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FORMULATION AND EVALUATION OF ORAL SUSTAINED RELEASE MATRIX TABLETS OF GLICLAZIDE

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ABSTRACT

Sustained release matrix tablet of Gliclazide were prepared by direct compression method using Kollidon SR as a release retardant. carbopol, HPMC K15 LV and di-calcium phosphate are used as polymers in different concentration. Compatibility study was carried out by FT-IR. The prepared blends for matrix tablet were evaluated for their flow properties by measuring angle of repose, Carr's compressibility index and Hausner's ratio and also were evaluated for post-compression parameters such as hardness, friability, thickness, % weight variation, % drug content and *in-vitro* dissolution test.

KEYWORDS: Sustained release; Matrix tablet; polymers; Gliclazide; FTIR studies; In-vitro drug release; Kollidon SR *etc.*

INTRODUCTION

Delivery of the drugs can be achieved using various types of dosage forms including tablets, capsules, creams, ointments, liquids, aerosols, injections and suppositories. Most of these conventional drug delivery systems are known to provide immediate release of the drug with little or no control over delivery rate. To achieve and maintain therapeutically effective plasma concentrations, several doses are needed daily, which may cause significant fluctuations in plasma levels was shown in the Figure 1. Because of these fluctuations in drug plasma levels, the drug level could fall below the minimum effective concentration (MEC) or exceed the minimum toxic concentration (MTC). Such fluctuations result in unwanted side effects or lack of intended therapeutic benefit to the patient. Sustained-release and controlled-release drug delivery systems can reduce the undesired fluctuations of drug levels, thus diminishing side effects while improving the therapeutic outcome of the drug.[1]

The terms sustained release and controlled release refer to two different types of drug delivery systems, although they are often used interchangeably. Sustained-release dosage forms are systems that prolong the duration of the action by slowing the release of the drug, usually at the cost of delayed onset and its pharmacological action. Controlled-release drug systems are more sophisticated than just simply delaying the release rate and are designed to deliver the drug at specific release rates within a predetermined time period. Targeted delivery systems are also considered as a controlled delivery system, since they provide spatial control of drug release to a specific site of the body.

The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects.

MATERIALS AND METHODOLOGY

Materials used

The following materials of Pharma grade or the best possible Laboratory Reagent (LR)

SR. No.	Materials used	Grade	Manufacturer
1	Gliclazide	Pharma	Strides Arco labs ltd, Bangalore
2	Kollidon SR	LR	Sigma-Aldrich, Bangalore
3	Carbopol-940	LR	S D fine chemical Ltd, Mumbai

4	HPMC E15 LV	LR	S D fine chemical Ltd, Mumbai
5	Dicalcium phosphate	LR	S D fine chemical Ltd, Mumbai
6	Magnesium stearate	LR	S D fine chemical Ltd, Mumbai
7	Talc	LR	S D fine chemical Ltd, Mumbai

6.4 Pre-formulation studies

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives extensive information to bring out good quality at high standard at which optimal dosage desired. Pre-formulation studies were performed on the drug (API), which included melting point determination, solubility and compatibility studies.

Formulation development

In this work, direct compression method with the aid of polymers was attempted for the formulation development of sustained release matrix tablet of Gliclazide, various polymers in different concentrations were used so as to get tablets with good physical properties. The formulation design of matrix tablet of Gliclazide is shown in Table.5

Table 5: Formulation design of matrix tablet of Gliclazide.

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gliclazide	150	150	150	150	150	150	150	150	150
Kollidon SR	150	225	300	150	225	300	150	225	300
Carbopol-940	200	125	50	-	-	-	-	-	-
HPMC E15 LV	-	-	-	200	125	50	-	-	-
Dicalcium phosphate	-	-	-	-	-	-	200	125	50
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0

Preparation of matrix tablet

Matrix tablet were prepared by direct compression method. To prepare the tablets, the ingredients were weighed accurately and were screened through mesh (No.60). Gliclazide and polymers were mixed in a polybag for 15 mints and the mixture was passed through mesh (No.60). Finally, Talc and Magnesium stearate was added to the previous blend and blended for (15-10 mints) for uniform distribution before the compression. Different formulae, having different combination and ratios of polymers were developed to study the effect of polymers on drug release.

