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Development and Optimization of Bilayer Floating Tablets of Glipizide

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Abstract

Present work was an attempt for the development of FDDS with sustained-release of Glipizide using HPMC K-grade and Xanthan gum. The formulations showed promising sustained-release floating matrix tablets of Glipizide. Being obvious, HPMC K15M shown better retardation as compare to HPMC K 4M due to higher viscosity grade. High concentrations of higher viscosity-grade polymers induced the creation of stronger viscous-gel, which retarded the water penetration rate in the tablet-matrix, which might resulted in the extended release of drug. Polymer to drug ratio 2:1 shown better retardation due to higher concentration of polymers, while polymer to drug ratio 1:1 was unable to retard the release for 12hrs. When HPMC K15M and HPMC K4M used in ratio of 9:1 with xanthan gum, they shown more retardation and less than 75 % drug released in 12hrs, but when these polymers used in ratio 1:1 with xanthan gum shown better control over release pattern of the drug.

Keywords: Floating microspheres, ionotropic gelation, sterculia gum, sustained release, factorial design.

Introduction

Glipizide is a 2nd generation sulphonylurea, which can reduce the glucose level of blood in human by increasing the insulin release from pancreatic cells. When it is given orally in healthy humans, it absorbs rapidly and completely. But, its absorption is unpredictable in diabetic patients due to impaired gastric motility or gastric emptying. This unpredictable absorption of glipizide is therapeutically significant because the effectiveness of short-acting sulphonylureas depends on the speed drug availability in sysytemic circulation. Glipizide have biological half-life of 3.4±0.7 hrs. This demands its administration twice or thrice in doses of 2.5-10 mg/day. Drug delivery systems which are maintained in the gastric region might enhance the absorption of drug, decrease dose and increase drug's effectiveness. The foremost possible technique for attaining an extended and predictabal dosage form in the GIT is to modify the stomach residence-time by employing floating drug delivery system. Hence, the formulation of floating sustained release drug delivery system will be noticeably useful[1,2].

Sustained release bilayer floating tablets of glipizide were developed by applying 2^3 factorial design. Firstly sustained release layer of glipizide were formulated and optimized using HPMC K4M, HPMC K15M and Xanthan gum, then floating layer was optimized using HPMC K100M, Sodium bicarbonate and starch 1500. The prepared batches of sustained release layer were evaluated for hardness, drug content, thickness, *in vitro* release of drug etc. Bilayer floating tablet was compressed in 8mm die and evaluated for hardness, drug content, thickness, *in vitro* release of drug, floating time, floating lag time, drug-polymer compatability study etc[3].

Material and Methods

Materials: Glipizidewas obtained as a gift-sample from Supra Pharmaceuticals Pvt. Ltd. Hyderabad, Xanthan-Gum was purchased from Krystal colloid, Mumbai. HPMC K100M, HPMC K4M, HPMC K15M and Starch-1500 were purchased from Colorcon Asia Pvt. Ltd, Mumbai. Sodium-Bicarbonate, Magnesium-stearate, MCC and Aerosil were bought from Loba chemicals, Mumbai.

Methods: Formulation of sustained release layer: Sustained release layer formulated using 2^3 factorial design shown in Table-1 and Table-2The tablets were manufactured by direct-compression technique.

All the components were sieved through sieve (#60) and blended well. Weighed quantity of sustained release layer equivalent to 110mg were compressed in die of 6mm (Cemach-12 station multitooling machine, Hyderabad) for optimization of the layer, for final compression of bilayer 8mm punch used[4].

Table-1
2^3 factorial design for formulation of sustained-release layer of Glipizide

Coded value	Polymers to drug ratio	Polymer-polymer ratio	Grade of Polymer
-1	1 : 1	1 : 1	-HPMC K4M
+ 1	2 : 1	9:1	-HPMC K15M

Table-2
Formulation chart of sustained release layer of Glipizide

S. No.	Ingredient (mg)	A 1	A 2	A 3	A 4	A 5	A 6	A 7	A 8
1	Glipizide,	10	10	10	10	10	10	10	10
2	-HPMC K4M	5	10	9	18	-	-	-	-
3	HPMC K15M	-	-	-	-	5	10	9	18
4	Xanthan gum	5	10	1	2	5	10	1	2
5	Starch 1500	20	20	20	20	20	20	20	20
6	MCC	67	57	67	57	67	57	67	57
7	Magnesium stearate	2	2	2	2	2	2	2	2
8	-Aerosil	1	1	1	1	1	1	1	1
	Total-weight	110	110	110	110	110	110	110	110

Formulation of Floating layer: All the components were sieved through sieve (#60) and blended well. Floating layer comprises three ingredients as shown in table-3.

