Formulation and Evaluation of SR Tablets of Anti-diabetic drug Gliclazide

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ABSTRACT

Recent advances in Sustained Release Drug delivery System (SRDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. This present study showed that the Gliclazide is an oral hypoglycemic (anti-diabetic drug) and is classified as a sulfonylurea. Its classification has been ambiguous, as literature used it as both a first generation and second generation sulfonylurea. Gliclazide was shown to protect human pancreatic beta-cells from hypoglycemia-induced apoptosis. It was shown to have an anti-atherogenic effect (preventing accumulation of fat in arteries) in type II diabetes. Gliclazide is used in the tablet form for antidiabetic effect.

Keyword: Gliclazide, Sustained release tablet, Pharmacokinetic study, diabetes, GLI, glipizide.

INTRODUCTION

The oral route of administration is the most preferred route because of its numerous advantages. Tablets and capsules are the most preferred dosage form of pharmaceutical scientists and clinicians because of its convenience in the term of self- administration, compactness, ease in manufacturing, high precision dosing, and relatively low cost production. Gliclazide is structurally classified as a sulphonyl urea second generation analogue. The mean absolute bioavailability of Gliclazide sustained release was 97%. It shows the linear pharmacokinetic . The objective of present work was to prepare sustained release tablet of GL by wet granulation method and study to effect on IR

MATERIALS AND METHOD

Materials

Gliclazide was received as gift sample from Micro Labs Hosur. All other chemicals used in this experiment were of analytical grade obtained commercially.

Tablet is prepared by following these methods-

Wet Granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

Important steps involved in the wet granulation

- Mixing of drug and excipients.
- Preparation of Binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Drying of moist granules.
- Mixing of screened granules with disintegrant, glidant and lubricant.

Advantages

1. Permits mechanical handling of powders without loss of mix quality.
2. Improves the flow of powders by increasing particle size and sphericity

Dry Granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is

recompressed and the resulting tablet or slug are milled to yield the granules. The other method is to recompress the powder with pressure rolls using a machine such as Chilosonator.

Roller Compaction

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened Use. Use in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations.

Direct compression.

Gliclazide tablet is prepared by wet granulation method-

The granules were prepared by wet granulation method. Gliclazide and MCC were passed through #40 mesh. The binder solution was prepared by dissolving the povidone in purified water. The sifted blend was mixed in rapid mixer granulator at 150 rpm for 15mints in slow speed. The binder solution was added to the blend and allowed to mix thoroughly until to get granules. The obtained granules was dried in fluidized bed drier at 60°C for 60mints until to get LOD of granules not less than 2%w/w. The dried granules were sifted through #20 mesh. HPMC-K100LV, Lactose DCL-15 and iron oxide red were sifted through sieve no#40 and 100 mesh and mixed with dried granules for 10 minutes in RMG. The granules thus obtained was mixed with magnesium stearate (which was sifted through sieve no#60) for 2mints. Final blend was collected and compressed.

Table 1: Formulation of Gliclazide tablet

Sr. no.	Ingredients	Formulation code(mg)				
		F1	F2	F3	F4	F5
1.	Gliclazide	30	30	30	30	30
2.	HPMC K4M	5	8	7	6	7
3.	HPMC K100M	8	10	5	8	7
4.	Ethyl cellulose	5	2	3	3	2
5.	$NaHCo_3$	5	2	5	5	5
6.	Talk	2	1	3	4	3
7.	Mg. stearate	2	5	5	2	4
8.	Lactose	Qs	QS	QS	QS	QS

Evaluation of Tablets Blend

Pre- compression

The quality of tablet, once formulated, is generally dictated by the quality of physicochemical properties of blend. There are many formulation and process variables involved in mixing step and all these can affect the characteristics of blends produced.

