Journal of Innovations in Applied Pharmaceutical Science
(JIAPS)

Content available at: www.saap.org.in ISSN: 2455-5177

Formulation and evaluation of microsphere of glipizide

V. Vasu Naik*[1], M.Nagavani[2]

[*1] Assistant Professor, Department of Pharmaceutics, Hindu College of Pharmacy, Amaravati Road, Guntur, AP, India

[2] Department of Pharmacy, Hindu College of Pharmacy, Amaravati Road, Guntur, AP, India

Article History

Received: 08-10-2022

Revised: 19-10-2022

Accepted: 27-11-2022

Abstract

The present study aims to carried out to prepare and evaluate the floating microsphere Glipizide using Eudragit RS 100 in a combination with Polyethylene Oxide in various proportions. The following experimental protocol was therefore designed to allow a systemic approach to the study and we concludes that Drug absorption in the GIT is a highly variable process, prolonging gastric retention of the dosage forms and extends the time of drug absorption. Floating hollow microspheres are preparedwith enteric coated polymer (Eudragit RS 100) successfully by the solvent evaporation technique.Upon incorporation of the hydrophilic polymer such as polyethylene oxide in the shell of microballoons, the amount of drug released from microspheres could be enhanced.

Keywords: Microsphere, Glipizide, Polyethylene Oxide, Eudragit, Drug absorption and GIT.

*Corresponding Author
V.Vasu Naik

https://doi.org/10.37022/jiaps.v7i3.362

Production and Hosted by
www.saap.org.in

Introduction

Oral Drug Delivery

Oral drug delivery has been known for decades as the most widely used route of administration among all the routes. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief. Pharmaceutical products designed for oral delivery which are currently available in themarket mostly are immediate-release or conventional release, which maintains the drugconcentration within the therapeutically effective range only even when administered several times a day. This results in a significant fluctuation in the drug level [1, 5].

Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits [6-11]. The most important objective of these New Drug Delivery Systems is it would be single dose, the duration of treatment, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directlyto the site of action, thus minimizing or eliminating side effects. Sustain-release formulation simply prolongs the release and hence plasma drug level maintained for an extended periodof time, not necessarily at a predetermined rate. These makes oral controlled release much important, which provides a complete and controlled release of drug throughout the GI tract [12-15].

Oral Controlled Drug Delivery System

The term oral controlled release implies a system that provides continuous delivery of drug for a predetermined period in a predictable and reproducible manner which increases the bioavailability [16]. It include the system and provides control over movement of dosage form through the GI tract for either a local or a systemic action. Increased bioavailability of CDDS excluded by several physiological difficulties and highly variable nature of gastric emptying process turns to unpredictable and reduced bioavailability [17-25].

Most limiting biological factor in development of once daily oral controlled release is the transit time of dosage form through the GI tract.

Objective and Plan of Work

Objective of the Research Work

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.

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).

Drugs that have narrow absorption window in upper part of GI tract i.e. stomach and small intestine, due to short transit time of dosage form,formulation of these drug leave upper part of GI tract and reaches to non-absorbing distal regiment, resulting lesser bioavailability.

Floating drug delivery systems prolong the drug release rate from formulation in stomach andupper part of small intestine until all the drug is released for the desired period of time.

The drug of choice, Glipizide, is an effective anti -diabetic drug particularly in Type II diabetes (Non-insulin dependent diabetes mellitus). It is a second generation sulfonylurea that actually lowers the blood glucose level in human by stimulating the pancreatic cell and thereby releasing the insulin. It has a short biological half-life of 2-5 hours which make it more suitable to be designed as a controlled release formulation. The main purpose of the present research was to develop a controlled drug delivery system of glipizide for per-oral administration using biocompatible Eudragit® polymers in order to increase its biological half-life and to determine the influence of formulation and preparation variables on microparticles characteristics, such as drug incorporation and in vitro drug release.

The predominant mechanism of action of glipizide appears to be by increasing the secretion of insulin from the pancreas in both normal and diabetic patients. Other proposed mechanisms include: increasing sensitivity of peripheral tissues to insulin effects, increasing the number of insulin receptors, and increasing binding to and/or affinity of insulin for its receptors.

Although sulfonylurea vary widely in their rate of intestinal absorption, the absorption of some drugs (particularly glipizide) is affected by food.

Plan of Work

The present work carried out to prepare and evaluate the floating microsphere Glipizide using Eudragit RS100 in a combination with Polyethylene oxide in various proportions. The following experimental protocol was therefore designed to allow a systemic approach to the study.