Table-3
Formulation chart for Floating layer

Sodium bicarbonate (mg)	HPMC K100M (mg)	Starch 1500 (mg)
45	46	49

Preparation of bilayer floating tablets: Accurately weighed amounts of sustained release layer correspondent to 110 mg were pre compressed. Then weighted quantities of floating layer equivalent to 140 mg added on pre compressed sustained release layers and both the layer were-compressed in a die of 8mm.

Physical Characterization of Tablets: Hardness of tablets was measured by utilizing Monsanto-hardness-tester. Weight variation test was carried out taking 20 tablets and analysed as per USP weight variation test. Friabilitytest was carried out using Roche-friabilatoras per USP standards.

Floating Behaviour: The *in-vitro* floating behaviour of the tablet in the 0.1N HCl (1000 ml) was determined by evaluating floating period and strengths. Floating-duration of the tablet was estimated by visual-observations for the duration of more than 12 hrs[5].

Floating lag time: Floating lag time was determined placing tablets into 200 ml 0.1N hyhrochloric acid in a beaker kept at 37^0C. The time taken by the tablets to go up to the surface and remain floating was considered as floating-lag-time[4].

***In- Vitro* Drug Release studies of Formulated tablets:** *In Vitro* drug dissolution study of Glipizidewas performed by utilizing USP-type II Dissolutions Testing Apparratus (6 vessel assembly, Paddle-type II) at50 revolutions per minute. 900 ml of 0.1 N HCL solution was used as dissolution-medium. Temperature was kept 37 ± 0.5^0C. Samples of 5 ml were taken at 1 hr. time intervals and an equal volume of pure dissolution-fluid maintained at identical temperatures was reinstated to maintain sink conditions. Samples were passed from a whatman filter-paper, suitably dilutted using 0.1 N HCl solution and examined spectrophotometrically at 276 nm[6].

Model fitting: The model fitting for percent cumulative release was done using PCP Disso software to find the best fitted kinetic equation for the dissolution profile.Correlation-Coefficient (R^2) value was determined for the linear-curves got by regression-analysis of the graphs[7].

Stability Studies of Glipizide floating Tablets: Gastroretentive tablet of optimized batch was examined for accelerated-stability study. Stability-studies were carried out at 40 ± 2^0C/75± 5% RH for a period of 6 months. The samples were taken at period of 0 month, 3 month and 6 months, and were tested forits hardness, thickness, drug-content, floating lag-time and floating duration[8].

Results and Discussion

Evaluation of compressed sustained release layer of Glipizide: From the observations as in table-4 it was confirmed that all batches comply with the Pharmacopoeiallimits (USP) for physical characteristics. The drug-content was observed to be consistent among all formulation and in the range from 95.10 ±0.38 to 100.10 ±0.87.

***In vitro* Drug-Release of sustained release layer:** Release of Glipizide from the matrices was mainly dependent on the swelling of polymers, matrix-erosion and diffusion of drug. Results of dissolution studies of formulations A1 to A4 composed of HPMC K4M shown sustained release of drug. Formulations A1 and A3 released more than 95% drug within 10 hrs. Formulation A2 was able to retard drug for 12hrs, releasing 98.22% drug in 12hrs. While formulation A4 could release 73.58 % drug in 12hrs, which was insufficient for a 12hrs, sustained release dosage form. Formulations A5 to A8 composed of HPMC K15M were also capable to prolong drug-release. Formulations A5 and A7 shown release of more than 90% drug within 9 hrs. Formulation A6 was able to retard drug for 12hrs, releasing 96.39% drug in 12hrs. While formulation A8 could release 70.36% drug in 12hrs, which was insufficient for a 12hrs sustained release dosage form[9] (figure –1).

