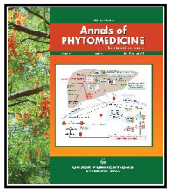
Annals of Phytomedicine 12(2): 957-962, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.2.114

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Development and validation of pharmaceutical oral formulation of bilayer tablet of sustained release and immediate release of gliclazide

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Article Info

Article history

Received 10 October 2023

Revised 26 November 2023

Accepted 27 November 2023

Published Online 30 December 2023

Keywords

Bilayer tablet

Gliclazide

Factorial design

Bioadhesive layer

Bilayer drug release

Abstract

The purpose of this study was to create a gliclazide bilayer tablet with bimodal drug release. The main objective of this study is to investigate the potential of xanthan gum as a bioadhesive, sustained-release layer. Here, xanthan gum is used with cross-carmellose, cross-povidone, and SSG. Swollen volume outside bioadhesion, dissolution kinetics, water absorption, and *in vitro* drug release were checked. A non-Ficki and diffusion-regulated release mechanism was used to study dissolution kinetics after the first burst, leading to the Higuchi model (R^2 = 0.9913). All 32 full factorial designs were considered in the current study. The optimal disintegration time for the direct compression technique utilizing cross-povidone resulted in the immediate release formulation (IR3). According to the disintegration testing results, the time was 13 seconds. In the formulation, the kind of polymers coupled with xanthan gum and the amount of polymer substituted with sodium cross-carmellose were considered independent variables. It was possible to adequately incorporate the mucilage into tablets while preserving high adhesiveness and sustained drug release by replacing only 20% of the natural mucilage, such as xanthan gum, with cross-carmellose sodium.

1. Introduction

A bilayer-layer tablet is considerably superior to a tablet of a single layer. Two-layer tablets have immediate and prolonged release layers. The instant release layers deliver the first dosage and contain a super disintegrate, which speeds drug release and delivers the commencement of action (loading dosage) quickly (Shelar *et al*., 2012). However, the maintenance dosage (sustained release) layer releases the medication, employing different polymers as release agents, in a sustained manner for an extended period. Retardants (*i.e*., sulfonylureas) are oral hypoglycaemics that bind specifically to the surface of pancreatic beta-cells with sulfonylurea receptors. That was displayed because it does not attach to sulfonylurea (SUR-2A) in the heart; it provides cardiovascular protection (Ritger and Peppas, 1985). This connection shuts down channels effectively. As a result, the potassium efflux results in the calcium ion channels in the cell opening upon depolarization, boosting the influx of calcium. After that, calcium can attach to and activate calmodulin, which causes insulin to undergo exocytosis. Vesicles cause the release of insulin. Gliclazide is prepared with SSG for instant release, dissolve due to its lengthy half-life of 6-8 h. Secretion increases as soon as it is implemented (Peppas, 1985; Das *et al*., 2021; Ali *et al*., 2022).

In diabetes mellitus, a person's high blood sugar levels increase and are caused by either insufficient insulin synthesis or by cells that do not produce insulin (Colombo *et al*., 1985; Massing *et al*., 2013).

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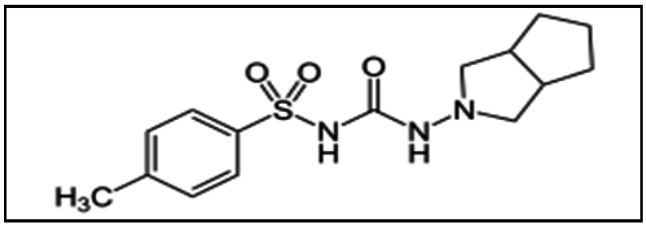

Figure 1: N-hexahydrocyclopentalepyrrol (Gliclazide).

2. Materials and Methods

The first step in the logical construction of a dose farm is formulation studies. It is an examination of the physical and chemical characteristics of a medicinal ingredient, both by itself and in combination with excipients. Preformulation analyses aim to pinpoint those physicochemical characteristics of excipients that could affect the manufacturing process, formulation design, and the final product's pharmacokinetic and biopharmaceutical characteristics. Here are the test results. Carrying out the preformulation research (Patel and Shah, 2013; Dhama *et al*., 2022, Duraisami *et al*., 2021, Singh *et al*., 2022).