Formulation study

Preparation of Standard Curves

Evaluation of floting microspheres for following physiochemical parameters

Formuation of floting microspheres

Particle size analysis

Materials and Instruments

Material Used

The following materials were used for the research work. The entire chemicals used were ofbest quality available.

Material Used For Research Work

Table: 01

S.No	Name
1.	Glipizide
2.	Eudragit RS 100
3.	HPMC
4.	Dichloromethane
5.	Ethanol
6.	Concentrated Hydrochloric Acid
7.	Sodium Hydroxide
8.	Disodium Hydrogen Phosphate
9.	Tween 20
10.	N-Hexanes
11.	Glyseryl monostearates
12.	Polyvinyl Alcohol

Instruments Used

The instruments used for the research work were as follows.

Instrument Used For Research Work

Table : 02

S.No.	Name
1.	Double Beam UV/Vis Spectrophotometer
2.	USP (XXIV) Type II Dissolution Apparatus
3.	FT-IR
4.	Scanning Electron Microscopy
5.	Electronic Balance
6.	Stirrer
7.	pH Meter
8.	Sieve

Experimental Procedure

Preparation of Standard Curve

Preparation of 0.1 N Hydrochloric Acid (pH 1.2)51:

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

Preparation of Standard Curve of Glipizide with 0.1 N HCI31:

100 mg of glipizide was accurately 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 100 ml with 0.1 N HCl. This was the primary stock solution, contained concentration of 1000 g/ml. From this primary stock solution 10 mlwas accurately pipetted out and transferred in to a 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl which contained the concentration of 100□□g/ml. From the second stock solution again 10 ml was pipette out and diluted up to 100 ml with 0.1 N HCl to get concentration of 10 □□g/ml.

From third stock solution aliquots equivalent to 1- were pipetted out in to a series

of 10 ml volumetric flask and volume was made up to 10 ml with 0.1 N HCI. The absorbance of these solutions was measured against the 0.1 N HCI as blank at 276 nm using UV-Visible double beam spectrophotometer. Then a calibration curve was plotted taking concentration in

-axis and absorbance on Y-axis.

Preparation of Phosphate Buffer pH6.852:

Placed 11.45 gm of potassium dihydrogen phosphate and 28.80 gm of disodium hydrogen phosphate and made up to 1000 ml with distilled water.

Preparation of Standard Curve of Glipizide with Phosphate Buffer pH 6.829

100 mg of Glipizide was accurately weighed and dissolved in a small portion of Methylene chloride (Dichloromethane) and make the volume with phosphate buffer pH 6.8 in a 100 ml volumetric flask. This was the primary stock solution, contained concentration of 1000 □□g/ml. From this primary stock solution 10 m1 was accurately pipetted out and transferredin to a 100 ml volumetric flask and volume was made up to 100 ml with phosphate buffer pH 6.8 which contained the concentration of 100 □□ g/ml. From the second stock solution again 10 ml was pipette out and diluted up to 100 ml with phosphate buffer pH 6.8 to get concentration of 10 □□g/ml.

From third stock solution aliquots equivalent to 1- were pipetted out in to a series

of 10 ml volumetric flask and volume was made up to 10 ml with phosphate buffer pH 6.8. The absorbance of these solutions was measured against the phosphate buffer pH 6.8 as blank at 276 nm using UV- Visible double beam spectrophotometer. Then a calibration curve was plotted taking concentration in -axis and absorbance on Y-axis

Preparation of Floating Microsphere of Glipizide 13;

Floating microsphere containing Glipizide was prepared using emulsion solvent diffusiontechnique. The drug to polymer ratio used to prepare the different formulations was 1:7. Thepolymer content was a mixture of Eudragit RS 100 (ES 100) Hydroxypropylmethyl cellulose (Polyethylene Oxide) as shown in table no.5. The drug polymer mixture is dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcoholsolution (200 ml). The solution was stirred with a propeller-type agitator at 40 temperature for 1 hour at 300 rpm. The formed floating microspheres were passed throughsieve no...-12 and washed with water and dried at room temperature in a desiccator. Thevarious batches of floating microsphere were prepared as follows.

