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Formulation and evaluation of Gliclazide sustained release tablets

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Abstract
Gliclazide Sustained release tablets were prepared by Direct Compression method using different polymers HPMC & Eutragit and combination of both show drug release in a sustain manner. Various solid matrix formulations were prepared with swellable and non-swellable polymers (HPMC K100CR, Eudragit L-100) in solid matrix using direct compression method. In the dissolution studies of all formulations, the formulation containing HPMC alone that is F1, F2, F3, F4 show 95% dissolution but shows fluctuations. The formulation containing Eudragit that is F5, F6, F7, F8 doesn't show better dissolution profile. In F3, F8, F9 formulations the first two formulations release of drug is completed within 8 to 10 hours. The later formulation gives a drug release in a sustain manner. The formulation F9, drug release profile is 99%, rest of all formulations. In the formulation F9 having swellable polymer HPMC K100CR and non-swellable polymer (Eudragit L-100) showing better drug release profile. Hence the combination of both polymers are better suitable for sustained release delivery. Thus, formulation F9 having both HPMC and Eudragit polymers in the ratio of 1:1 show 99% drug release for prolong time.

Keywords: Gliclazide, sustained release tablets, HPMC, Eudragit l-100

1. Introduction

Sustained release systems [1-3]

These systems include any drug delivery system that achieves slow release of drug over a prolonged period of time are known as sustain release systems. The goal of sustained –release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constituents drug release from the dosage form that is independent of the amount of drug in the delivery system (a constant release rate). Sustained release system generally do not attain this type of release and usually try to mimic Zero order release by providing drug in a slow first order fashion (concentration dependent) as shown in figure 1.4.1. Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery. Repeat – action tablets are an alternative method of sustained release in which multiple doses of the drug are contained within a dosage form, and each dose is released at a periodic interval.

Delayed release system in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun**.**

Advantages of sustained release products [4, 5]

- Decreased local and systemic side effects
- Reduced gastro intestinal irritation.
- Better drug utilization
- Reduction in the total amount of drug used.
- Minimum drug accumulation on chronic dosing.
- Optimized therapy.
- Reduction in fluctuation in drug level and hence more uniform pharmacological response.
- More uniform blood concentration.
- For drugs with very short elimination half–lives, sustained release products maintain efficacy over a long duration.

- Improved patient compliance
- Less frequent dosing.
- Reduced night time dosing.
- Reduced patient care time.
- Economy result from a decrease in nursing time and hospitalization.

Oral sustained drug delivery systems

Oral sustained release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a determined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action [6].

2. Materials & Methods

2.1. Materials Used

Gliclazide, Hydroxy Propyl Methyl Cellulose K100 CR, Eudragit L100, Aerosil, Microcrystalline cellulose 102, Polyvinyl pyrollidine.

2.2. Methods Used

Angle of Repose [7]

It was measured by fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height 'h', above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel, 'r' being the radius of base of the conical pile. The angle of repose is then calculated as:

$$\tan\theta = h / r \quad \text{(or)} \quad \theta = \tan^{-1} h / r$$

Where θ = angle of repose

Table 1: Flow Properties and corresponding Angle of repose

S.no	Flow Property	Angle of repose(degree's)
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55

Bulk Density and Tapped Density [8]

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the difference between two consecutive readings was found to be less than 2.0 %.

$$\text{Bulk density} = W / Vo \quad \text{Tapped Density} = W / V_f$$

The bulk density, and tapped density were calculated using the following formulas

Where,

W = weight of the powder, Vo = initial volume,

V_f = final volume.

Compressibility index or Carr's index [9]

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. It can be calculated as:

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 2: Relation of flow property with Hausner's ratio & Compressibility index

Compressibility Index (%)	Flow Character	Hausner's Ratio
10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59

Hardness [10]

Monsanto hardness tester was used to evaluate the hardness of tablet. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bold until the tablet fractures. As the spring is compressed, a pointer rises along a gauge in the barrel to indicate the force. The force of fracture was recorded, and the zero force reading was deducted from it. Ten tablets of each formulation were evaluated. It is measured in kg/m2.

Thickness and diameter [11]

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier calipers. It was determined by checking ten tablets from each formulation.

Friability [12]

Weigh accurately 20 tablets and place them in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus at 25 ±1 RPM and observe the tablets while rotating, such that no tablet sticks to the walls of the apparatus. Take the tablets out and observe for possible capping / breaking as none of these should be observed for the test to be valid. Weigh the tablets, after dusting excess powder from their surface.

Friability in % is calculated using the formula as:

$$\text{Friability} = (W1-W2)*100/W1$$

Where, W1 = Initial weight of the tablets taken,

W2 = Final weight of the tablets after testing.