RESULT AND DISCUSSION

Pre-formulation testing is an investigation of physical and chemical properties of drug substance alone and when we combined with excipients. It is the first step in the rational development of dosage forms. The scope of pre-formulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product. In this regard formulation studies were carried out and the results for the experiment conducted are as follows.

7.1 Pre-formulation studies

7.1.1 Identification of drug

The results are shown in Table 7.

Table 7: Standards for Carr's index.

Carr's Index	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
35 – 38	Very poor
More than 40	Extremely poor

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by using the formula

Hausner's ratio=Pt/Pd

Where, Pt is tapped density and Pd is bulk density lower hausner's ratio (<1.25) indicates better flow properties than higher ones (> 1.25)

Table 8: Standards for Hausner's ratio.

Hausner's ratio	Flow
1.2 – 1.3	Excellent
1.3 – 1.4	Good
1.4 – 1.5	Fair
1.5 – 1.6	Poor

❖ **Post compression parameters**[72-75]

➢ **Weight variation**

In this method twenty tablets are selected and individually weighed of twenty tablets was noted. The average weight of these tablets is determined. The weight variation of individual tablet is determined with respect to average weight and percentage weight variation.

%Weight variation = (Individual weight- Average weight/Individual weight) 100

Table 9: Standards for percentage weight deviations.

Average weight	% difference
130 mg or less	±10.0
130 – 324 mg	±7.5
324 mg and greater	±5.0

➢ **Melting point determination**

Table 10: Melting point report of Gliclazide.

Sr. No.	Reported	Observed		
		Trail 1	Trail 2	Trail 3
1	180ºC	179ºC	180ºC	180ºC

B. Solubility analysis

Table 11: Solubility of Gliclazide in different solvents.

Sr. No.	Solvent	Solubility
1	Methanol	Freely soluble
2	Ethanol	Sparingly soluble
3	Water	Practically insoluble

C. Determination of λmax

The λmax of the Gliclazide in phosphate buffer pH 7.4 was found to be 226 nm and the curve was shown in Figure No 2.