Formulation of the Floating Microspheres Prepared

Table: 03

Sr. No	Formulation Code	Glipizide (gm)	Eudragit RS 100 (gm)	Polyethylene Oxide (gm)
1	F1	0.1	0.7	0.0
2	F2	0.1	0.6	0.1
3	F3	0.1	0.5	0.2
4	F4	0.1	0.4	0.3
5	F5	0.1	0.3	0.4
6	F6	0.1	0.2	0.5
7	F7	0.1	0.1	0.6
8	F8	0.1	0.0	0.7

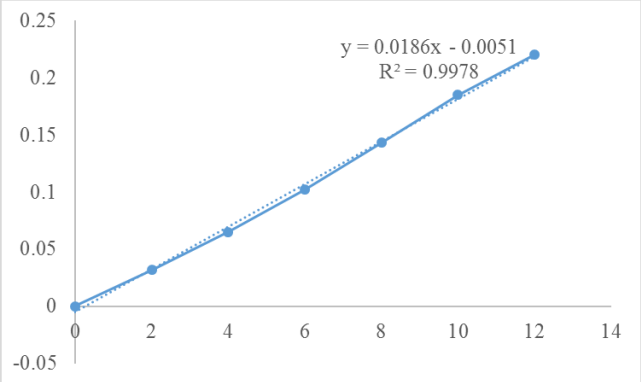
Result and Discussion

Standard Curve in 0.1 N HCl

Table: 04

S.No.	Concentration(µg/ml)	Absorbance at(276nm)
01	0	0
02	2	0.032
03	4	0.065
04	6	0.102
05	8	0.143
06	10	0.185
07	12	0.211

Graph: 01

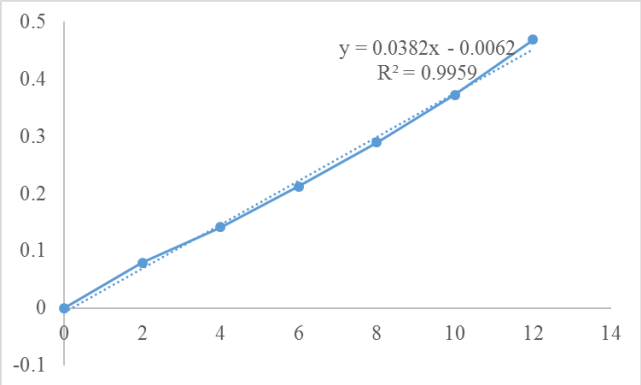


Standard Curve in Phosphate Buffer pH 6.8

Table: 05

S.No.	Concentration(µg/ml)	Absorbance at(276nm)
01	0	0
02	2	0.079
03	4	0.141
04	6	0.212
05	8	0.289
06	10	0.372
07	12	0.469

Graph 02



Evaluation of Hollow Microspheres

Particle size analysis

Particle size was determined by Optical microscopy method. It plays important role infloating ability and release of drug from microballoon. If size of microballoons is less than 500 µm release rate of drug will be high and floating ability will reduce, white microballoons ranging between 500µm - 1000µm, the floating ability will be more and release rate will bein sustained manner.

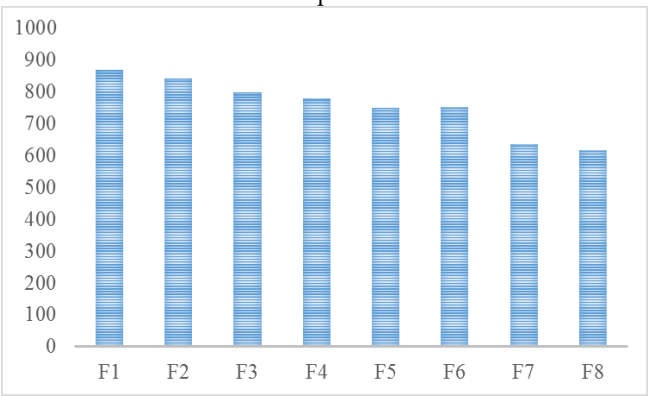
The mean particle size of hollow microsphere was in range 616. - 869 µm as shown inTable 07.

Mean particle size of Different Batches of Hollow microsphere

Table : 06

S. No	Formulation code	Mean particle size (mm)
01	F1	869
02	F2	841
03	F3	797
04	F4	780
05	F5	748
06	F6	751
07	F7	636
08	F8	616

Graph 03



Floating behaviour of microsphere

Hollow Microsphere were dispersed in 0.1 HCl containing Tween 20 (0.02% w/v) to simulate gastric fluid. Floating ability of different formulation were found to be differed according to Eudragit and Polyethylene Oxide ratio. F1-F4 formulations showed best floating ability (97.16-87.45%) in 6 hours. F5-F8 formulation showed less floating ability (83.37-56.57%) as showed in Table-8. The floating ability of microsphere is decreased by increasing the Polyethylene Oxide ratio.

