AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Design and In vitro Evaluation of Glyburide Controlled Release Trilayer Matrix Tablets Using Natural Gums

B. Ram Prasad[1], D.V.R.N. Bhikshapathi*[2]

[1]Research Scholar, Mewar University, Chittorgarh, Rajasthan, India

[2]Research Supervisor, Mewar University, Chittorgarh, Rajasthan, India

ABSTRACT:

The aim of the present study is to design and evaluate the controlled release Glyburide trilayer matrix tablets, to achieve zero-order drug release for sustained plasma concentration. Matrix tablets were prepared by direct compression whereas three-layer tablets were prepared by compressing polymer barrier layers on both sides of the core containing the drug. Formulations were prepared by using different grades of hydroxy propyl methyl cellulose and Ethyl cellulose. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF16 was found to be optimized formulation. These results also demonstrated the suitability of three-layered tablet formulation of Glyburide to provide controlled release for prolonged period and improved linearity for Glyburide in comparison to marketed product in the management of Diabetes.

Keywords: Glyburide, Type II Diabetes, HPMC Grades, EC, MCC, Release order kinetics.

*Corresponding Author Email: dbpathi71@gmail.com

Received 06 July 2018, Accepted 15 July 2018

Please cite this article as: Bhikshapathi DVN *et al*., Design and In vitro Evaluation of Glyburide Controlled Release Trilayer Matrix Tablets Using Natural Gums. American Journal of PharmTech Research 2018.

INTRODUCTION:

Conventional oral dosage forms such as tablets and capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability [1]. Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet [2]. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active ingredient and one or two impermeable or semipermeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tableting [3,4].

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Hydrophilic polymers have been given considerable attention in the formulation of controlled release drug delivery systems for various drugs. HPC, HPMC and sodium CMC & Carbopol are a few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release systems [5].

Geomatrix technology

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release [6].

Glyburide is a second-generation sulfonyl urea that is an orally bioavailable hypoglycaemic agent used in the management of type 2 diabetes. Different research has reported that glyburide has a low bioavailability, which is attributed to its poor dissolution properties. It has short half-life of 4-6 hours. Glyburide in oral conventional dosage form has the dosage regime of three times a day due to having short elimination half-life of 5 hour. Controlled release concept and technology has received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs. When drugs are administered as conventional dosage forms such as tablets, capsules etc. usually produce wide ranging fluctuations in drug concentration in the blood stream and tissues and consequently undesirable toxicity and efficiency [7].

MATERIALS AND METHOD

Materials

Glyburide pure drug was generous gift from Aurobindo Pharma Ltd., Hyderabad. Sodium carboxyl methyl cellulose, Ethyl cellulose, HPMC K 4 M, HPMC K 15 M & HPMC K 100 M was obtained from Rubicon labs, Mumbai. Carbopol-934P was obtained from Hetero health care, India. Karaya Gum was obtained from Nutriroma, Hyderabad. Magnesium stearate, Talc, Dibasic calcium phosphate was obtained from S D Fine - Chem Ltd, Mumbai. All other chemicals used were of analytical grade.

Methods

Micromeretic Studies of Glyburide

Angle of Repose [8], **Carr's compressibility Index** [9], **Bulk Dentistry** [10], **Tapped Density** [11], **Hausner Ratio.**

Formulation of controlled release Glyburide Trilayer matrix tablets

The Trilayer matrix tablets of Glyburide were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90% drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) to continue the drug release for 24 h.

Preparation of middle active layer

Sixteen formulations (F1-F16) for active layer were prepared by direct compression method using polymers like different HPMC grades, Sodium CMC and Ethyl Cellulose. All the formulations were varied in concentration of polymers, talc (1.5mg) & magnesium stearate (1.5mg) constituted in all the formulations. These materials were screened through ≠60 and mixed together in motor by using pestle. Final mixtures were compressed by using 11mm diameter flat punches on a sixteen-station rotary tablet press. Formulation of active layer was depicted in Table 1, 2. The prepared tablets were subjected to dissolution studies.

Table 1: Formulation trails for Glyburide middle active layer

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Glyburide	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
HPMC K 4M	25	30	35	---	---	----	----	----	----	15	15	15	----	----	----	----
HPMC K 15M	---	----	----	25	30	35	----	----	----	10	15	20	----	----	----	----
HPMC K 100M	---	---	---	----	---	----	25	30	35	-----	----	----	25	30	35	40
Gum Karaya	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
MCC	30	25	20	30	25	20	30	25	20	30	25	20	30	25	20	15

Dibasic calcium phosphate	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

Table 2: Composition of Glyburide trilayer matrix tablet

Ingredients	**AF16**	**BF16**	**CF16**	**DF16**	**EF16**	**FF16**	**GF16**	**HF16**
Middle active layer (f16) (mg)								
Glyburide	5	5	5	5	5	5	5	5
HPMC K 100M	40	40	40	40	40	40	40	40
Gum Karaya	20	20	20	20	20	20	20	20
MCC	15	15	15	15	15	15	15	15
Dibasic calcium phosphate	20	20	20	20	20	20	20	20
UPPER AND LOWER LAYER (mg)								
Carbopol-934P	20	25	30	35	40	42.5	45	50
Ethyl cellulose	52	50	52	47	50	42.5	42	42
Dibasic calcium phosphate	50	47	40	40	32	35	35	30
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Preparation of upper and lower layers

The barrier layers were formulated employing hydrophobic swellable polymer natural wax i.e. Carbopol-934P the swelling erosion modelling fillers which include water soluble DCP, EC and Gum Karaya. The procedure tried to make the compacts was via direct compressions. For the first procedure the wax, Gum Karaya and the filler was mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in Table 1,2.