Angle of Repose (θ)

The frictional forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of repose was determined by using funnel method. Powder was poured from funnel, which can be raised vertically until a maximum cone height. *(Chaulang et al., 2008 &Lakshmi et al., 2011)*

$$\theta = \tan^{-1}\frac{h}{r}$$

Whereas;

θ is angle of repose h is height of pile and r is the radius of the base pile.

Standard range for measurement of angle of repose

Angle of repose (θ)	Type of flow
< 25	Excellent
25-30	Good
30-40	Passable (addition of 0.2% Glidant is required)
> 40	Poor

Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) into a measuring cylinder and the initial volume was noted. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by (*Lakshmi et al., 2011*)

$$Db = \frac{M}{Vb}$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density (Dt).

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 100 times. Tapping was continued until the difference between

successive volumes is less than 2% (in a bulk density apparatus). It is expressed in g/ml and is given by (*Lakshmi et al., 2011*)

$$Dt = \frac{M}{Vt}$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

Compressibility Index (Carr's Consolidation Index)

One of the ways of measurement of free flowing powder is compressibility as computed from density of a powder. It was calculated by using the formula. (*Lakshmi et al., 2011*)

$$\% \text{ Compressibility} = \left(\frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \right) \times 100$$

Standard values for Carr's index (% compressibility)

Carr's index	Type of flow
5-15	Excellent (free flowing granules)
12-16	Good (free flowing powdered granules)
18-21	Fair (powdered granules)
23-35	Poor (fluid cohesive powder)
33-38	Very poor (fluid cohesive powder)
> 40	Extremely poor (cohesive powder)

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. If the Hausner ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the formula **(Lakshmi et al 2011)**

$$Hausner\ Ratio = \frac{Dt}{Db}$$

Where,

Db = Bulk density of the powder

Dt = Tapped density of the powder.

EVALUATION OF SR TABLETS:

Post compression parameters:

Appearance:

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Dimension:

Thickness and diameter were measured using a calibrated barmier calliper. Six tablets of each formulation were picked randomly and dimensions determined. and it was determined to within +_ 0.01mm.

Weight Variation Test

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percent deviation was calculated using the following formula.*(Kuchekar et al., 2004).*

$$\textbf{Percentage Diviation} = \left(\frac{\textbf{Individual weight} - \textbf{Average weight}}{\textbf{Average weight}}\right) \times \textbf{100}$$

The weight was determined by using Sartorius balance and there is shown that every individual in a batch should be in uniform weight and weight variation within the permissible limits.

IP Standards for Percentage Weight Variation

Average weight.	Percentage deviation
80 mg or less.	10
More than 80 mg but less then 250 mg	7.5
250 mg or more	5

Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Six tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated. *(Lachman et al., 1991)*

A tablet hardness about is 6-8kg was considered adequate for mechanical stability.

Friability test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche Friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. The percent friability was determined using the following formula ;*(Lachman et al., 1991).*

$$\textit{Friability} = \left[\frac{\textbf{W1} - \textbf{W2}}{\textbf{W1}}\right] \times \textbf{100}$$

Where,

W1 = weight of the tablet before test,

$W2$ = weight of the tablets after test

Drug Content Estimation

Twenty tablets were weighed and powdered, 20 mg of equivalent of Gliclazide was weighed and dissolved in 100 ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 226 nm using UV- spectrophotometer (UV 1800 Shimadzu, Japan).*(Kumaran V et al., 2004)*

In vitro dissolution studies:

In vitro drug release of Miloxicame mouth dissolving tablet was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L, India). The dissolution test was performed using 900 ml of Phosphate buffer SSF pH 6.8 at 37 ± 0.5^0C. The speed of rotation of paddle was set at 50 rpm. 2 ml sample were withdrawn at time points of 2, 4, 6, 8, and 10 min and same volume was replaced with fresh media. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with pH 6.8 Phosphate buffer. Absorbance of solution was checked by using UV- spectrophotometer (UV 1800 Shimadzu, Japan) at a wavelength of 302 nm and drug release was determined from standard curve.