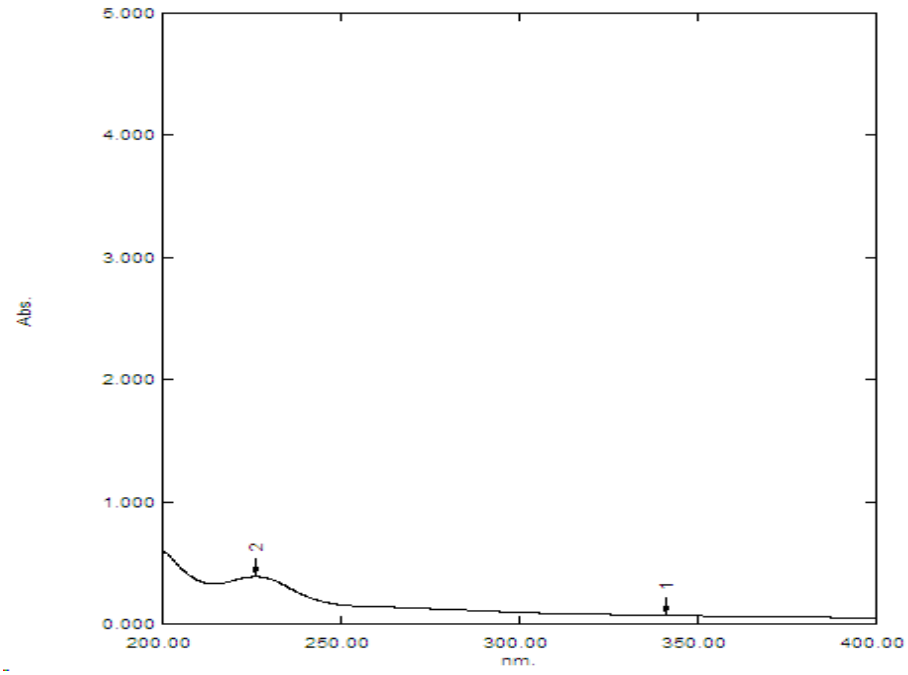


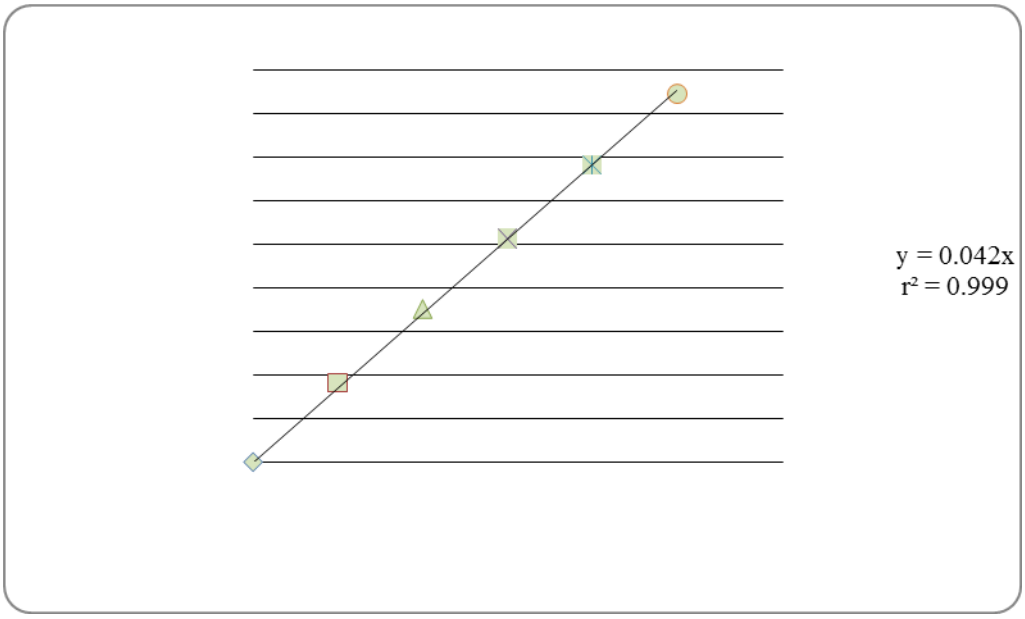
Figure No.2: λmax of pure drug Gliclazide.

7.1.2 Standard calibration curve of Gliclazide

Gliclazide obeys the Beer's law in concentration range of 4-10 µg/ml in phosphate buffer pH 7.4 with regression of coefficient of 0.9997. The calibration data is given in Table 13 and calibration curve was constructed in Figure 3.

Table 12: Standard plot of Gliclazide in phosphate buffer pH 7.4.

Sr. No.	Concentration in µg/ml	Absorbance at 226nm
1	4	0.182
2	8	0.352
3	12	0.513
4	16	0.683
5	20	0.846