Weight variation [13]

Twenty tablets were sampled randomly. Tablets were weighed individually and average weight was calculated. Deviation of each tablet from average weight was calculated and percent deviation was computed. IP limit for weight variation in case of tablets weighing more than 325mg is ± 5%.

Table 3: Weight variation tolerance

Average weight of tablets (mg)	Percentage deviation (±)
130 or less	10
More than 130	7.5
More than 325	5

Content uniformity test [14]

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at 276 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

***In vitro* drug release kinetics** [15, 16]

The in–vitro drug release studies were carried out in Basket type Dissolution apparatus. An accurately weighed quantity equivalent to 120 mg of drug of sustained release tablet was suspended in 900 ml phosphate buffer of pH 6.8 The dissolution medium was stirred at 37 ± 0.5 ºC. At the predetermined time interval the measured volume of samples was withdrawn with the help of pippetes and replacing the same volume with the fresh dissolution medium. All the samples were diluted to suitable concentrations with the same dissolution medium and measured the absorbance at 276 nm by using UV Spectroscopy. The amount of drug released was calculated with the help of regression equation of the calibration curve. The cumulative percentage of drug released was then calculated accordingly.

Stability studies [17, 18]

Stability is defined as the capacity of drug product to remain within established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating periods. So, in the present study, the stability of the drug product is assessed by exposing the product to various temperatures and humidity conditions. The optimized matrix tablets were subjected to stability studies at 250C+_20C/ 60%_+5% RH and 400C+_20C/75%_+5%RH the product were evaluated for their physical characteristics drug content and *in-vitro* drug release profiles over a period of 3 months.

3. Results

Table 4: Master formulation Table of Different Formulations

Ingredients	F1 (3%)	F2 (6%)	F3 (9%)	F4 (12%)	F5 (3%)	F6 (6%)	F7 (9%)	F8 (12%)	F9 (1:1)
Gliclazide(mg)	10	10	10	10	10	10	10	10	10
MCC 102(mg)	98	94.4	90.8	87.2	98	94.4	90.8	87.2	94.4
HPMC K100 CR(mg)	3.6	7.2	10.8	14.4	-	-	-	-	3.6
Eudragit L- 100(mg)	-	-	-	-	3.6	7.2	10.8	14.4	3.6
PVP K-30 (5%)	6	6	6	6	6	6	6	6	6
Aerosil (2%)	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Total tab wt (mg)	120	120	120	120	120	120	120	120	120

Table 5: Pre-compression parameters of Gliclazide

Formulation	Bulk Density (gm\ml)	Tapped Density (gm\ml)	Carr's Index (%)	Hausne r Ratio	Angle Of Repose
F1	0.510 gm/ml	0.598 gm/ml	15.81%	1.17	26.28
F2	0.512 gm/ml	0.597 gm/ml	15.38%	1.18	26.85
F3	0.515 gm/ml	0.602 gm/ml	14.43%	1.168	29.02
F4	0.505 gm/ml	0.591 gm/ml	14.64%	1.17	27.75
F5	0.507 gm/ml	0.595 gm/ml	14.72%	1.17	28.07
F6	0.507 gm/ml	0.597 gm/ml	14.97%	1.176	28.07
F7	0.512 gm/ml	0.595 gm/ml	13.846 %	1.16	29.39
F8	0.515 gm/ml	0.598 gm/ml	13.91%	1.161	29.74
F9	0.512 gm/ml	0.600 gm/ml	14.87%	1.17	27.14

Table 6: Post compression parameters of Gliclazide

Formulation	Avg. Wt (mg)	Diameter(mm)	Hardness (Kg\cm2)	Friability	Thickness (mm)
F1	121	6	5.5	0.11	4.60
F2	122	6	5.4	0.06	4.71
F3	122	6	5.4	0.02	4.90
F4	124	6	6.0	0.04	4.10
F5	120	6	5.1	0.14	4.90
F6	120	6	5.4	0.06	4.56
F7	121	6	5.5	0.16	4.44
F8	123	6	5.5	0.41	4.70
F9	119	6	5.6	0.14	4.80

