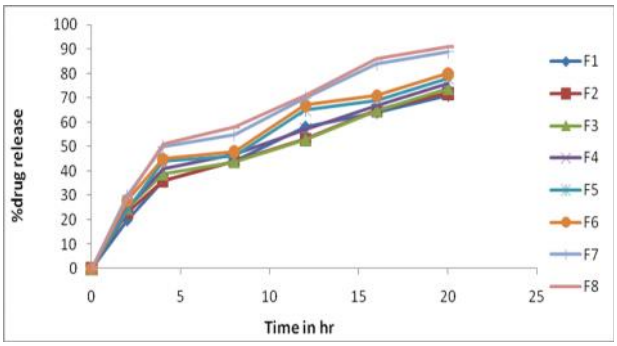

Fig 10: Cumulative drug release profile of Glipizide floating microspheres F1-F8 formulations containing HPMC K4M, HPMC K15M polymers

Drug release kinetics

The release rate kinetic data for the F8 is shown in Table.No.10. As shown in Figure. No. 10, drug release data was best explained by First order equation, as the plots showed the highest linearity (r^2 = 0.976), followed by Higuchi's equation (r^2= 0.970) . As the drug release was best fitted in First order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

As shown in Figure.No 14 the corresponding plot (log cumulative percent drug release vs log time) for the Korsmeyer-Papas equation indicated a good linearity (r^2= 0.960). The diffusion exponent "n" was between 0.45-0.89, which indicates the diffusion mechanism is non-fickian diffusion. And indicates that the drug release was more than one process (both diffusion and dissolution).

Table 10: Mathematical modelling and drug release kinetics of F8 optimized formulation.

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
0	0	1	-	-	100	2
2	0.30103	1.414214	29	1.462398	71	1.851258349
4	0.60206	2	51	1.7075702	49	1.69019608
6	0.90309	2.828427	58	1.763428	42	1.62324929
8	1.079181	3.464102	71	1.8512583	29	1.462397998
10	1.20412	4	86	1.9344985	14	1.146128036
12	1.30103	4.472136	91	1.9590414	9	0.954242509

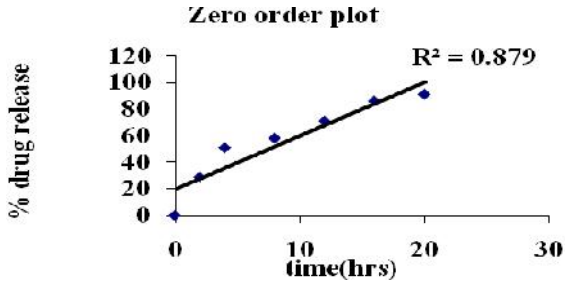

Fig 11: Zero Order Graph by F8 optimized Formulation

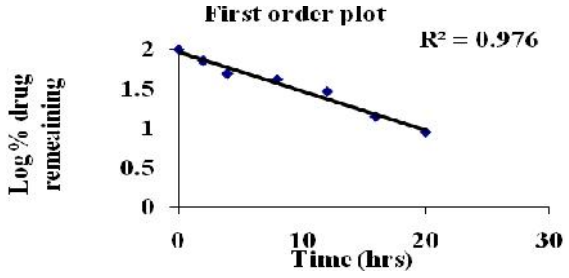

Fig 12: First Order Graph by F8 optimized Formulation

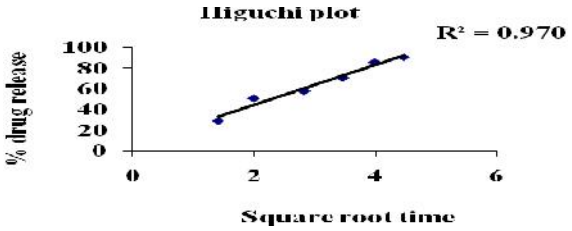

Fig 13: Higuchi Plot by F8 optimized Formulation

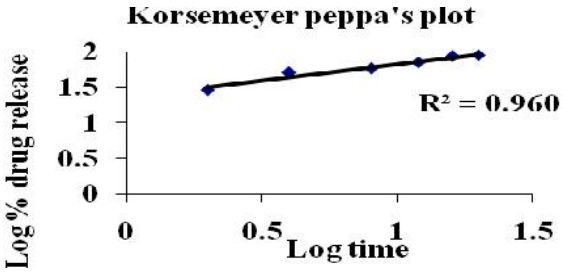

Fig 14: Korsmeyer-Peppas plot by F8 optimized Formulation

Stability studies

Optimized formulation F8 was chosen for stability studies based on their percentage yield, percentage drug entrapment efficiency and *in-vitro* drug release characteristics. [23] The stability data showed that there was no change in the appearance of the microspheres indicating that the formulations were stable at all the conditions to which they were exposed. It was observed that there was slight reduction in the drug content of the Floating microspheres which were stored at 40°C / 75% RH at the end of 90days and no significant change in drug content were observed for formulations stored at room temperature and at 5°C.

In-vitro drug release studies for all the Optimized formulation F8 were carried out at the end of 90 days and did not show any significant change in drug release and the stability study data is given the Table No.11 and 12. Thus, we may conclude that, the drug does not undergo degradation on storage**.**

Percentage drug entrapment efficiency of the formulations

Table 11: Percentage drug entrapment efficiency of the selected formulations

Stability condition	Sampling (days)	% Drug entrapment efficiency
		F8
5°C/Ambient	30	85.63
	60	85.62
	90	85.62
25°C / 60 % RH	30	85.65
	60	85.62
	90	85.62
40°C / 75 % RH	30	85.65

	60	85.62
	90	85.61

Table 12: In-vitro drug release profile of the Optimized formulation F8 at the end of 90 days

Stability condition	Sampling (days)	% Drug release F8
5°C/Ambient	90	91
25°C / 60 % RH	90	90.95
40°C / 75 % RH	90	90.98

4. CONCLUSION

These results clearly indicate that formulating floating microspheres of Glipizide offers a suitable, practical approach to achieve a prolonged gastric residence time and continuous release of the medication over an extended period of time thus oral bioavailability of the drug and subsequent efficacy is improved.

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