Formulation of Glyburide Trilayer tablets:

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20 minutes. Initially, the volume of die cavity; (12mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (600mg). Then the pre-weighed amount of powder equivalent to bottom layer (125mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted and 100mg of the drug containing middle active layer optimized formulation (F16) was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre-weighed (125mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test.

Evaluation of Trilayer matrix tablets of Glyburide

Hardness [12], **Friability** [13], **Weight variation** [14], **Drug content / Assay** [15].

In-vitro drug release profile

In vitro drug release studies for developed Trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± 0.5^0C temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 242nm.

Drug release kinetics

To describe the kinetics of the drug release from matrix tablet, mathematical models such as Zero-order, first order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen based on the goodness-or fit test [17].

Drug-excipient compatibility studies: FTIR & DSC studies [18].

Stability studies

The stability study of the formulated Trilayer tablets were carried out under different conditions according to ICH guidelines using stability chamber (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION

Pre-compression parameters

All the powder mixture belonging to different formulations was tested for micrometrics studies in order to determine the flow properties. All the formulations AF16 to HF16 showed good flow properties, the results are summarized in Table 5.

Table 5: Powder flow properties of Glyburide, powder blends of active layer and barrier layer polymers

Powder propertis	AF16	BF16	CF16	DF16	EF16	FF16	GF16	HF16
Bulk density (g/cc)	0.7151±0.04	0.7121±0.46	0.512±0.02	0.7050±0.14	0.714±0.56	0.684±0.78	0.695±0.02	0.704±0.56
Tapped density(g/cc)	0.787±0.10	0.790±0.93	0.629±0.17	0.767±0.2	0.795±0.93	0.746±0.82	0.781±0.048	0.796±0.93
Angle of repose(o)	33.69±0.63	34.93±0.66	33.12±0.63	31.89±0.43	24.39±0.66	33.09±0.27	28.15±0.02	26.39±0.66
Carr's index	8.09±0.91	8.02±0.93	9.49±0.51	8.29±0.91	8.35±0.94	7.62±0.58	7.28±0.33	8.15±0.94

Preparation of middle active layer

The matrix tablets of Glyburide were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profiles.

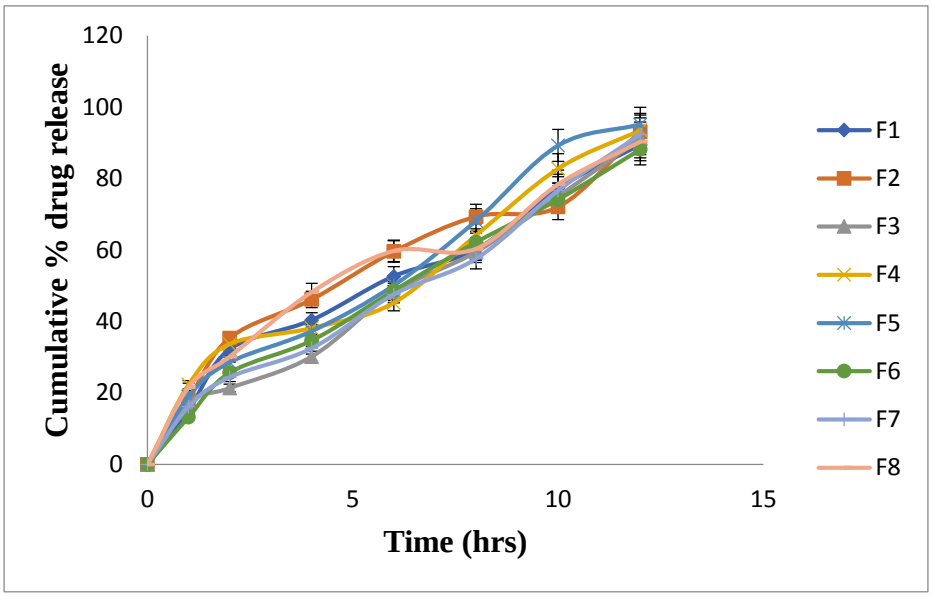


Figure 1: In vitro Dissolution profile of F1-F8 Glyburide active layer formulations