2.1 Determining the active components melting points

Different capillary tubes were filled with specific amounts of the active chemicals, and the ingredient's melted points were calculated and compared to the requirements.

2.2 Calculating the λmax

Gliclazide: Ten milliliters of methanol were added to a precisely weighed quantity of 5 mg of gliclazide. To make a 100 pg/ml stock solution, add distilled water to the desired volume. The prepared

mixture is filtered through a Whatman semipermeable membrane with No. 41. Volume was made up with distilled water, and a volumetric flask was filled with stock solution up to 10 ml, providing a concentration range of 2 g/ml. The absorbance was taken at a wavelength of 200-400 nm in the UV spectrum. An instant-release pill recipe each tablet was crushed into a 6 mm diameter flat punch. The gliclazide layer was created *via* prompt release and direct compression. Pass talc, MCCP pH 102, magnesium stearate in 100 mesh, gliclazide, and cross-povidone. Well, combine the ingredients. A head of pressure 50 milliliter volumetric flask, with the volume being modified (Manoranjan *et al*., 2010).

2.3 Properties on granules

Bulk density (Db): It is measured in grams per milliliter.

$$M/Vb = Db$$

where, M specifies total weight of the powder. Vb denotes total quantity of the powder.

Tapped density (Dt): Tapped the powder upto 750 times. It is provided by and is measured in grams per milliliter.

$$M/Vt = Dt$$

where, M denotes the powders mass. The powders tapped volume is denoted by Vt.

Angle of repose: It used to calculate flow property of powder.

Table 1: Flow property of powder flow

S.No.	Angle of repose	Flow property
1	<20	Best
2	20-30	Better
3	30-34	Good
4	>34	Passable

Powder flow properties are shown by Carr's index (or) % compressibility. The following is a percentage representation: Table 2 shows the tapped density of the powder.

Table 2: Tapped density of the powder

S.No.	% Flattened volume	Flow property
1	5-12	Best
2	12-16	Better
3	18-21	Good
4	23-35	Passable
5	33-38	Poor
6	>40	Very poor

2.4 Post compression studies of tablets

Description: It is important to note a tablet's overall look, including its shape, colour, and coating or lack thereof. Both customer acceptability and physical storage changes require it. May occur that is easily consistent with the description (Bagyalakshmi *et al*., 2011; Priyal *et al*., 2013; Pooja *et al*., 2016).

Weight variation: A random sample of 20 pills was taken from the lot and weighed. Separately look for variations in weight. Specifications for weight fluctuation per I.P. are displayed in the following table.

Table 3: Weight variation as per IP

Average weight of tablet	% Deviation
Less than 80 mg	± 10
80 to 250 mg	± 75
More than 250 mg	± 5

Thickness: Hardness, disintegration time, and rate of dissolution are all affected by thickness. Vernier calipers can be used to measure the thickness of six tablets.

Hardness: The power needed to weaken a tablet in a given situation is known as tablet crushing strength (fe). A tablet hardness tester made by Monsanto was used to assess diametric compression. It is said in lbs/cm^2.

Friability (F): The tablet's friability was assessed using the Roche friability test. This gadget exposes the tablet to shocks and abrasions while rotating a plastic container at 25 rpm and releasing a tablet six inches above the ground in each. Six pre-weighed samples, after being put in the friability test, were rotated 100 times in 4 min. Tablet computers were cleaned with a gentle muslin towel and weighed again; the formula determines the friability (F).

Tablet disintegration: The research was limited to tablets with instant release and to the layer of the inlay tablet with instant release. The USP pill was used to measure disintegration time. A disintegration tester is with pure water.

2.5 Assay

For instant-release tablets, break off one tab with butter paper, then transfer a carefully weighed Gliclazide into a 500 ml volumetric flask with no loss. After that, add 20 ml of methanol, sonicate it for 5 min, then add 200 ml of diluents and physically shake it for 60 min. Finally, add diluents to get the desired volume. Fill a 20 ml volumetric flask halfway with filter solution that has been diluted with appropriate diluents. Use diluents to create a blank absorbance at 226 nm for background correction. In triplicate, measure the absorbance of a duplicate of the sample preparation and a standard solution (Jeyaprabha *et al*., 2010; Shinde *et al*., 2010; Raja *et al*., 2011).