Conclusion

Drug absorption in the GIT is a highly variable process, prolonging gastric retention of the dosage forms and extends the time of drug absorption. Floating hollow microspheres are prepared with enteric coated polymer (Eudragit RS 100) successfully by the solvent evaporation technique. Upon incorporation of the hydrophilic polymer such as Polyethylene Oxide in the shell of microballoons, the amount of drug released from microspheres could be enhanced.

In-vitro data obtained from floating microspheres of Glipizide showed excellent floatability, goodbuoyancy and prolonged drug release. Microspheres of different size and drug content could beobtained by varying the formulation variables. Diffusion (Anamolous transport diffusion) wasfound 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. The formulations were evaluated for various micromeritics and characteristic studies.

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 entrapment efficiency slightly decreases with increase the Polyethylene Oxide content.

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. In order to increase the release rate of drug the ratio of Eudragit RS100 is decreased and the Polyethylene Oxide is increased. Ideal property of hollow microsphere includes high buoyancy and sufficient release of drug in pH 1.2. It isnecessary to select an appropriate balance between buoyancy and drug release rate from all developing hollow microsphere. 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. When it is been formulated in large scale, the formulation will be economical, due to its ease of preparation, and good buoyancy due to the polymers used in the formulation.

References

1. Robinson, J., Vincent, H.L.L.; Controlled Drug Delivery Fundamentals and Applications, II Edn., Marcel Dekker, Inc, New york, 1968: 346-374.
2. Chien, Y.W.; Noval drug delivery system, II Edn., Marcel Dekker, New York, 1997; 50: 161- 163.
3. Vyas, S.P., Khar, R.K.; Controlled drug delivery concepts and Advances, I Edn., Vallabh prakashan, Delhi, 2002: 196-205.
4. Guyton, A.C., Hall, J.E.; Text book of medical physiology, IX Edn., Sqender company, Piladelpcia, 1996: 803-805.
5. Tortora, G.J., Grabowski., S.R.; Principles of Anatomy and Physiology, X Edn, John Willey & Sons, Inc., USA, 2002: 868-870.
6. Uppugalla S, Male U, Srinivasan P. Design and synthesis of heteroatoms doped carbon/polyaniline hybrid material for high performance electrode in supercapacitor application. Electrochimica Acta. 2014 Nov 10;146:242-8.
7. Ojha, G.; Floating microspheres development characterization & application. Review, AAPS Pharm. Sci., 2006, 129-140.
8. Arora S., Ali J., Ahuja A.; floating drug delivery system. Review. AAPS Pharm. Sci.,. 2005,372-39.
9. Yeole P.G.; Floating drug delivery system, need & development. Indian J.Pharm. Sci., 2005; 67(3): 265-272.
10. Garg. S., Sharma. S; Gastro-retentive drug delivery system, Pharma Tech., 2003, 27, 50-68.
11. Sato. Y., Kawashima Y., Takeuchi, N.; Physicochemical Properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, Eur. J. Pharm. & Biopham., 2003; 55: 297-304.
12. Male U, Uppugalla S, Srinivasan P. Effect of reduced graphene oxide–silica composite in polyaniline: electrode material for high-performance supercapacitor. Journal of Solid State Electrochemistry. 2015 Nov;19(11):3381-8.
13. Sato, Y., Kawashima, Y., Takeuchi, H.; Invitro evaluation of floating drug releasing behaviour of hollow microspheres (microballoons) prepared by emulsion solvent diffusion method, Eur. J. of Pharm. & Biopharm, 2004; 57: 235-243.
14. atel V.F., Patel N.M., Yeole P.G.; Studies on formulation & Evaluation of Ranitidine Floating tablet, Indian J. Pharm. Sci., 2004; 5(2),34,1-6.
15. Kale R.D., Tayade, P.; A Multiple unit floating drug delivery system of piroxicam using eudragit polymer, Indian J. Pharm. Sci., 2007; 67 (1): 120-123.
16. Dave B.S., Amin, A. F., Patel, M. M.; Gastro-retentive Drug Delivery System of Ranitidine Hydrochloride: formulation and in vitro evaluation, AAPS Pharm Sci. Tech., 2004; 5(2): 34.
17. Uppugalla S, Srinivasan P. High-performance supercapacitor coin cell: polyaniline and nitrogen, sulfur-doped activated carbon electrodes in aqueous electrolyte. Journal of Solid State Electrochemistry. 2019 Jan;23(1):295-306.
18. Muthusamy, K., Govindatuzan. G.; Preparation & Evaluation of Lansoprazole floating Micropellets, Indian. J.Pharm. Sci., 2005; 67(1): 75-79.
19. Streubel, A., Siepmann, J., Bodmeier, R.T.; Floating matrix tablets bared on low density foam powder effects of formulation, processing on drug release, Eur. J. Pharm. Sci.,2003; 13: 37-45.
20. Sato, Y., Kawashima, Y., Takeuchi, H.; Invitro and in vivo evaluation of riboflavin– Containing microballoons for a floating controlled drug delivery system in healthy humans, Int J Pharmaceutics, 2004;