Table-4
Standard Physical Tests for sustained release layer

Formulation	Thickness (mm)	Diameter (mm)	Hardness	Wt. variation	Percent friability (%w/w)	Uniformity of Content (%)
A1	3.1±0.02	6.11±0.01	6.7±0.06	Passes	0.52±0.05	97.89±0.48
A2	3.1±0.04	6.12±0.01	6.4±0.05	Passes	0.61±0.02	99.22±0.77
A3	3.2±0.03	6.11±0.01	6.5±0.02	Passes	0.49±0.03	97.00±0.64
A4	3.1±0.00	6.11±0.01	6.6±0.04	Passes	0.39±0.02	95.10±0.38
A5	3.2±0.02	6.11±0.01	7.0±0.05	Passes	0.58±0.04	96.00±0.46
A6	3.2±0.01	6.14±0.00	6.2±0.05	Passes	0.67±0.01	99.30±0.54
A7	3.2±0.05	6.11±0.01	6.8±0.02	Passes	0.81±0.02	100.10±0.87
A8	3.1±0.01	6.14±0.01	6.5±0.06	Passes	0.75±0.03	96.70±0.42

*All value represent as Mean± S. D. (standard-deviation) (n=5)

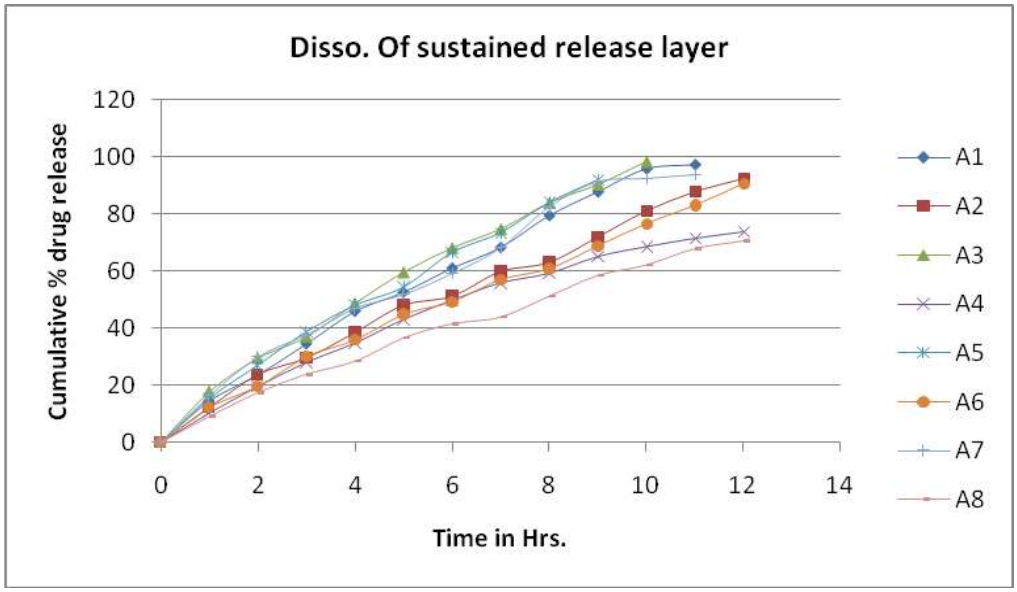

Figure-1
Drug-release profiles of sustained-release layer of formulations A1 to A8

Optimization of floating release layer: Main role of floating layer was to swell reduce density of the system (bilayer tablet) for floating ability up to atleast12hrs, various formulations for floating layer were tried with HPMC K100M, HPMC K15M, Starch 1500 and sodium-bicarbonate considering the floating-duration and floating lag-time. After trial batches combination of HPMC K100M (46mg), Sodium bicarbonate (45mg) and starch1500 (49mg) was chosen as an optimized floating layer[10] (table–3).

Compression of floating Bilayer tablets: Among the all batches of sustained release layer (A1 – A8), formulation A2 and A6 shown satisfying release pattern, hence selected for the preparation of bilayer tablet. Amounts of sustained release layer corresponding to 110 mg were precompressed. Then weighted quantities of floating layer equivalent to 140 mg added on precompressed sustained release layer and compressed both layers in a die of 8mm.

Evaluation of compressed floating bilayer tablet of Glipizide: From the observations in table-5 it was confirmed that both the batches comply with the Pharmacopoeial limits (USP) for physical characteristics.

***In vitro* Drug-Release of Bilayer tablet:** Formulation A2 released 96.72% and A6 released 93.22% drug in 12hrs, as shown in figure-2. The results of dissolution studies of formulation A2 and A6 composed of floating layer and sustained release layer were promising. The releases from both the formulations were quite similar as predicted while studying release pattern of sustained release layer only. Glipizide release from floating tablet was largely reliant on polymers swelling and drug diffusion.