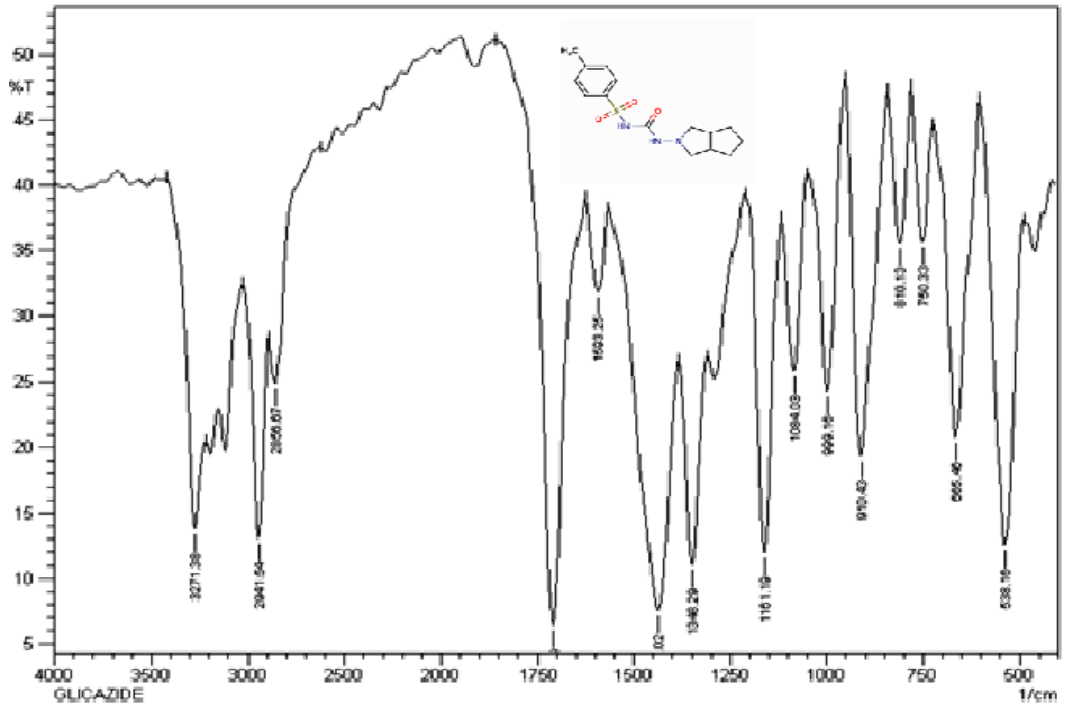


Figure No 3: Standard plot of Gliclazide.

7.2 Compatibility studies

❖ **FT-IR Studies**

Table 13: IR interpretation of pure drug Gliclazide.

Function group	Wave number (cm^{-1})
C=O Stretching	1708.99
S=O Vibration	1161.19
C=$(CH)_2$ Bending	1084.03
C=C Bending	999.16
Aromatic P-substitution phenyl	910.43
Aromatic ring	665.46

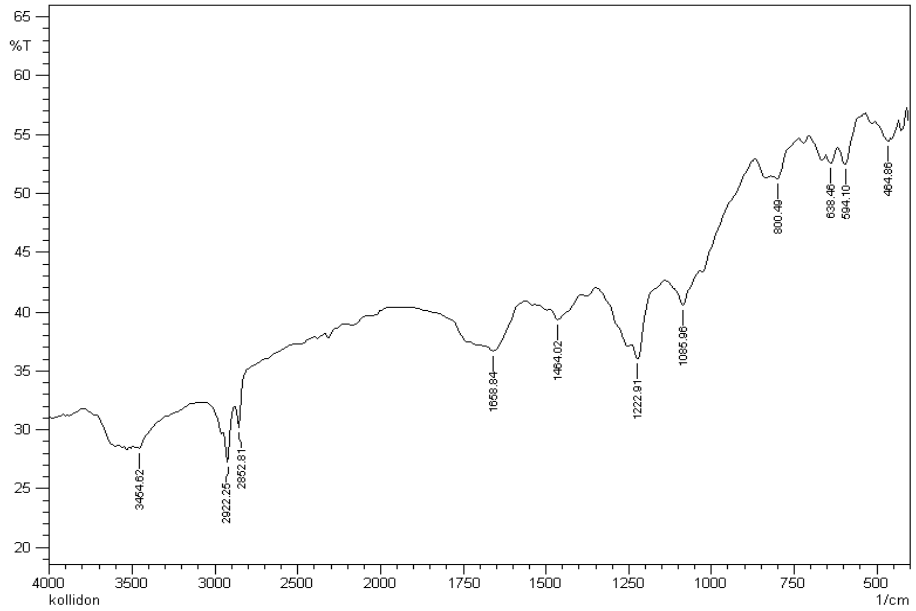


Figure No 5: FTIR spectrum of Kollidon SR.