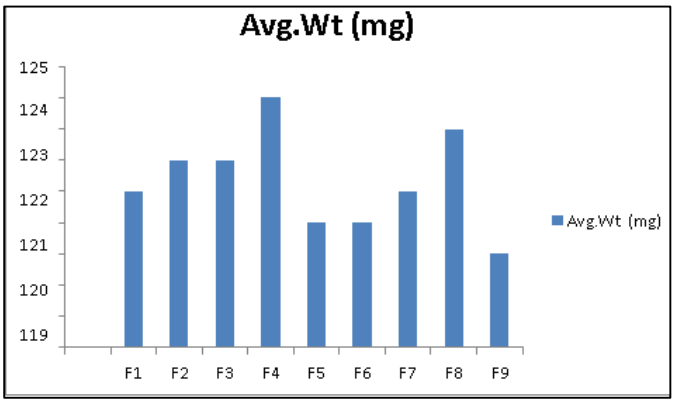

Fig 1: Bar diagram of average wt of formulations

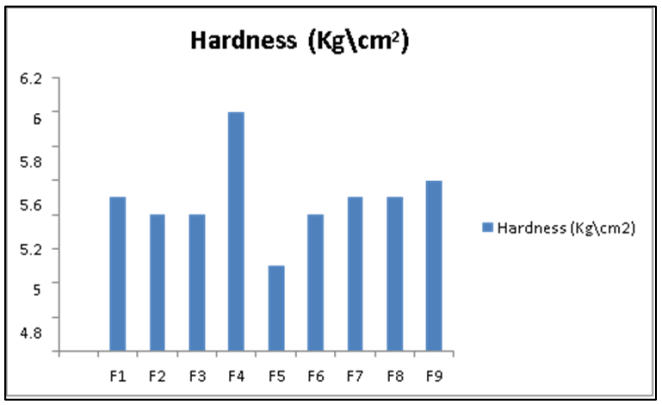

Fig 2: Bar diagram of Average hardness of formulations

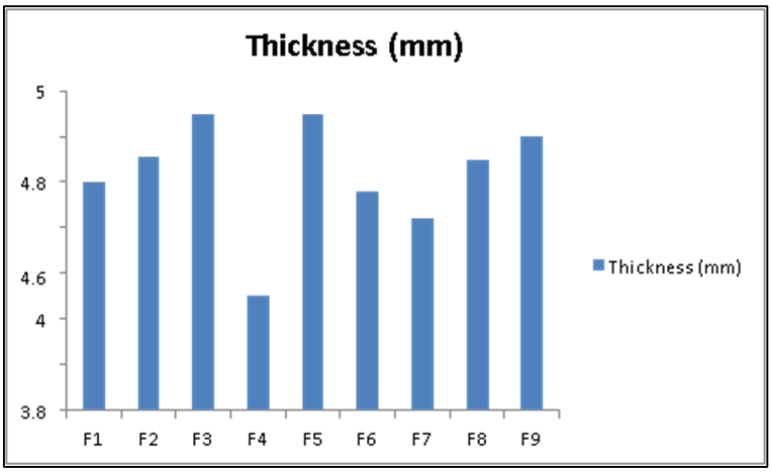

Fig 3: Bar diagram of Average thickness of the formulations

Table 7: Dissolution table of formulations in 6.8 Phosphate buffer

Time(hrs)	0hr	1hr	2hr	4hr	6hr	8hr	10hr	12hr	14hr
F1	0	22.36	34.23	55.63	69.77	76.54	81.43	93.52	96.07
F2	0	23.46	33.12	53.73	60.26	77.02	82.45	96.9	96.9
F3	0	17.94	34.23	45.82	58.66	64.32	71.42	85.30	96.62
F4	0	23.74	30.92	54.66	68.74	76.28	77.54	81.71	89.44
F5	0	25.39	35.88	59.35	67.71	73.56	79.43	96.62	97.17
F6	0	24.29	36.99	58.25	63.98	70.39	80.64	93.31	98.28
F7	0	26.22	34.23	51.57	61.01	69.67	73.53	77.57	83.92
F8	0	20.70	39.75	54.93	70.64	78.09	84.12	91.38	99.11
F9	0	21.53	36.44	67.63	79.91	85.51	89.65	94.41	99.38