Dissolution of the tablet with immediate release: 900 milliliters of phosphate buffer pH 1.2 dissolution medium were used for the USP paddle method apparatus dissolution investigations, which were conducted at 374.50°C. The Paddle apparatus was rotated at 50 rpm, and at 226 nm, the absorbance of the sample was taken with a UV spectrophotometer. Two devices with pH 6.8 phosphate buffer, spinning at 100 rpm and at 370.5°C, were used. After closing off the extra test liquid with tissue paper, the tablet was reweighed. After that, each basket was removed from the dissolving device. Following the swelling trials, the wet samples were weighed until a constant weight was obtained (final dry weight, W^2), after which they were dried in an oven at 80°C for 12 h and allowed to cool. New samples were utilized for every time point in the six times, the experiment was run. The proportion of was weight gain attributable to water or liquid absorption (Chandra *et al*., 2011; Colombo *et al*., 1995).

The bilayer tablet: Studies on swelling and erosion by using the equilibrium weight gain method, the polymer's rate of test medium uptake was ascertained. Fresh samples were utilized for every time point in the experiment, which was run six times in total. Every time, the percentage of weight gain attributed to absorbed liquid or water intake was calculated point from the equation that follows:

Percentage of W_1 – Wo/Wo × 100

Percentage of W_e – Wa/Wo × 100

Firstorder equation: The graph showed the cumulative medication remaining as a logarithmic function of time in working hours.

C-log Co-Kt log2.303

where,

K-first order constant, co-initial drug concentration, and t-time:

Higuchi kinetics: The drug release percentage was plotted against the amount of time in hours on the graph.

Kt1/2=Q

where, the design variable system t-time in hours is represented by the K-constant:

As a result, the rate of drug release is proportional to the square root of the reciprocal of time. The specific dose form is taken into account when tracking the straight line of drug release with a slope of one.

- **The Hixson-Crowell erosion equation:** The Hixson and Crowell rates were utilized to represent the outcomes of medicine release in response to surface changes in area and particle diameter.
- **Korsmeyer-Peppas equation:** To examine the drug release mechanism, it was also shown in Peppa's equation as a log cumulative percentage of medication released vs. time.

Mt/Moe = Ktn

Table 4: Amount of ingredients required for formulation

Ingredients	IR1	IR2	IR3
Gliclazide	40	40	40
MCCP PH102	12	12	12
Cross-carmellose sodium	7	-	-
SSG	-	7	-
Cross-povidone	-	-	7
Indigo blue	q.s.	q. s.	q. s.
Mg stearate	0.5	0.5	0.5
Talc	0.5	0.5	0.5
Weight of tablet	60	60	60

3. Results

Preformulation studies main goal is to provide the formulator with relevant data, so they can create stable, bioavailable dosage forms that are scalable for mass production. Preformulation studies are designed to create insights that will aid the formulator in producing mass-producible, stable, and bioavailable dosage forms. The active compound melting point was based on capillary data. The outcome appears in the table below.

Table 5: Melting point

The outcome in the following Table 5.

Drug	Melting point	Observation
Gliclazide	181^{0}C	180 ± 0.8^{0}C

Using methanol and distilled water as a blank, the gliclazide medication solution was scanned using a UV spectrophotometer between 210-400 nm. The maximum absorbance (A max) was discovered at 229.5 nm. Studies of chemical compatibility using FTIR.

Gliclazide: To prepare a solution, 10 ml of methanol was mixed with 5 mg of properly weighed gliclazide in a 50 ml volumetric flask. After that, the volume was adjusted with distilled water until a stock solution containing 100 g/ml was obtained. A Whatman No. 41 paper filter was used to filter the mixture. To achieve a concentration of 2 to 10 g/ml, a series of precisely proportioned aliquots of the stock solution ranging in volume from 0.2 to 1.0 ml were added, and the capacity of each 10 ml volumetric flask was adjusted using pure water.

