INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION AND DEVELOPMENT OF GLIPIZIDE CONTAINING FLOATING MICROSPHERE

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ARTICLE INFO

Article history
Received 15/08/2015
Available online
31/08/2015

Keywords
Glipizide,
Floating Microspheres,
Solvent Evaporation Technique,
In- Vitro Buoyancy,
Percentage Drug Release.

ABSTRACT

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. 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 employing polymers like ethylcellulose, poly vinyl alcohol and solvents like methanol, 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 exhibited excellent Micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release when compared to HPMC and Ethyl Cellulose polymer. 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.

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*Please cite this article in press as **Dheerendra Singh Rathore** et al. Formulation and development of glipizide containing floating microsphere. Indo American Journal of Pharmaceutical Research.2015:5(08).*

INTRODUCTION

Floating Drug Delivery Systems (FDDS) are among the several approaches that have been developed in order to increase the gastric residence time of dosage forms. Both single and multiple unit systems have been developed. Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained controlled release formulations have been developed in an attempt to release the drug slowly into the gastro-intestinal tract and maintain an effective drug concentration in the blood over long period of time. However, such oral drug delivery devices have a physiological limitation of low gastric retention time. Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system in the absorption zone (stomach or upper part of small intestine), leading to diminished efficacy of the administered dose (Shinde and More, 2008; Singh et al 2009; Nayak et al 2010). To overcome these limitations, approaches being proposed to prolong the gastric residence time, include floating drug delivery systems, swelling or expanding systems, mucoadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices (Ma et al 2008). Floating drug delivery is of particular interest for drugs that (1) act locally in the stomach, (2) are primarily absorbed in the stomach, (3) are poorly soluble at an alkaline pH, (4) have a narrow window of absorption, and (5) are unstable in the intestinal or colonic environment (Jain et al 2006). To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (≈1.004 g/cm3). Diabetes is one of the major causes of death and disability in the world. Glipizide is used to control hyperglycemia in type II diabetes. It is commercially available as conventional tablets. Drugs that are easily 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. 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[1-6].

MATERIAL & METHODS

Glipizide is used to control hyperglycemia in type-I diabetes was procured from Micro labs Ltd, Hyderabad ,Ethyl acetate, Poly vinyl alcohol and Tween -80 were procured from Sigma-Aldrich, Mumbai and SD fine chemicals, Methanol was procured from Spectrochem Labs Ltd. Mumbai

Preformulation studies[7]

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.

Infra Red 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 FTIR spectra of the pure chemicals.

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

Differential Scanning calorimetry

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.

Formulation and composition[8-12]

Preparation of floating microspheres of Glipizide

Floating microspheres of Glipizide were prepared by using following table 1

Table 1: Formula for Method.

Batch	Drug/polymer ratio	Stirring rate in RPM
F1	1:1	600
F2	1:2	600
F3	1:3	600
F4	1:4	600
F5	1:5	600
F1.1	1:1	400
F1.2	1:1	800

***Evaluation and characterization of prepared microspheres*[13]**

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.

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.

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 spectrophotometrically at 278nm. The amount of drug entrapped in the floating microspheres was calculated by using following formula.

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

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).

RESULT & DISCUSSION

Preformulation studies

Solubility studies

The solubility of glipizide was found in methanol, dimethyl sulfoxide and water which was shown in table 2.

Table2: Solubility data of glipizide.

Solvent	Solubility(mg/ml) Trial I	Trial II	Trial III	Mean
Methanol(ml)	1.8	1.8	1.9	1.8±0.1
Dimethyl sulfoxide (ml)	2.0	2.1	2.1	2.05±0.1

Melting point determination

Melting point of glipizide was found to be 209^{O}C. It complies with standard thus indicating that the sample was pure without any impurity hidden during the melting point determination.

Drug-polymer compatibility studies.

IR spectroscopic studies

The IR studies was carried out and shown in figure 1 and table 3.

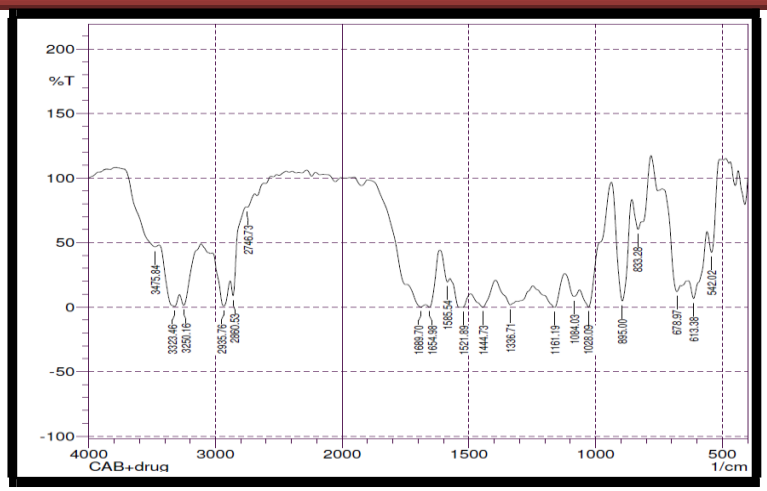

FIGURE1: IR SPECTRUM OF Glipizide and Polymer.