Wetting time:

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure.

Method

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 ml of water containing methylene blue 2 % w/v, a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as wetting time. *(Park et al., 2008& Gattani et al., 2009).*

It shown in table no. 1.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petridish containing 10 ml of PB pH 6.8. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation –

$$R = \left(\frac{Wa - Wb}{Wb}\right) \times 100$$

Where,

Wa = weight of tablet after absorption

Wb = weight of tablet before absorption

Six tablets from each formulation were analyzed performed and standard deviation was also determined. *(Park et al., 2008)*

In vitro dispersion time:

In vitro dispersion time of prepared tablet was done by dropping the tablet in 10 ml measuring cylinder containing 6 ml of simulated salivary fluid (pH 6.8). Time required for complete dispersion of tablet was measured. *(Metkar et al., 2011)*

In vitro disintegration time:

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined by using modified disintegrating test.

Disintegration test: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at $37^0 \pm 2^0$C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at $37^0 \pm 2^0$C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.*(Suresh S et al., 2007)*

Modified disintegrating test: The test is carried out in a Petridish (10 cm in diameter) filled with 10 ml of phosphate buffer pH 6.8. The tablet is carefully placed in the center of the petridish and the time for the tablet to disintegrate completely into the particles is noted.*(Goel et al., 2004 & Park et al., 2008).*

In vivo **studies** –

Male Wister rats weighing 150-220g fed with a standard diet are injected with 30mg/kg Gliclazide intravenously. As with alloxan ,three phases of blood glucose changes are observed . Initially, blood glucose is increased ,reaching values of 150-200mg% after 3h. six-eight h after gliclazide, the serum insulin values are increased up to 4 times ,resulting in a hypoglycemic phase which is followed by persistent hypoglycemia. Several diabetic symptoms depend on the dose of gliclazide. After the dose of 60mg/kg i.v. , symptoms occur already after 24-48h with hyperglycemia up to 800mg %,glucosuria and ketonemia . Histologically, the beta-cells are degranulated or even necrotic. A steady state is reached after 10-14 days allowing to use the animals for pharmacological tests.

RESULTS AND DISCUSSION

From the result it is concluded that there was no interference in the functional groups as the principle peak of the drug gliclazide were found to be unaltered in the drug polymer physical mixture indicating that they were compatible chemically.

The granules from the different formulation are evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner ratio and then the result were shown in the table no.

The *in vitro* result of all the formulations were obtained by dissolution testing and similarity factors value was calculated.

Pre-compression Parameters-

Evaluation of Granules.

This is the first parameter of pre-compression parameters. Which shows the- The angle of repose- for all the formulations was within 35° indicates all the formulations have good flow property. The compressibility index and Hausner's ratio- it was 11.76 to 14.54 and 1.13 to 1.17 indicating good flow character of the granules. So, all the results are within the prescribed limits. It indicates all the formulations have good flow property.

Evaluation of compressed tablets

Hardness of the tablets was in the range of 6.10 to 8.10 kg/cm2.This ensures good handling characteristics of all the batches. Weight loss in the friability test was less than 1% in all the cases, ensuring that the tablets were mechanically stable. All the tablets prepared contained the drug within 99.93 and 100.63±5% of the label claim. All the formulated tablets passed the weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 5% of the average weight.

IR Spectral Analysis

FTIR spectral studies.-

The FTIR spectra of pure GLI (crystalline), amorphous GLI, and all the substances. The IR spectrum of GLI presents characteristics peak at 3,273.57 and 3,192.58 cm-1 (NH amide stretch) 3,112.55 cm-1 (C-H aromatic streatch), 2,949.59 cm-1 (C-H aliphatic streatch – asymmetric),2,867.63 cm-1 (C-H aliphatic streatch- symmetric),1,709.59 cm-1 (C=O amide carbonyl streatch),1,595.81 cm-1 (N-H amide bend), 1,590 and 1,473.35 cm-1 (C=C aromatic streatch), 1,348 cm-1 (S=O sulfonyl streatch), 1,240.97 cm-1 (C-N ring streatch , heterocyclic), and 811.885cm-1 (p- phenyl group in fingerprint region).