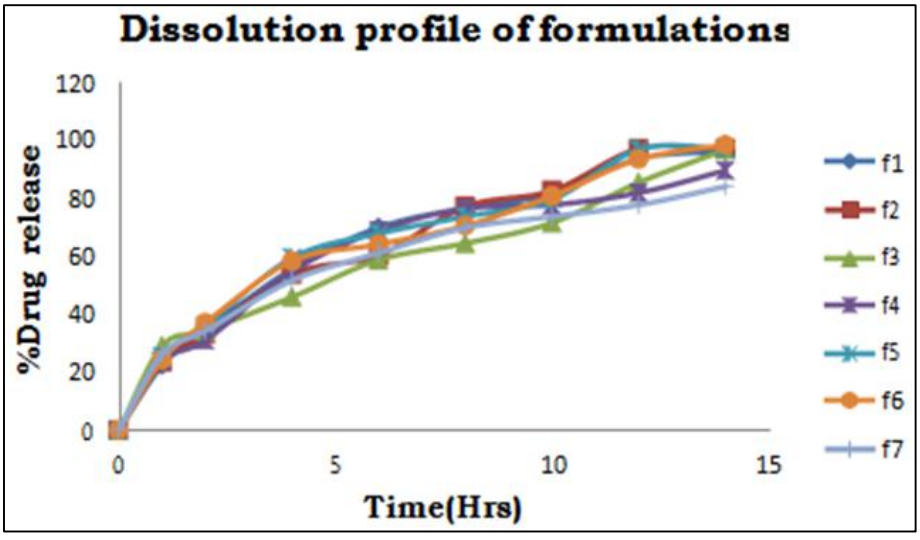

Fig 4: Dissolution profile of different formulations

Table 8: Percentage drug release in different time

Time in(Hr)	%Drug released	%Drug unreleased	Log% drug released	Log% drug unreleased	Log T	Sqt T
0	0.0	100	0.0	2.0	0.000	0.000
1	21.53	78.47	1.333	1.895	0.000	1.000
2	36.44	63.56	1.5616	1.803	0.301	1.414
4	67.63	32.37	1.8301	1.510	0.602	2.000
6	79.91	20.09	1.9026	1.303	0.778	2.449
8	85.51	14.49	1.9320	1.161	0.903	2.828
10	89.65	10.35	1.9526	1.015	1.000	3.162
12	94.41	5.59	1.9750	0.747	1.079	3.464
14	99.38	0.62	1.9973	0.207	1.146	3.742

Table 9: Stability Data of Optimized Formulation (F9) at 40 ± 20C / 75 ± 5% RH.

S. No.	Time(days)	Physicalchanges	%drug content*±SD	Moisture content	%drug release *±SD
1.	1stday (initial)	Round, white color uncoated tablets with plain on both side.	98.95±0.48	0.82	99.5%
2.	30th day (1 month)	No changes	98.81±0.11	0.78	98.6%
3.	60th day (2 month)	No changes	98.12±0.13	0.80	97.3%
4.	90th day (3 month)	No changes	98.01±0.28	0.78	97.2%

4. Discussion

Gliclazide showed maximum absorbance at 276nm. Gliclazide was prepared at different concentrations and absorbance was observed at 276nm.A calibration curve was plotted and the curve observed is linear. Bulk density of all formulations range from 0.505 to 0.515.Tapped density of all formulations range from the 0.591 to 0.602.Hausner's ratio of alla formulations range varied from1.16 to 1.18.Compressibility Index of all formulations was found to be 13.84% to 15.81%. Angle of repose of all formulations was found to be 26.28 to 29.75.Hence by the above values, it is confirmed that all the formulation prepared showed good flow properties. The results of the weight variation tests showed values in the desired range varying from 120mg to 123 mg. The thickness of tablets prepared for all formulations ranges between 4.1mm to 4.9mm.The hardness of the tablets for the prepared formulations varied between 5.1kg/cm2 to 6.0kg/cm2. Various solid matrix formulations were prepared with swellable and non-swellable polymers (HPMC K100CR, Eudragit L-100) in solid matrix using direct compression method. In the dissolution studies of all formulations, the formulation containing HPMC alone that is F1, F2, F3, F4 show 95% dissolution but shows fluctuations.

The formulation containing Eudragit that is F5, F6, F7, F8 doesn't show better dissolution profile. In F3, F8, F9 formulations the first two formulations release of drug is completed within 8 to 10 hours. The later formulation gives a drug release in a sustain manner. The formulation 9, drug release profile is 99%, rest of all formulations. In the formulation 9 having swellable polymer HPMC K100CR and non-swellable polymer (Eudragit L-100) showing better drug release profile. Hence the combination of both polymers are better suitable for sustained release delivery. Thus, formulation 9 having both HPMC and Eudragit polymers in the ratio of 1:1 show 99% drug release for prolong time. So, all the in-vitro evaluation studie, preformulation studies, powder characteristics, tablet evaluation studies proved to be satisfactory for the drug delivery.

5. Conclusion

In the conclusion Gliclazide Sustained release tablets were prepared by Direct Compression method using different polymers i.e HPMC & Eutragit and combination of both show drug release in a sustain manner. Although there are number of difficulties to be worked out to achieve prolong time of drug release a large number of companies are focusing towards commercializing this technique ie in a inexpensive, less dose, high drug release effect for a prolong time. So Gliclazide, an antidiabetic drug which is sulphonyl urea derivative used to treat Type II diabetis can be delivered by using Matrix tablet by sustain drug delivery to increase pharmacological activity with a reduced dose and frequency.

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