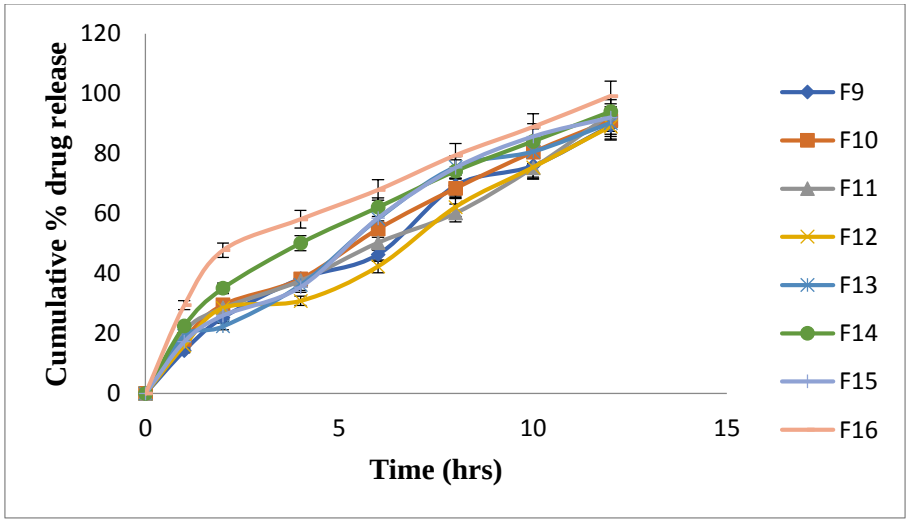


Figure 2: In vitro Dissolution profile of F9-F16Glyburideactive layer formulations

Figure 3: Glyburide Trilayer matrix tablets

From the above results, among all the formulations the formulation F16 was decided as optimized formulation for active layer based on the highest drug release i.e. 99.24±5.25 within 12hrs when compared with other preparations (Tables 3,4; Figures 1,2). Formulation F16 was chosen as active layer for further studies.

Evaluation of Trilayer matrix tablets of Glyburide

The Glyburide Trilayer matrix tablets are shown in Figure 3. Sustained release tablets generally have hardness in the range of 7-10 kg/cm^2. In case of Trilayer tablets the hardness of the tablets was found to be 7.2 to 8.4 kg/cm^2. The friability of the formulations was found to be less than 1% and hence the tablets with lower friability may not break during handling on machines and or shipping. All the batches of the tablets complied with the weight variation limits as per the IP. The drug content in different formulation was highly uniform and the results are depicted in Table 9. In phosphate buffer pH 6.8, HPMC showed good swelling property. In Trilayer tablets of Glyburide, HF16 showed highest degree of swelling index 209.11%, where as in AH16 showed leased swelling with a swelling index of 126.99%.

In vitro dissolution studies of Glyburide Trilayer tablets

The release of Glyburide from different formulations was carried out in phosphate buffer pH 6.8 and the results are depicted in Table 7. The Trilayer tablets extended the drug release up to 24 hrs. The highest drug release was found in the formulation HF16 i.e. 99.26 % within 24 h. HF16 was found to be optimized formulation based on the dissolution and other evaluation parameters. The results are shown in Table 6. The comparison of marketed product and optimized formulation HF16 was shown in figure 4. The drug release from marketed product was 94.21% within 24hrs.

***In vitro* dissolution studies of Glyburide Trilayer tablets formulated in different trails**

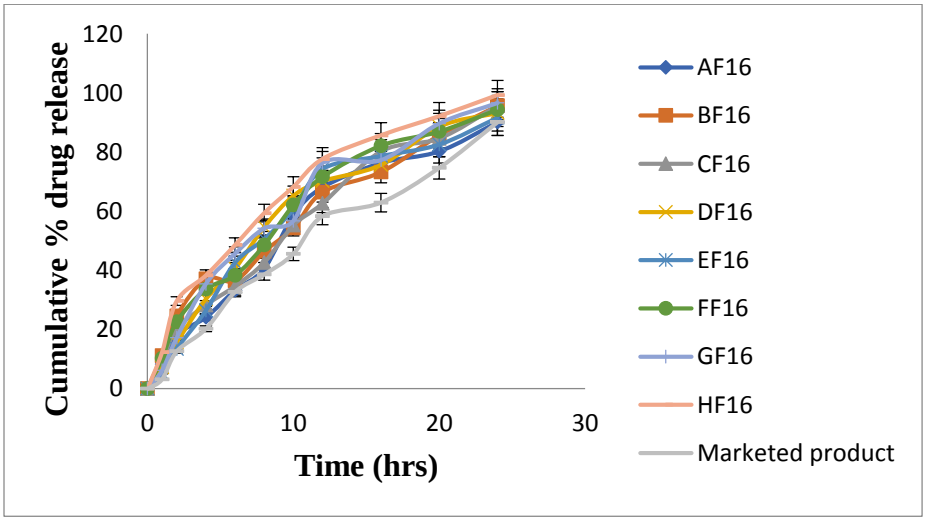


Figure 4: In-vitro dissolution studies of AF14-HF14

Table 3: Dissolution profile of different formulations of Glyburide active layer (F1-F8):