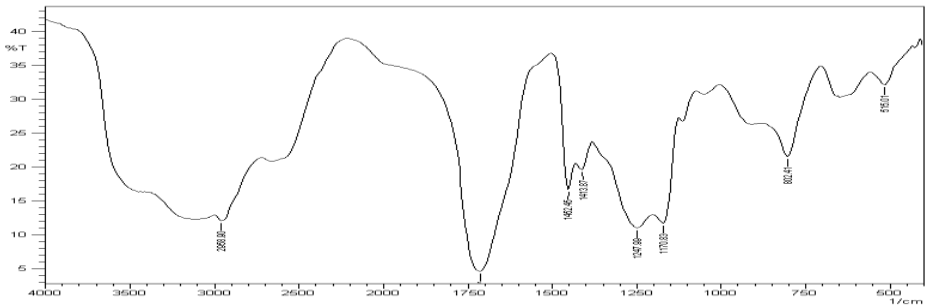


Figure No 9: FTIR spectrum of Gliclazide, HPMC K15 LV.

7.3 Evaluation parameters

A. Pre-compression parameters

Table 14: Pre-compression evaluation of tablet blend of Gliclazide.

Sr. No	Formulation	Angle of repose (ɵ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio
1	F1	25.3±0.76	0.45±0.012	0.57±0.010	14.4±0.77	1.23±0.03
2	F2	27.3±0.50	0.45±0.011	0.54±0.014	16.7±0.60	1.20±0.05
3	F3	26.1±0.52	0.47±0.010	0.55±0.007	17.7±0.44	1.18±0.02
4	F4	26.6±0.36	0.46±0.015	0.55±0.001	16.9±0.69	1.18±0.03
5	F5	25.5±0.32	0.46±0.011	0.55±0.014	17.6±0.62	1.20±0.04
6	F6	27.0±0.51	0.45±0.01	0.54±0.017	16.8±0.67	1.21±0.04
7	F7	26.0±0.65	0.45±0.013	0.55±0.010	16.9±0.60	1.20±0.01
8	F8	25.5±0.30	0.43±0.022	0.54±0.011	17.1±0.27	1.25±0.07
9	F9	26.0±0.51	0.46±0.014	0.54±0.01	16.0±0.57	1.17±0.04

Tablet 15: Post-compression evaluation of Gliclazide matrix tablets.

Sr. No	Formulation	Hardness *(kg/cm^2)	Thickness* (mm)	Friability # (%)	**Weight variation	**Drug content
1	F1	5.75±0.27	4.26±0.12	0.45	0.017±0.38	99.4±0.7
2	F2	6.00±0.31	4.25±0.10	0.51	0.037±0.20	99.9±0.8
3	F3	5.91±0.20	4.18±0.07	0.49	0.075±0.22	100±1.4
4	F4	6.00±0.31	4.23±0.08	0.62	0.018±0.21	99.8±1.3
5	F5	6.08±0.37	4.11±0.11	0.53	0.028±0.21	100±1.1
6	F6	6.00±0.31	4.26±0.12	0.55	0.075±0.23	98.9±0.6
7	F7	5.91±0.37	3.96±0.12	0.65	0.065±0.23	99.8±0.8
8	F8	6.16±0.25	4.21±0.09	0.63	0.028±0.20	100±0.8
9	F9	6.08±0.37	4.15±0.10	0.59	0.056±0.22	99.8±1.3
Mean ±SD *n=6, **n=10 and #n=20						