Table-5
Standard Physical Tests for Glipizide floating bilayer Tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness	Wt. variation	Percent friability (%w/w)
A2	4.3±0.03	8.12±0.01	6.5±0.06	Passes	0.72±0.04
A6	4.2±0.05	8.06±0.01	6.2±0.05	Passes	0.84±0.02

*All value represent as Mean± S. D. (standard-deviation) (n=5)

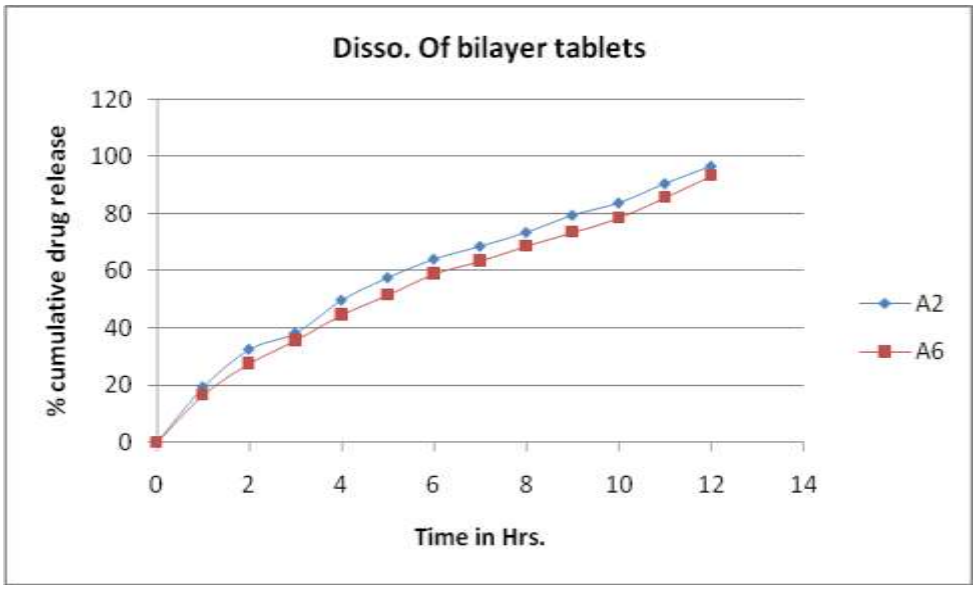

Figure-2
Drug release profile of Glipizide bilayer tablet

Floating behavior and floating lag time: The *in-vitro* test shown the capability of the both formulations to remain floating for excess of 12 hrs and floating lag time was observed less than 2 min. Table -6. This suggested that the layers of gel, produced by the studied gums, allowed well-organized entrapments of the produced gas-bubbles. The probable boost in tablets porosities made it buoyant on the dissolution media (0.1N HCl) for the prolonged periods[11].

Table-6
Floating lag-time and Buoyancy of Glipizide bilayer tablet

Formulation	Floating lag time (sec)	Buoyancy duration (hrs)
A2	110.00±2.64	>12
A6	114.00±2.64	>12

*All value represent as Mean± S. D. (standard-deviation) (n=5)

Release Kinetics: From table-7, it was observed that the best fitting linear parameter for formulation A2, A6 was Higuchi model. Higuchi explained the release pattern of drug from insoluble matrices as square root of time dependent process. The drug release from the formulations was by diffusion from the intragranular opening formed by porous matrices. This signifies that the release of drug was controlled by Fickian-diffusion of drug[7].

Table-7
Estimated values of n, k and R^2 for Glipizide bilayer tablet

Formulation Code	n	K	(R^2)	Best Fit Model
A2	0.2682	1.8597	0.9950	Higuchi
A6	0.2780	2.5027	0.9916	Higuchi

Accelerated stability study: Stability study showed that there were no considerable changes in thickness, hardness, drug content and floating lag time of A2 and A6 formulations before and after accelerated stability study. Hence bilayer floating tablets prepared were found to be stable.

Conclusion

The formulations showed promising sustained-release floating matrix tablets of Glipizide. Being obvious, HPMC K15M shown better retardation as compare to HPMC K 4M due to higher viscosity grade. High concentrations of higher viscosity-grade polymers induced the creation of stronger viscous-gel, which retarded the water penetration rate in the tablet-matrix, which might resulted in the extended release of drug. Polymer to drug ratio 2:1 shown better retardation due to higher concentration of

polymers, while polymer to drug ratio 1:1 was unable to retard the release for 12hrs. When HPMC K15M and HPMC K4M used in ratio of 9:1 with xanthan gum, they shown more retardation and less than 75 % drug released in 12hrs, but when these polymers used in ratio 1:1 with xanthan gum shown better control over release pattern of the drug[11].

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