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	15.08±0.95	22.04±1.32	14.09±0.93	17.28±0.95	19.34±0.99	20.24±1.30	18.93±0.99	21.32±0.94
2	24.17±1.35	31.15±2.09	27.25±1.35	24.16±1.35	30.28±2.09	32.28±2.02	29.05±2.08	28.05±1.89
4	35.36±2.05	46.20±2.50	40.32±2.46	42.05±2.46	46.17±2.51	44.16±2.50	43.36±2.46	46.45±2.49
6	47.20±2.50	55.56±2.89	52.40±2.81	50.34±2.83	58.36±2.96	56.38±2.89	58.27±2.96	58.36±2.99
8	59.19±2.90	69.39±3.19	62.28±3.10	64.28±3.15	70.45±3.82	68.20±3.18	62.54±3.09	68.28±3.58
10	78.24±3.93	79.26±3.93	82.36±4.90	85.08±4.89	82.19±4.28	75.19±3.80	80.38±4.25	81.37±4.05
12	88.39±4.97	90.74±5.01	89.74±4.44	93.36±5.06	92.36±5.04	91.02±5.02	94.37±5.12	90.12±5.01

Table 4: Dissolution profile of different formulations of Glyburide active layer (F9-F16)

Time (hrs.)	F9	F10	F11	F12	F13	F14	F15	F16
0	0±0	0±0	0±0	0±0	0±0	**0**±0	0±0	0±0
1	17.12±0.94	25.24±1.37	19.56±0.99	16.17±0.96	22.67±1.20	20.12±1.20	24.45±1.36	28.16±1.97
2	25.36±1.37	29.39±1.97	28.24±1.97	24.34±1.36	30.42±2.08	38.18±2.18	27.20±1.96	36.24±1.36
4	38.29±2.42	38.15±2.40	37.30±2.40	32.54±2.10	42.19±2.61	45.67±2.65	30.14±2.08	53.15±2.40
6	46.68±2.67	54.29±2.70	50.15±2.60	47.67±2.66	54.36±2.70	52.20±2.75	52.35±2.62	65.47±2.63
8	69.07±3.26	68.38±3.25	60.39±3.10	57.38±2.99	65.17±3.22	65.89±3.52	67.47±3.25	79.34±3.10
10	75.36±3.83	80.17±4.32	75.28±3.83	76.94±3.83	78.48±3.83	89.36±4.98	72.36±3.80	88.67±3.94
12	89.17±4.99	91.60±5.02	93.56±5.10	92.56±5.08	90.56±5.01	96.46±5.42	94.19±5.12	99.24±5.25

Table 6: Physical evaluation of Trilayer tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)	% Drug content
AF16	5.58	7.2±0.24	0.15	596±20	97.51
BF16	5.60	6.3±0.38	0.28	599±20	96.82
CF16	5.45	6.5±0.45	0.26	595±20	96.25
DF16	5.73	7.3±0.24	0.30	594±20	97.08
EF16	5.71	6.5±0.45	0.35	597±20	95.74
FF16	5.62	7.6±0.42	0.18	595±20	97.47
GF16	5.54	6.1±0.23	0.23	596±20	96.25
HF16	5.70	7.8±0.50	0.24	600±20	98.91

Table 7: In-vitro dissolution studies of Glyburide Trilayer Table

TIME (hrs)	AF16	BF16	CF16	DF16	EF16	FF16	GF16	HF16	Diabeta (5mg)
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	8.24±0.45	11.21±0.85	9.67±0.48	7.28±0.43	5.21±0.35	10.24±0.80	6.21±0.40	12.36±0.90	3.20±0.30
2	18.24±0.98	24.61±1.36	20.13±1.20	15.64±0.95	13.48±0.89	22.65±1.20	17.21±0.97	29.63±1.97	12.63±0.90
4	24.13±1.36	37.12±2.17	28.31±1.97	30.31±2.08	26.45±1.95	33.67±2.12	35.45±1.30	38.29±2.18	20.24±1.20
6	33.29±2.12	36.51±2.15	34.67±1.29	40.67±2.60	42.67±2.61	38.29±2.18	45.67±2.67	48.56±2.70	32.67±2.10
8	40.61±2.25	46.39±2.68	42.68±2.61	54.66±2.70	50.61±2.60	48.61±2.70	54.23±2.70	59.36±2.99	38.63±2.18
10	58.63±2.99	54.32±2.41	55.31±2.71	65.23±3.52	60.67±3.10	62.14±3.20	56.74±2.72	68.24±3.26	45.60±2.67
12	68.12±3.26	66.45±2.64	62.67±3.12	70.21±3.79	74.32±3.82	71.67±3.80	76.34±3.83	77.66±3.84	58.34±2.99
16	76.36±3.83	73.24±3.80	80.24±4.32	75.69±3.82	78.69±3.83	82.19±4.34	80.29±3.84	85.64±3.96	62.93±3.12
20	80.29±4.32	85.63±3.90	84.66±3.89	88.63±4.88	82.61±4.34	86.98±3.96	89.68±4.98	92.13±5.01	74.67±3.81
24	90.16±5.01	95.64±5.15	92.67±5.02	93.29±5.05	91.67±5.02	94.38±5.10	96.62±5.18	99.26±5.45	94.21±5.01