Table 4: Characteristic peaks of Glipizide and polymer.

S.No	Peak(cm^{-1})	nctional group
1	3325	$-NH_2-$
2	3250	-NH-
3	2935	-CH-
4	1689	-C=O-
5	1656	-C=N-
6	678	-S-

Characterization of floating microsphere of glipizide

Evaluation and characterization 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 21content. 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 5 Data of characterization of glipizide floating microspheres F1-F5 (CA).

Batch Code	anParticle size(µm)	Bulk Density (gm/ml)	Carr's Index	usner's ratio	Angle of repose(θ)
Glipizide	***	0.167 ±0.01	24.38±0.16	1.43 ±0.07	***
F1	164.56±3.78	0.277±0.01	4.77±0.16	0.96 ±0.07	22.73±0.22
F2	169.43±4.27	0.270±0.02	6.15±0.12	0.98 ±0.02	22.81 ±0.62
F3	172.64±1.47	0.267±0.02	8.33 ±0.21	0.99 ±0.08	21.27 ±0.56
F4	175.72±2.69	0.264 ±0.01	10.34±0.26	1.01 ±0.06	23.64 ±0.45
F5	189.64±0.53	0.261 ±0.03	12.62±0.19	1.04 ±0.04	24.70 ±0.59

Note:*** the particular test was not carried out for Glipizide drug (n=3±SD)

Table 6: Data of characterization of glipizide floating microspheres.

F6(CAB)-F7(CA)

Batch Code	Mean Particle size(μm)	Bulk Density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose(θ)
F6	205.62±5.54	0.256 ±0.04	14.56±0.09	1.07 ±0.09	27.33±0.19
F7	212.44±3.72	0.255±0.01	14.47±0.17	1.11 ±0.06	26.47±0.58

(n=3±SD)

Determination of percentage yield

The prepared microspheres were collected, weighed and percentage yield was calculated. The drug loading (%) and encapsulation efficiency (%) were found out by UV-Visible Spectrophotometer. This was shown in table 7.

Table 7: Data of Percentage yield, drug loading and encapsulation efficiency of Glipizide microspheres forF1-F5 (CA)

Batch code	Percentage Yield (%)	Drug loading (%)	Encapsulation efficiency (%)
F1	94.33	44.52±0.27	89.5±0.65
F2	93.24	27.46±0.02	82.66±0.35
F3	90.53	19.82±0.40	81.12±0.76
F4	87.55	15.51±0.85	77.74±0.62
F5	86.26	12.44±0.05	74.82±0.09

(n=3±SD)

Floating behavior (bauonacy)

The results are shown in table 8.

Table 8: Results of buoyancy(%)for Glipizide floating microspheres F1- F5(CA)

Batch code	Buoyancy (%)
F1	72.2±0.4
F2	73.3±1.5
F3	75.6±2.2
F4	76.7±3.4
F5	77.4±2.1

(n=3±SD).

In-vitro drug release study

The drug release studies were carried out using six basket dissolution apparatus USP type II. The microspheres were placed in an on reacting mesh that had a smaller mesh size than the microspheres. The dissolution medium used was 900ml of 1.2 pH buffer at 37°C. At specific time intervals, 5ml aliquots were withdrawn and analyzed by UV spectrophotometer at the respective λmax value 276 nm after suitable dilution against suitable blank. The withdrawn volume was replaced with an equal volume of fresh1.2 pH buffer.

Table9: Cumulative percentage drug release profile of Glipizide floating Microspheres F1-F5 (CA).

Time (hrs)	Batchcode F1	F2	F3	F4	F5
0.5	4.15±0.74	3.35±0.73	2.59±0.06	2.03±0.02	1.52±0.01
1	7.28±0.01	5.99±0.89	4.47±0.64	3.38±0.60	2.82±0.48
1.5	10.66±0.61	10.08±0.22	7.77±0.77	6.54±0.78	5.43±0.38
2	14.05±0.58	14.17±0.01	10.61±0.18	9.26±0.21	8.04±0.58
3	21.86±0.65	19.46±0.16	17.92±0.25	14.91±0.19	11.09±0.50
4	26.30±0.80	23.79±0.97	22.18±0.05	17.86±0.09	16.53±0.63
5	32.05±0.36	28.86±0.20	26.20±0.78	22.84±0.35	20.46±0.36
6	40.14±0.41	35.84±0.83	33.30±0.04	28.73±0.39	25.26±0.38
7	49.28±0.29	39.96±0.47	37.57±0.54	34.63±0.08	30.28±0.65
8	56.87±0.28	44.08±0.57	40.44±0.24	38.05±0.29	33.57±0.74
9	60.57±0.35	48.45±0.09	46.13±0.80	40.57±0.64	36.87±0.20
10	69.73±0.48	55.21±0.91	52.31±0.07	45.58±0.40	39.95±0.30
11	77.86±0.69	61.75±0.48	58.25±0.48	53.52±0.97	45.42±0.62
12	81.59±0.06	71.17±0.55	66.08±0.90	61.03±0.30	52.20±0.84
13	86.61±0.76	79.40±0.75	71.34±0.20	65.16±0.08	57.04±0.36
14	90.35±0.09	85.01±0.07	76.12±0.97	69.51±0.88	61.01±0.54

(n=3±SD).