In case of GLIA slight shift in few characteristics peaks was observed with no major difference in overall spectrum. The IR spectra of all solid dispersion systems showed disappearance of some peaks of gliclazide as well as shifting of some peaks to lower wave number.

The binary dispersion systems GLIKN 1 and GLISD 2 showed almost all peaks with low peak intensity as compared with pure and amorphous form of drug. Both GLIKN 1 and GLIKN 2 showed broadening of amide stretching vibration (N-H) and amide carbonyl stretching vibration (C=O) peaks characteristics of gliclazide . The graph is shown in figure.
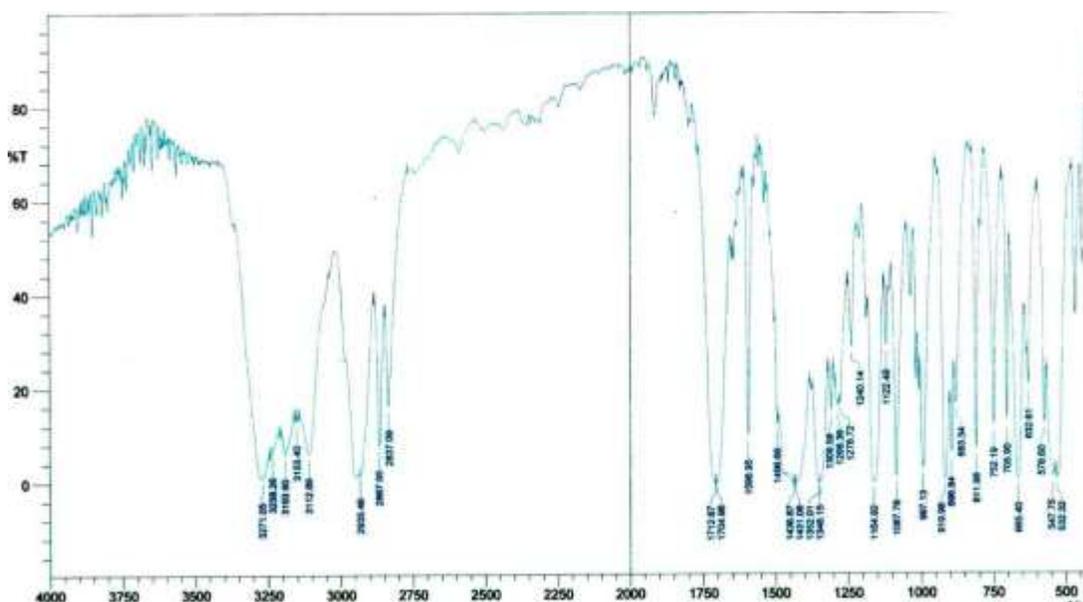
Figure 1: FTIR of gliclazide
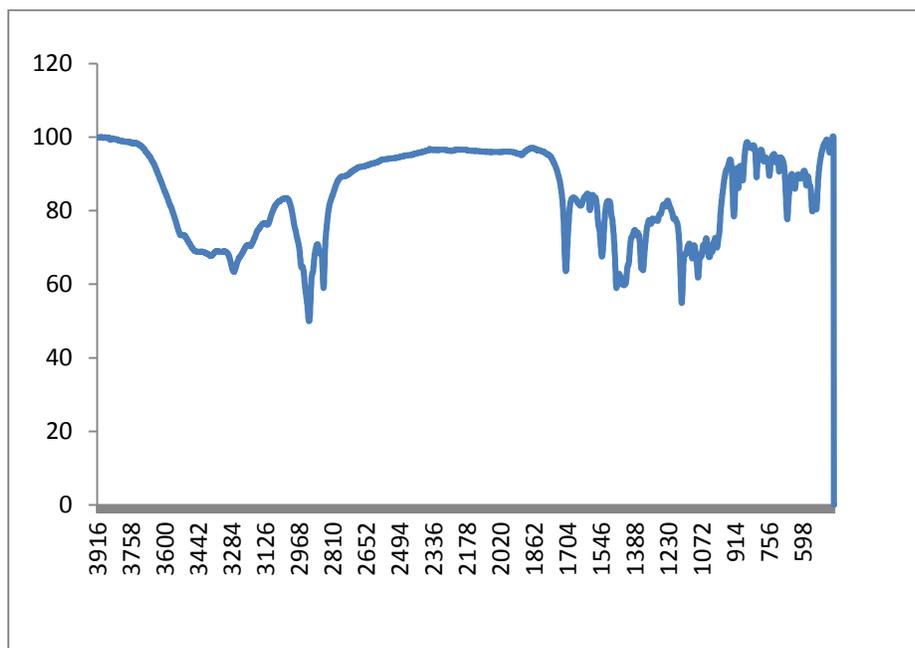
Figure 2: FTIR of gliclazide +ethyl cellulose
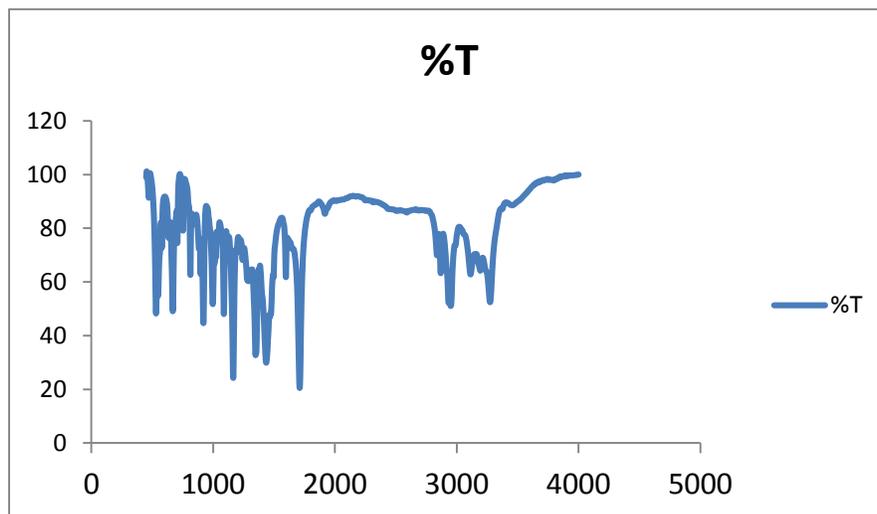
Figure 3: FTIR of gliclazide +ethyl cellulose +sod. bicarbonate.