Table 8: Release kinetics of innovator product with correlation coefficient

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
HF16	0.9825	4.118	0.9302	0.0706	0.979	21.453	0.962	0.616
Marketed product	0.9612	3.1699	0.835	0.0652	0.948	15.753	0.833	0.638

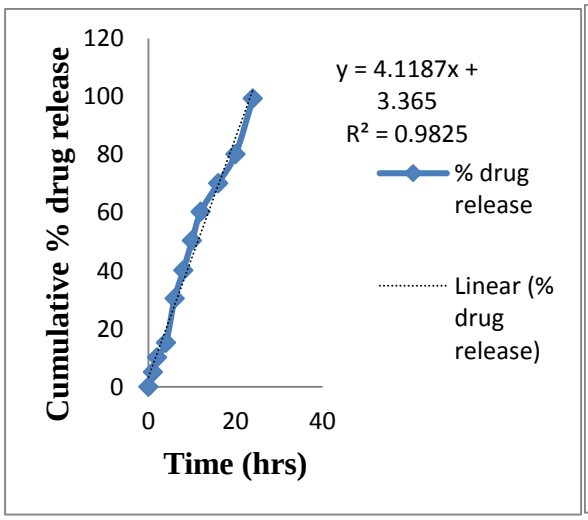
Table 9: Physico-chemical characteristics of optimized formulation HF16

Retest Time for optimized formulation (HF16)	Friability (%)	Hardness (kg/cm^2)	Drug content uniformity (%) ± SD	*In-vitro* drug release profile (%)
0 days	0.24	7.8	98.91	99.26
30 days	0.23	7.2	97.56	98.85
60 days	0.21	6.9	97.05	98.02
120 days	0.20	6.1	96.24	97.56
180 days	0.19	5.7	95.01	97.05

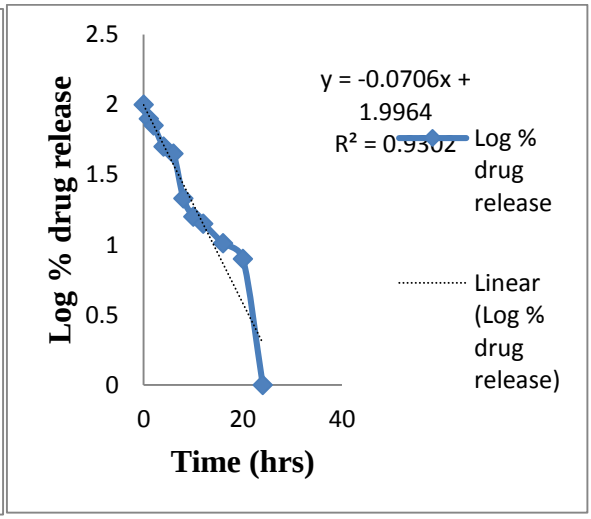
Release order kinetics

From the below results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.982 indicates that the drug release follows a zero-order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics (Figure 5(a, d, c & d).

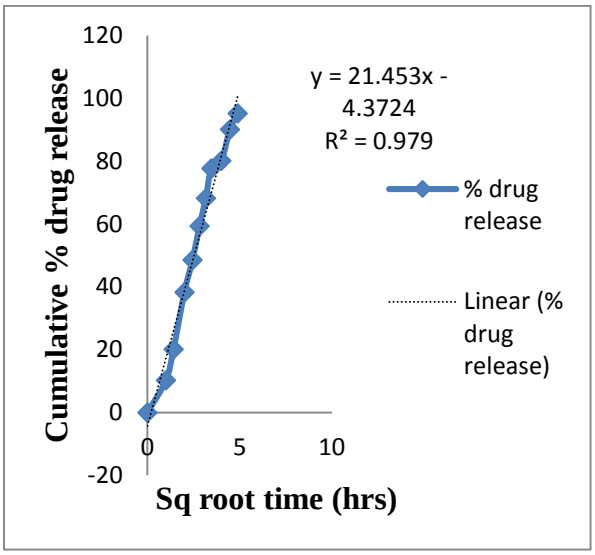
Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.979 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.616 suggest that the drug release was anomalous Non Fickian diffusion (Table 8**)**.