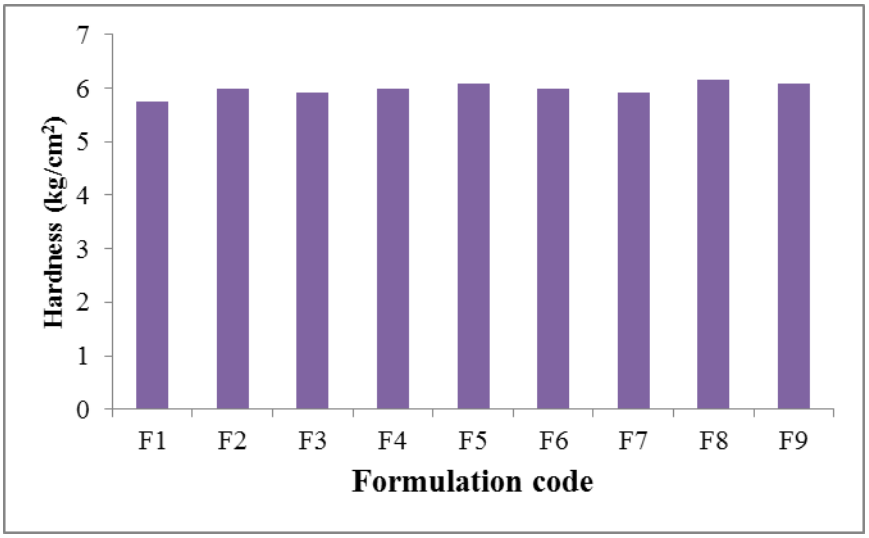


Figure No 6: FTIR spectrum of Carbopol 940.

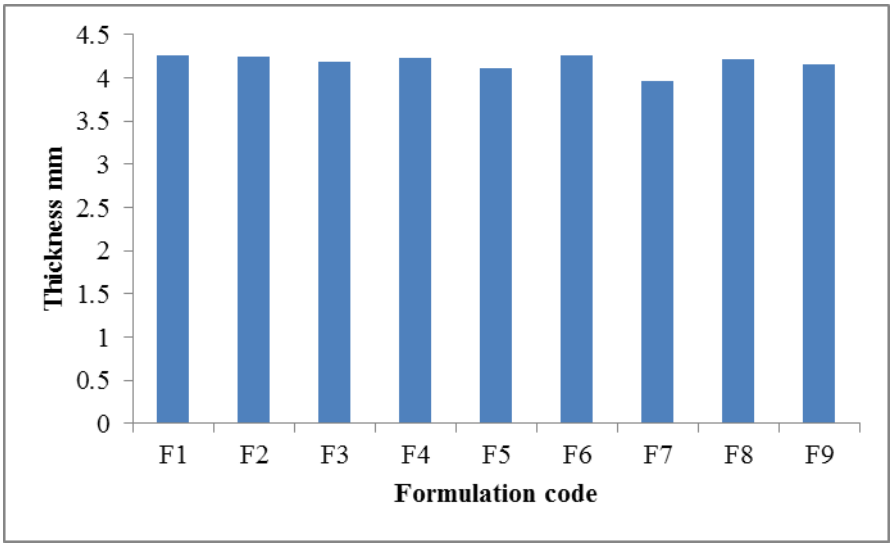


Figure No 15: Graphical representation of hardness.