Table 6: Absorbance of gliclazide

Gliclazide	
Concentration (µg/ml)	Absorbance
0	0
2	0.159
4	0.316
6	0.443
8	0.611
10	0.775

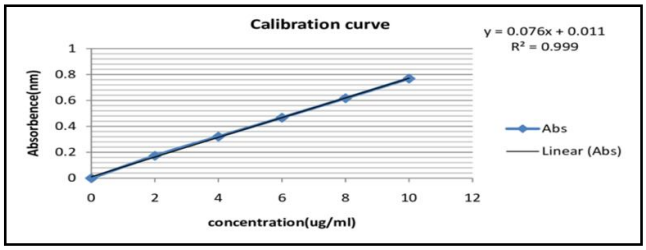

Figure 2: Calibration curve.

3.1 Preformulation recompression study

Total density: Using a graduated cylinder, the bulk densities of several powder mixed blends made with distinct super disintegrates were determined. The bulk density range was discovered to be between 0.52 and 0.55 g/cm^3.

Tapped density: The density of different powder mixtures made using a measuring cylinder was used to measure the super disintegrates. The greatest density was discovered in the fall between 0.60 and 0.63 g/cm^3.

Compressibility index: A flow characteristic that is crucial in the pharmaceutical industry, particularly in tablet formulation, as inefficient flow could lead to greater weight fluctuation (compressibility). Readings below 15% typically result in favourable flow qualities, whereas readings over 25% denote poor flow attributes. The compressibility index of diverse powder mixtures made using distinct super disintegrates was determined by data on both bulk density and tapped density. It turned up in the range of 13.50 to 14.20%, indicating an excellent flow characteristic. The calculation of different powder mixed mixes made with various super disintegrates was done using data on both bulk density and tapped density. It was discovered to be between 1.14% and 1.15%, which suggests an improved property of flow.

Degree of repose (ϕ): Using the funnel method, the angle of repose of many powders blended mixes made with distinct super disintegrates was determined. The ranges from 22.90° to 23.50° were determined to contain the angle of repose. The angle of repose thus provides additional proof that granules have a good flow characteristic.

Table 7: IR Tablet post-compression studies

Formulation	Bulk density*g/cm³	Tapped density*g/cm³	Compressibility index*g/cm³	Hausner's ratio*	Angle of repose*
F1	0.52 ± 0.013	0.61 ± 0.001	14.20 ± 0.625	1.15 ± 0.018	22.90 ± 0.259
F2	0.55 ± 0.002	0.60 ± 0.006	13.74 ± 0.829	1.15 ± 0.014	23.50 ± 0.621
F3	0.53 ± 0.007	0.63 ± 0.003	14.20 ± 0.120	1.14 ± 0.012	23.50 ± 0.860

Weight variation: Theoretically, 60 mg was the average weight of several formulations of tablets. According to each monograph, the weights percentage variance was under 10%.

Hardness: The tablets hardness was determined to be between 3.06 to 35 kg/cm^2. Thus, it was the right amount of hardness for packing, shipping, and coating tablets.

Thickness: The tablets thickness was measured between 2.91 and 2.94 mm. That was crucial for tablet acceptability and packaging.

Friability: The tablets friability was determined to be between 0.61 to 0.67%. Morals are within the official monographs bounds, that is, not more than 1%.

Disintegration time: It was discovered that the formulation IR3 had the shortest disintegration time content of drugs.

Table 8: Post compression study

Formulation	Weight variation*	Hardness* kg/cm^2	Thickness* (mm)	Friability* (%)	Disintegration time	Drug content* (%)
F1	100.38 ± 0.7	3.53 ± 0.255	2.92 ± 0.92	0.67 ± 0.329	32 ± 3.719	100.38 ± 0.728
F2	100.32 ± 0.6	3.20 ± 0.045	2.98 ± 0.69	0.61 ± 0.441	24 ± 2.281	100.32 ± 0.623
F3	100.27 ± 0.7	3.06 ± 0.076	2.94 ± 0.80	0.66 ± 0.019	13 ± 1.005	100.27 ± 0.761

*Mean ± SD (n=3)

IR tablet and *in vitro* dissolution release profile optimization: Different formulations' *in vitro* dissolution and release profiles were investigated. When all of the formulations were compared, it was shown that formulation IRS released 99% of the drug in 15 min. As a result, formulation IR3, which incorporates cross-povidone, was chosen as the best of the three. This may be because it has a higher water uptake tendency and less swelling than the other super disintegrated cross-carmellose sodium and SSG.