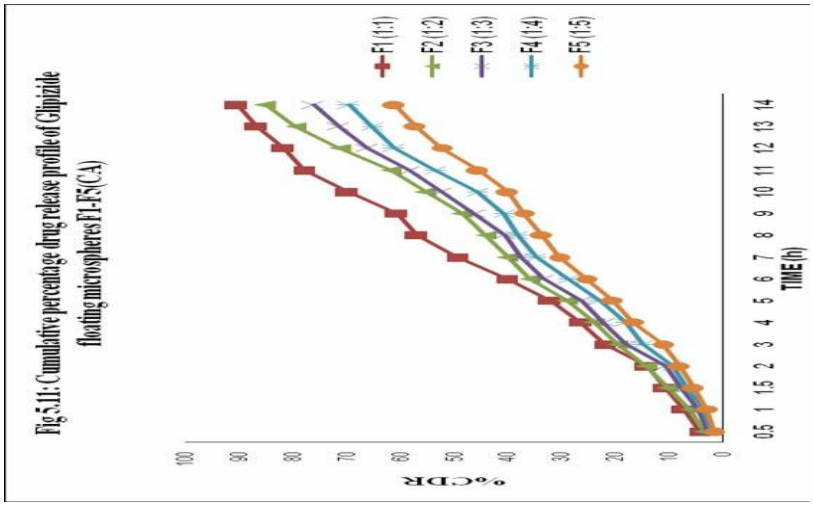

Figure 1: Cumulative percentage drug release profile of Glipizide floating Microspheres F1-F5 (CA).

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. This information can useful for future development of gastrotentive delivery system.

ACKNOWLEDGEMENT

I am thankful to management of Shri Ramnath singh institute of pharmaceutical science and technology, Gwalior (M.P.) for providing co-operative environment. I also thanks to all persons related directly or indirectly to this work.

REFERENCES

1. Shinde A.J., More H.N. Gastroretentive drug delivery system: an overview. Pharm. Rev. 2008;6(1)
2. Singh S., Joshi V., Barpete P.K. Gastroretentive drug delivery system: current approaches. J. Pharm. Res. 2009;2(5): 881-86.
3. Ma N., Xu L., Wang Q., Zhang X., Zhang W., Li Y., Jin L., Li S. Development and evaluation of new sustained-release floating microspheres. Int. J. Pharm. 2008;358(1-2):82- 90.
4. Nayak A.K., Maji R., Das B. Gastroretentive drug delivery systems: a review. Asian J. Pharm. Clin. Res. 2010;3(1): 2-10.
5. Jain S.K., Agrawal G.P., Jain N.K. Evaluation of porous carrier based floating or listat microspheres for gastric delivery. AAPS Pharm SciTech. 2006;7(4):E54-E62.
6. Tripathi M., Radhika P.R., Shivakumar T. Formulation and evaluation of glipizide hollow microballoons for floating drug delivery. Bulletin of Pharmaceutical Research 2011;1(1):67-74.
7. Monika divya salomy A., Rakesh Kumar V. Formulation and In-vitro evaluation of Floating microsphere of gilipizide. International Journal of Pharma research and health science.2015;3(2):606-615.
8. Garg R., Gupta G.D. Progress in Controlled gastro retentive delivery systems. *Tropical Journal of Pharmaceutical Research.*2008; 7:1055-1056.
9. Patil J.M., Hirlekar R.S., Gide P Sand, Kadam V.J. Trend sin Floating Drug Delivery Systems .*Journal of Scientific and Industrial Research.*2006; 65:11-21.
10. Furquan Khan N., Mohamed Dehghan H.G. Gastro retentive drug delivery systems: A patent perspective. *International Journal of Health research*. 2009; 2:23-44
11. Shweta A., Javed Ali, Alka Ahuja, Roop Khar K. Sanjula B. Floating Drug Delivery Systems:A Review .*AAPS Pharm Sci Tech.*2005;6: E372-390.
12. Mayavanshi A.V., Gajjar S.S. Floating drug delivery systems to increase gastric retention of drugs: A Review. *Research J.Pharm and Tech*. 2008; 1:345-348.
13. Ramesh Putheti R., Mahesh Patil C. Pharmaceutical Formulation and Development of Floating and Swellable Sustained Drug Delivery Systems: A Review. *e-Journal of Science and Technology*. 2009; 4:1-12.

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