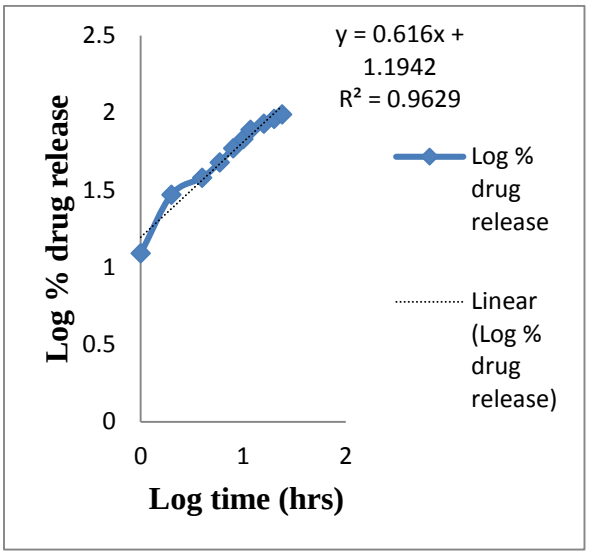
(a): Zero order plot of HF16



(b): First order plot of HF16

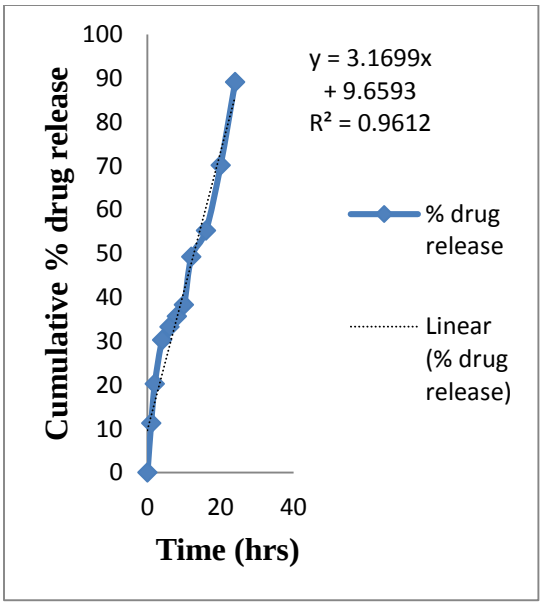


(c): Higuchi plot of HF16

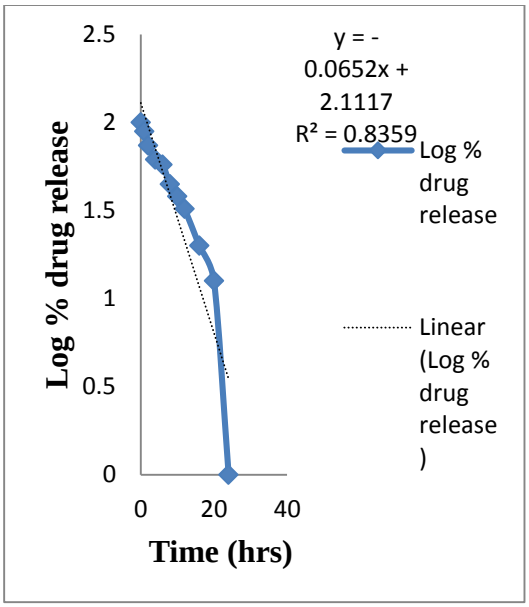


(d): Korsmeyer –Peppas plot

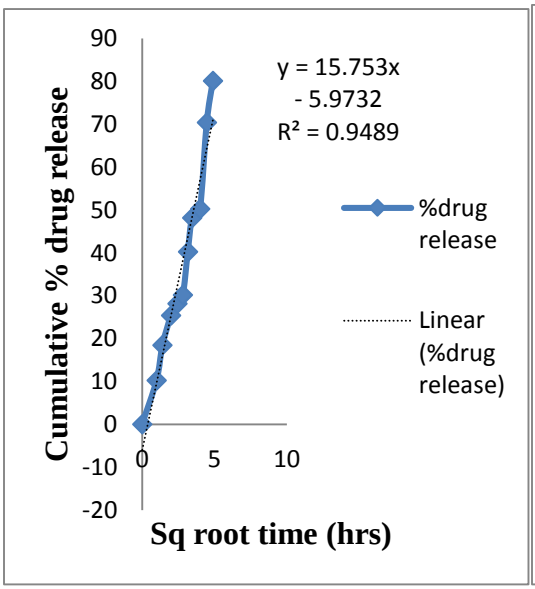
Figure 5: Pictorial representation for release order kinetics of Optimized Glyburide formulation (HF16):



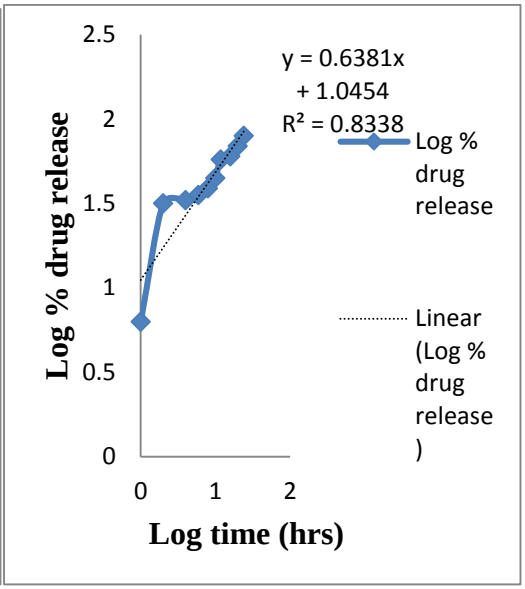
(a): Zero order plot



(b): First order plot



(c): Higuchi plot



(d): Korsmeyer- Peppas plot

Figure 6: Pictorial representation for release order kinetics of Marketed Product

CHARECTERIZATION

FT-IR studies:

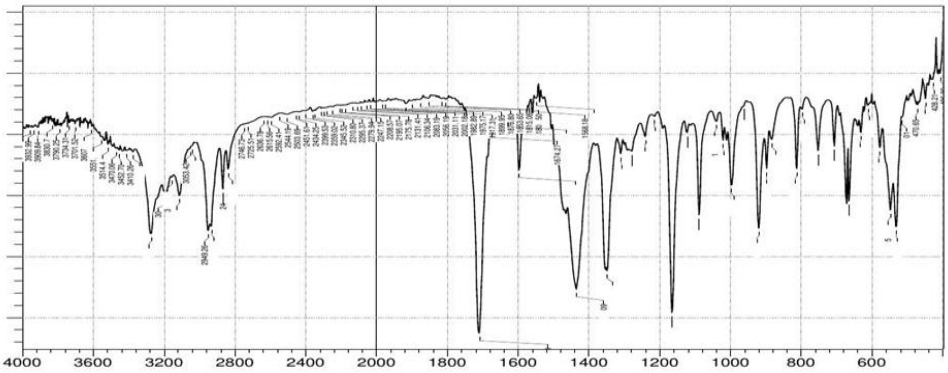


Figure 7:FT-IR spectrum of pure drug Glyburide

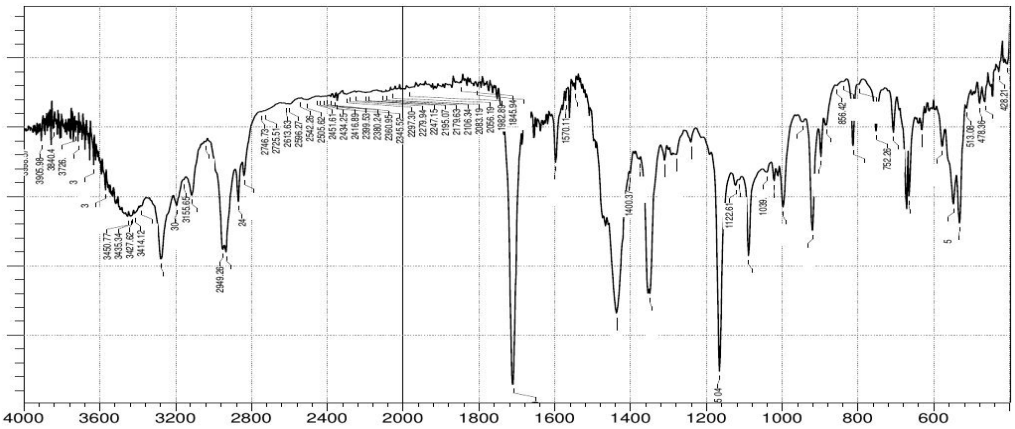


Figure 8: FT-IR spectrum of Glyburide and other polymers

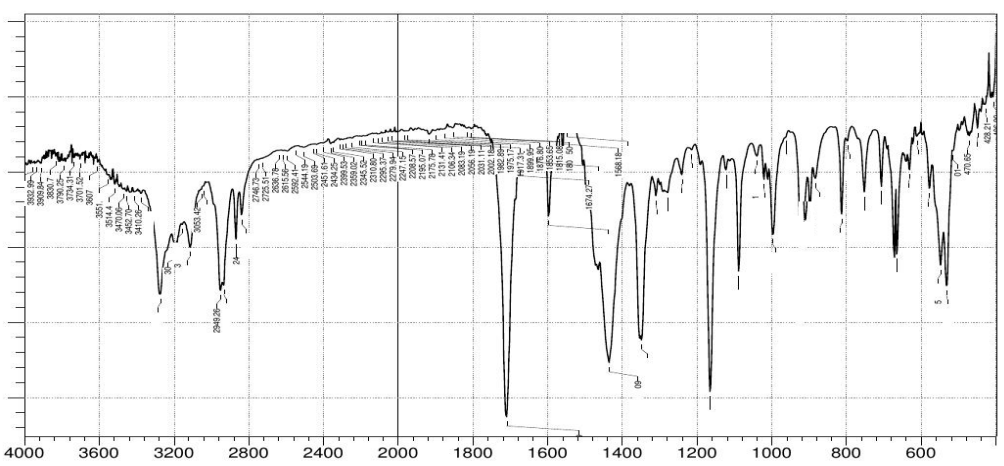


Figure 9: FT-IR spectrum of Glyburide **optimized formulation HF16**

There was no alteration in peaks of Glyburide pure drug (**Figure 7**) and optimized formulation (**Figure 9**), suggesting that there was no interaction between drug & excipients. FT-IR spectrum of pure drug and other polymers are shown in **(Figure 8)**. There are additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug, indicating absence of any interaction.