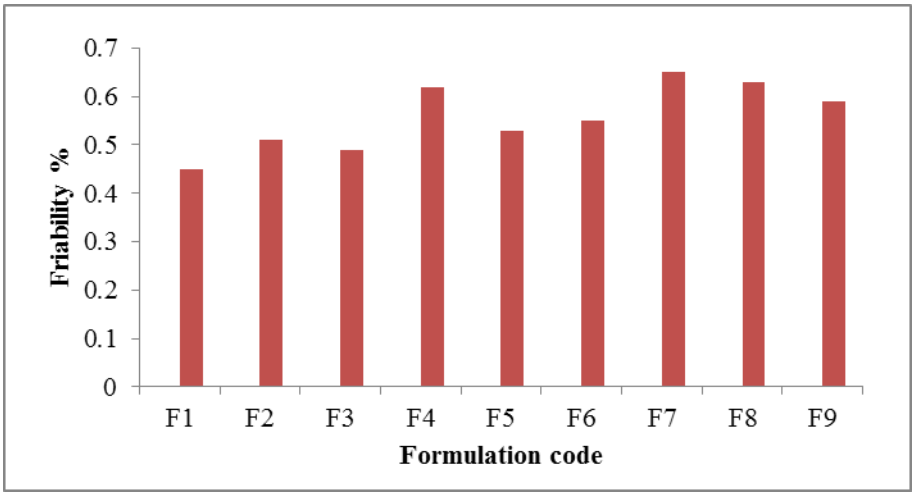


Figure No 16: Graphical representation of thickness.

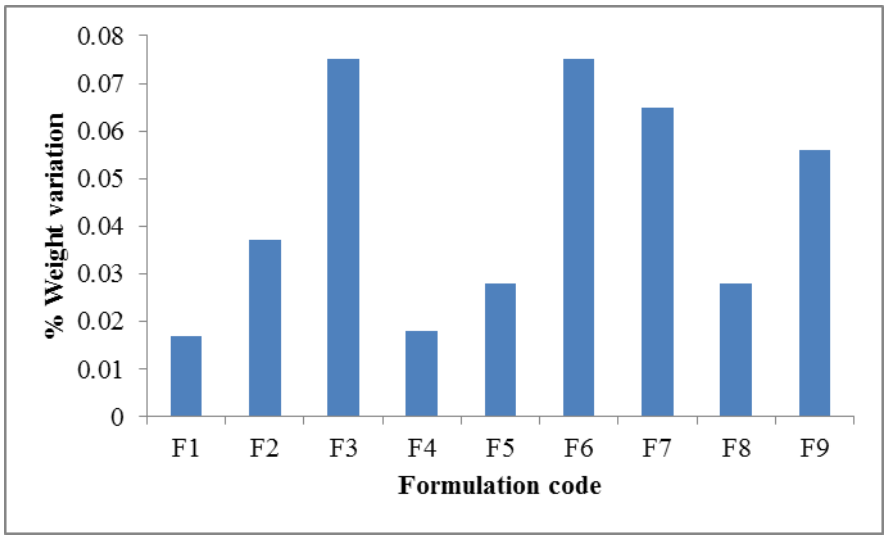


Figure No 17: Graphical representation of friability.

7.4 *In-vitro* release studies

Table 16: *In-vitro* release study of formulation F1-F3.

Sr.No	Time (hr)	%CDR		
		F1	F2	F3
1	0	0	0	0
2	1	35.26±0.33	33.96±0.503	31.86±0.251
3	2	56.27±0.61	52.61±0.29	50.04±0.250
4	4	75.6±0.54	73.00±0.769	70.02±0.250
5	6	84.17±0.50	82.3±0.503	80.82±0.888
6	8	90.61±0.51	87.57±0.296	85.76±0.66
7	12	96.2±0.32	94.42±0.444	92.51±0.56

Tablet 17: *In-vitro* release study of formulation F4-F6.

Sr.No	Time(hr)	%CDR		
		F4	F5	F6
1	0	0	0	0
2	1	25.04±0.140	23.19±1.015	21.06±0.255
3	2	35.29±0.355	32.86±0.665	30.59±0.475
4	4	51.37±0.498	47.28±0.351	44.25±0.285
5	6	70.73±0.604	67.20±0.236	65.91±0.541
6	8	84.48±0.518	78.67±0.499	75.68±0.335
7	12	93.92±0.684	91.93±0.285	89.22±0.466

Tablet 18: *In-vitro* release study of formulation F7-F9.