Drug- excipients interaction studies

It is used to determine the interaction between the drug polymer and excipients. The drug, polymer and excipients must be compatible with one another to produce a product stable, efficacious and safe. The IR spectrums were represented in Figure.
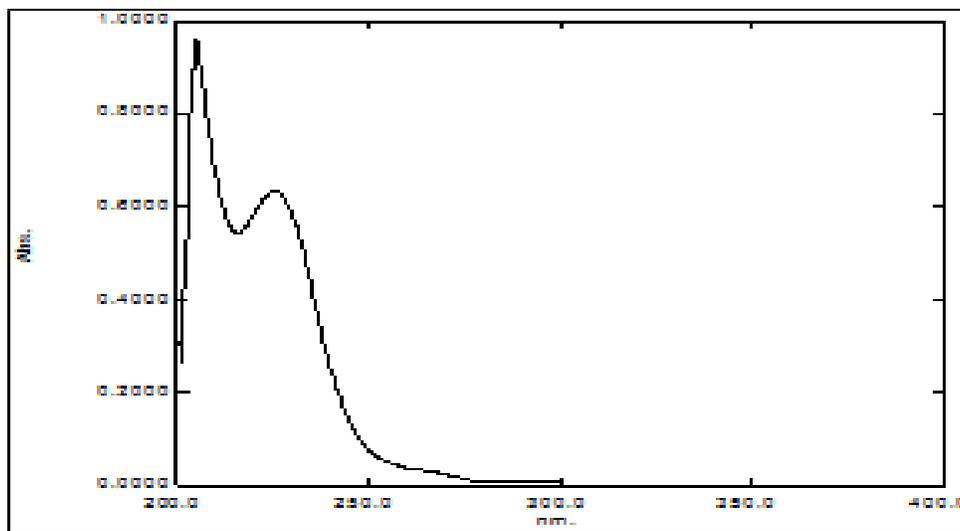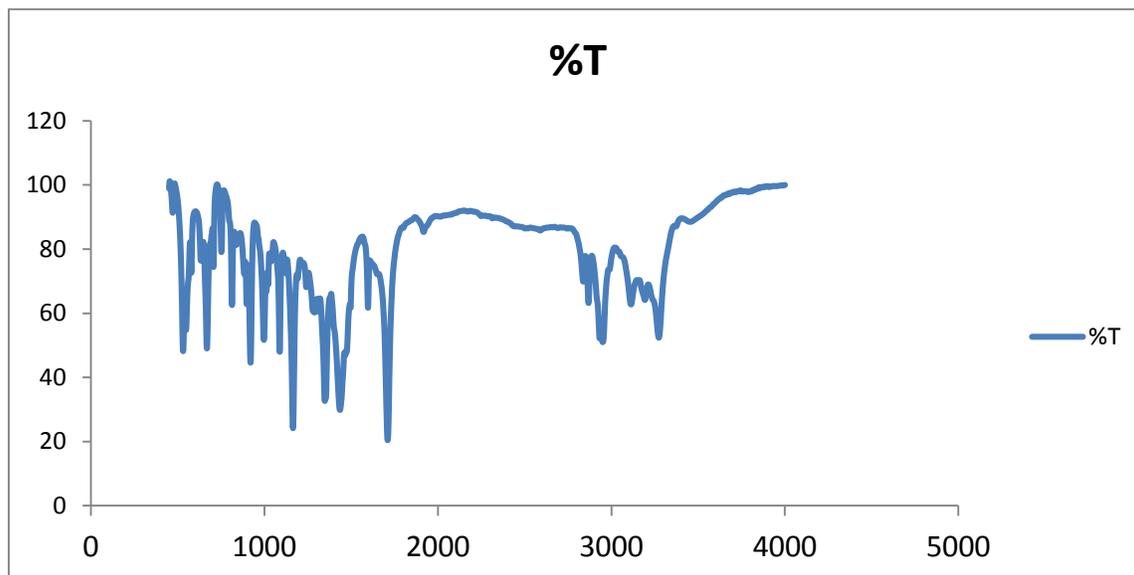

Figure 4: Gliclazide curve

Figure 5: Gliclazide + ethyl cellulose.