275: 97-107.

21. Srivastava, A.K., Ridhurkar, D.N.; Wadhwa, S.; Floating microspheres of cimetidine: Formulation, characterization and *in vitro* evaluation, Acta Pharm., 2005; 55: 277– 285.
22. Choi, B.Y., Park, H.J., Hwang, S.J.; Preparation of alginate beads for floating drug delivery system effects of CO2 gas forming agents, Int. J. Pharm., 2002; 239: 81-91.
23. Uppugalla S, Srinivasan P. Polyaniline nanofibers and porous Ni [OH] 2 sheets coated carbon fabric for high performance super capacitor. Journal of Applied Polymer Science. 2019 Nov 5;136(41):48042.
24. Patel, V.F., Patel, N.M.; Intragastric floating drug delivery system of Cefuroxime Axetil, AAPS. Pharm. Sci., 2006; 7(1): 17.
25. Jain, S.K., Agrawal, G.P., Jain, N.K.; evaluation of Porous carrier – bared floating orlistat Microsphere for gastric delivery, AAPS Pharm. Sci. Tech., 2006; 7(4) : 90.
26. Krogel, I., Bodmeier, R.; Floating or pulsatile drug delivery system based on coated effervescent cores, Int. J. Pharm., 1999; 187: 175-184.
27. K.P.R.Chowdary, Y.Srinivasa Rao. Design and In-Vitro evaluation of Mucoadhesive Microcapsules of Glilpzide for Oral Controlled release: A Technical Note. AAPS.Pharm.Sci.Tech2003; 4(3) Article39
28. Ali Mehramizi, Behnaz Alijani, Mojgan Pourfarzib, Farid A. Dorkoosh, Morteza Rafiee- Tehrani. Solid Carriers for improved solubility of Glipizide in Osmotically Controlled Oral Drug Delivery System. Drug Development and Industrial Pharmacy33, 812-823,2007.
29. Shahla Jamzad, Reza Fassili. Role of Surfactant and pH on Dissolution Properties of Fenofibrate and Glipizide –A technical Note. AAPS.Pharm.Sci.Tech.2006, 7(2) Article33
30. N. Vishal Gupta, C.S. Satish and H.G. Shivakumar. Preparation and characterization of Gelatin-Poly(methacrylic acid) Interpenetrating. Polymeric Network Hydrogels as a pH-sensitive system for Glipizide.Indian Journal of Pharmaceutical Sciences Jan- Feb2007,69(1),64-68.
31. Uppugalla S, Boddula R, Srinivasan P. Methyl triphenylphosphonium permanganate as a novel oxidant for aniline to polyaniline-manganese (II, IV) oxide: material for high performance pseudocapacitor. Journal of Solid State Electrochemistry. 2018 Feb;22(2):407-15.
32. K.P.R. Chowdary, N. Koteswara Rao and K.Malathi. Ethyl Cellulose Microspheres of Glipizide: Characterization, In-Vitro and In-Vivo evaluation. Indian J.Pharm.Sci.2004,66(4):412- 416.
33. Radha Yeganarayan, Mahesh Surryavanshi, Manmohan Singh, Supriya Desai. A Comparative study of the Glycemic control of various antidiabetic agents and the role of Homocysteine in the therapy of type 2 diabetes mellitus.Journal of Diabetes and its Complications22(2008)104-111.
34. Rajan K. Verma, Sanjay Garg. Selection of excipients for extended release formulations of Glipizide through Drug-excipient compatibility testing.Journal of pharmaceutical and Biomedical Analysis. 38(2005)633-644.
35. E.M. Ghoneim, M.A.El-Attar, E. Hammane, P.Y. Khashala. Stripping Voltametricquantification of the anti-diabetic drug Glipizide in bulk form and pharmaceutical formulation.Journal of pharmaceutical and Biomedical analysis, 43(2007)1465-1469.