Sr.No	Time(hr)	%CDR		
		F7	F8	F9
1	0	0	0	0
2	1	31.25±0.644	28.67±0.810	26.36±0.503
3	2	41.07±0.407	37.39±0.202	35.62±0.320
4	4	62.17±0.233	60.33±0.190	55.28±0.652
5	6	71.18±0.879	69.95±0.658	66.39±0.539
6	8	85.78±0.600	83.2±0.360	81.59±0.857
7	12	91.68±0.314	90.83±0.550	89.05±0.674

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch and the weight of the tablet. The thickness of the batch from F1-F9 was found to be 3.96 ± 0.12 4.26 ± 0.12 mm and hardness was found to be 5.75 ± 0.27 6.16 ± 0.37 kg/cm2. The results are shown in Figure No 15 - 16 and Table 15.

This results confirmed that the tablets prepared from all the formulation batch showed uniform size of the tablet and with sufficient hardness of having good mechanical strength.

Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets. The friability of all the formulated tablets of Gliclazide was found to be between 0.45 - 0.65 % are shown in Figure No 17 and Table 15 and all the formulated tablets of Gliclazide were shown the % friability within the official limits(i.e. not more than 1%) Prepared tablets were evaluated for weight variation and percentage deviation from the average weight is shown in Figure No 18 and Table 15. From the results it was found to be within (±5) the prescribed official limits.

In-vitro drug release of Gliclazide matrix tablet in phosphate buffer pH 7.4 was performed. The in-vitro drug release profile of matrix tablet from different batches of formulated matrix tablets is illustrated in Figure No 20 - 22 and Table 16 - 18. The release of Gliclazide from matrix tablet was varied according to concentration of Kollidon SR and polymers used. It has been concluded that, if we increase the concentration of Kollidon SR, decrease in drug release rate was observed. This may be due to the reason that the polymer in higher concentrations in the tablets might have produced dense matrix around the drug particles, providing more barriers for them to escape and dissolve.

In-vitro drug release data of all formulations were fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release. And also In-vitro drug release data for all the formulations were subjected to release kinetic study according to Zero order, First order, Higuchi and Korsemeyer-Peppas equation to ascertain the mechanism of drug release. Accelerated stability studies were carried out at 40 ± 2 ºC and 75 ± 5 % RH for the optimized formulation F6 and monitored for physical appearance, drug content, and dissolution profile study. The results are shown in Table- 29, which indicated that all the tablets were stable during storage period.

CONCLUSION

- Nine batches of sustained release matrix tablet of Gliclazide were successfully prepared by using Kollidon SR, with different polymers like carbopol, HPMC K15 LV and dicalcium phosphate by direct compression method.
- Pre-formulation studies of Gliclazide were carried out by determination Melting point, solubility, λ-max. The obtained results complied with IP standards, thus indicating the purity of drug.
- FTIR study revealed that there was no interaction between the drug Gliclazide, polymers like Kollidon SR, carbopol, HPMC K15 L V and di-calcium phosphate used.
- The tablets were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index and the results confirmed the suitability of powder blends for direct compression with good flow property.
- The evaluation of post-compression parameters like hardness, thickness, friability, % weight variation, % of drug content confirmed that the results were within the specified limits.
- The *in-vitro* release of Gliclazide from sustained release matrix tablet was found to vary according to the type and ratio of polymer used. The release of Glicalzide was decreased with increasing polymer concentration. Among the different formulation, the formulation F6 and F9 is showed better sustained release.
- Based on the results, formulation (F6) containing 300mg of Kollidon SR was identified as ideal and better formulation among all formulations developed for Gliclazide matrix tablets. F6 formulation taken as a optimized formulation and taken for stability study.
- Accelerated stability studies of selected formulation F6 showed that, negligible changes in hardness, drug content uniformity and percentage of drug release revealed that the formulations are stable on storage.
- Overall the curve fitting in to various mathematical models confirmed that the *in-vitro* release of the formulations was best fitted in to first order model. The 'n' values more than 0.5 indicates that the mechanism in which the drug release from Glicazide

tablets follows Non-Fickian diffusion controlled system.

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