Dissolution release for Gliclazide

In vitro drug release of gliclazide was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L, India). The dissolution test was performed using 900 ml of Phosphate buffer SSF pH 6.8 at 37 ± 0.5^0C. The speed of rotation of paddle was set at 50 rpm. 2 ml sample were withdrawn at time points of 2, 4, 6, 8, and 10 min and same volume was replaced with fresh media. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with pH 6.8 Phosphate buffer. Absorbance of solution was checked by using UV- spectrophotometer (UV 1800 Shimadzu, Japan) at a wavelength of 302 nm and drug release was determined from standard curve. More than 70% of Gliclazide was released from all the formulation at the end of 8th hr of dissolution study.
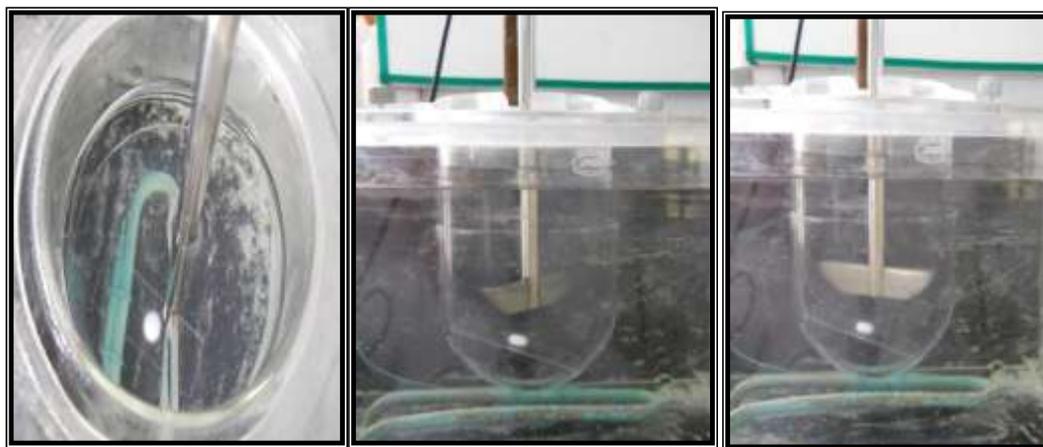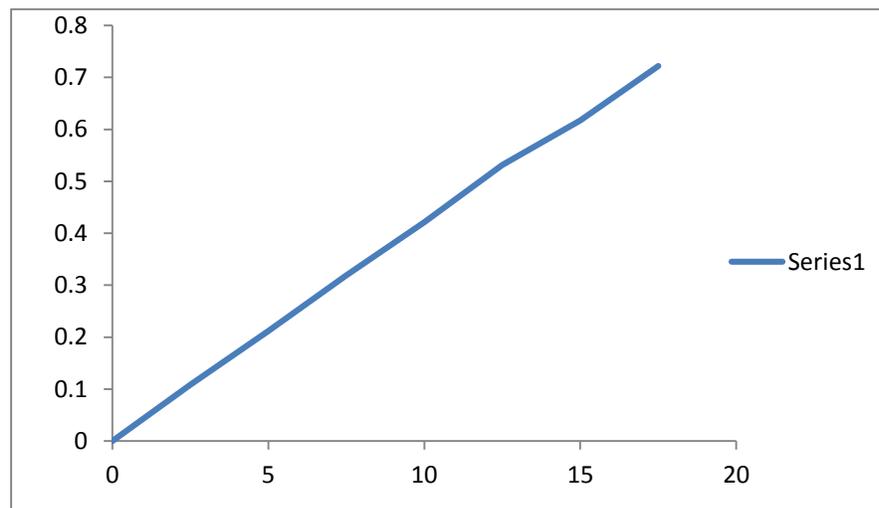

Figure 6: Photograph of dissolution studied.

Figure 7: Standard curve of dissolution

STABILITY STUDIES

Accelerated Stability study.

After determining the drug content and release studies, the optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40+_20c and 75 +_ 5% RH) for a period of 3 months in a stability chamber (Thermolab, Mumbai, India). The optimized formulations were placed in USP type-1 flint vials and hermatically closed with bromobutyl rubber plugs and sealed with aluminium caps . The samples were withdrawn at 15, 30, 60, 90 days and evaluated for the drug content and in vitro drug release.

CONCLUSION

From these results, it was found that all the pre-formulation characteristics of the formulation were found to be within the specified limits. From the drug content, post-compression parameters, in-vitro drug release studies it was found that among the various formulations. The formulation is further taken for pilot scale up studies and stability studies.

ACKNOWEDGEMENT

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