Table 9: Drug release profile of immediate layer

Time in min.	Formulation		
	IR1	IR2	IR3
5	41.12 ± 1.07	42.93 ± 1.54	51.55 ± 1.92
10	59.95 ± 1.52	59.41 ± 1.41	63.70 ± 1.40
15	81.93 ± 1.82	83.92 ± 1.79	89.55 ± 1.71
20	92.81 ± 1.02	92.93 ± 1.83	99.48 ± 1.29
30	96.31 ± 1.53	94.64 ± 1.62	99.79 ± 1.22

Formulation and evaluation of bilayer tablets

IR formulations optimal bilayer tablets were created based on the findings of *in vitro* dissolving investigations.

Table 10: Weight of ingredients

Immediate release layer	Per tablet (mg)
Gliclazide	40
MCCP pH102	12
Cross-povidone	7
Magnesium stearate	0.5
Talc	0.5
Indigo blue	q. s.

Table 11: Post compression study

Parameters	Result
Weightuniformity* (mg)	810.62 ± 5.49
Thickness of tablet*(mm)	6.952 ± 0.041
Hardness* (kg/cm^2)	6.73 ± 0.416
Friability*(%)	0.042 ± 0.022
Time of disintegration* (sec)	2.83 ± 0.065

*Mean ± SD (n=3). All the parameters shown in the table complies with official monograph.

Drug content: Gliclazide was found in a bilayer tablet by two different methods, the results of which are displayed in a table.

Table 12: Drug content of bilayer tablet

Bilayer tablet	Drug content
Gliclazide	100.29 ± 0.48

Bilayer tablet release profile *in vitro* table displays data acquired from the dissolution profile of the immediate release layer.

Table 13: Drug release profile

Immediate release layer	
Time in min	Cumulative % of drug release
5	50.52 ± 1.83
10	65.30 ± 1.50
15	88.27 ± 1.46
20	99.04 ± 1.71
30	99.64 ± 1.42

IR layer dissolution profile *in vitro*.

Bilayer tablet assay and dissolution profile during a stability investigation at 40°C/75% RH.

Table 14: Stability study

Interval in months	Drug	% Drug content		% Drug content	
		RT	4^{0}C	RT	40^{0}C
1st Month	Gliclazide	99.16	98.28	98.42	97.37
2nd Month	Gliclazide	99.15	98.22	97.57	96.37
3rd Month	Gliclazide	99.14	98.20	98.72	97.24

4. Discussion

The disintegration studies showed that immediate release formulation IR3 prepared by direct compression technique using cross-povidone was best disintegrating within 13 sec. *In vitro* dissolution studies were performed for all the IR formulations. Among all the formulations, IR containing cross-povidone showed fastest release, *i.e.*, 95.48% of drug within 10 min. Bilayer tablet formulation was prepared using optimum formulation of sustained release granules and immediate release granules. Initially, gliclazide granules were filled in the die cavity, over that immediate release tablet was placed and then compressed finally to get bilayer tablet.The bilayer tablets evaluated for assay, weight hardness, thickness, inability and disintegration time and the results were found to be within the official limits.

5. Conclusion

Physical properties, disintegration, an *in vitro* dissolution investigation, and a stability study were assessed for each formulation. The results of this investigation have led to the following conclusions: FTIR was used to look into any potential interactions between pharmacological excipients. The actual blended formulation's features were acceptable. The ready-made pills for weight fluctuation, hardness, and test performance were assessed for both immediate and prolonged release.

Acknowledgments

The authors would like to express their heartfelt gratitude to ZIM Laboratories Pvt Ltd, Ahmadabad for giving a free sample of pure gliclazide. We also want to thank the Principal of Agnihotri College of Pharmacy in Wardha for providing the essential resources.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Awdhut D. Pimpale, Priyanka S. Waghmare, Pravin B. Suruse, Neha P. Rumale and Mrunal T. Deshmukh (2023). Development and validation of pharmaceutical oral formulation of bilayer tablet of sustained release and immediate release of gliclazide. Ann. Phytomed., 12(2):957-962. http://dx.doi.org/10.54085/ap.2023.12.2.114.**