DSC studies:

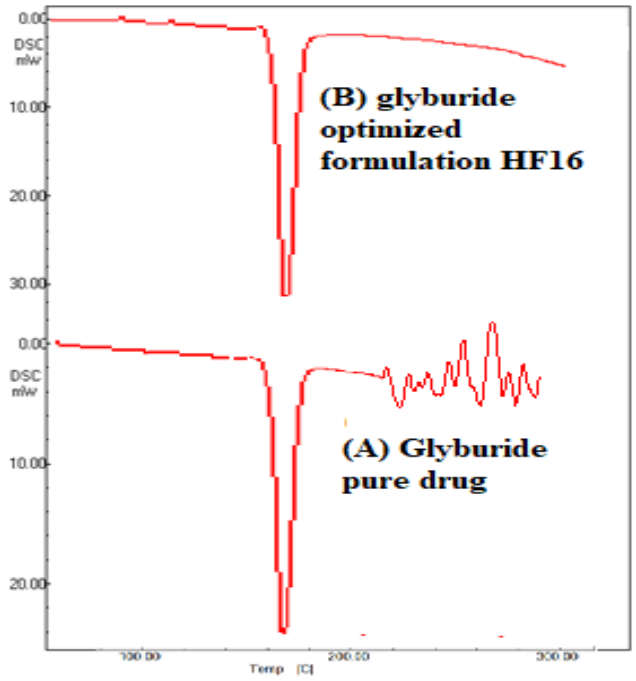


Figure 10: DSC thermogram of Glyburide **pure drug (A) and optimized formulatin HF16 (B)**

DSC was used to detect interaction between Glyburide and excipients. The thermogram of Glyburide exhibited a sharp endotherm melting point at 169 ^{0}C. The thermogram of optimized formulation of Glyburide exhibited a sharp endotherm melting point at 172 ^{0}C. The DSC thermogram retained

properties of Glyburide, as well as polymer properties. There is no considerable change observed in melting endotherm of drug in optimized formulation (**Figure 10**). It indicates that there is no interaction between drug & excipients used in the formulation.

Stability studies:

The optimized trilayer matrix tablets (HF16) formulation was subjected to stability studies for 6 months to evaluate its stability and the integrity of the dosage form. There was no significant change observed in the friability, hardness, cumulative % drug content and in vitro drug release of HF16 at 40 ^{0}C / 75 % RH for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug released during the stability study

period. From these results it was concluded that, optimized formulation was stable and retained their original properties with minor differences which depicted in

CONCLUSION

It was concluded that Trilayer matrix tablets of Glyburide can be successfully prepared by direct compression technique using different polymers combination. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF16 was found to be optimized formulation. The drug release from HF16 was found to fit Zero order of concentration independent and best fitted to Higuchi's model confirming to be diffusion assisted mechanism. *In vivo* bioavailability studies were conducted for optimized Glyburide trilayer tablets and marketed product, the results were indicating that the optimized Glyburide formulation was shown sustained release patterns where marketed product was shown immediate release. So, the optimized formulation was shown significant plasma concentrations with controlled release and maintained for 24 hrs.

REFERENCES

1. Uddhav S, Bagul, Ramakant V, Patil Niranjan V, Patil Kishore N, Gujar. Trilayer Mucoadhesive Gastro Retentive Tablets. Formulation and In vitro Evaluation Journal of Pharmacy Research 2012; 5(5):2463-2466.
2. Colombo P, Conte U, Gazzaniga A, Maggi L, Sangalli M. E, Peppas N. Drug release modulation by physical restrictions of matrix swelling. Int J Pharm 1990; 63: 43-48.
3. Conte U, Maggi L. Multi-layer tablets as drug delivery devices. Pharm Techn 1998; 2: 18–25.
4. Chidambaram N, Porter W, Flood K, Qiu Y. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J. Control. Release 1998; 52: 149–158.

5. MC Gohel, RK Parikh, MN Padshala, KG Sarvaiya, DG Jena. Formulation and optimization of directly compressible isoniazid modified release matrix tablet. Indian Journal of Pharmaceutical Sciences 2007; 69(5): 640-645.
6. Praveen Kumar T, Pallavi Y, Deepthi K and Narayana Raju P. Formulation and evaluation of Entacapone sustained release matrix tablets. The Pharma Innovation 2014; 3(8): 80-88.
7. Lohithasu D, Harsha INS, Krishna Swaroop K, Madhu G, Bhagya Lakshmi S, Lavanya K. Formulation development and evaluation of glyburide beads for controlled release Der Pharmacia Lettre 2013; 5 (3):170-177.
8. Rohini D, Alexandar S, Chandrasekhar MJN. Preparation and in vitro evaluation of sustained release tablet formulations of metformin HCL. Asian Journal of Pharmaceutical and Clinical Research 2012; 5(1):45–48.
9. Shirse P. Formulation and evaluation of bilayer tablets of HP-β-cyclodextrin complexed Glimepiride with Metformin hydrochloride for immediate and sustain release. International Journal of Pharmacy and Biological Sciences 2012; 3(2):148–160.
10. Patel JR, Patel BA, Patel DG, Patel DS, Patel VB. Formulation and evaluation of oral controlled drug delivery system for a model anti diabetic drug metformin. International Journal of Current Pharmaceutical Research 2011; 3:37–39.
11. Sinko P.J. Martin's Physical Pharmacy and Pharmaceutical Sciences. Published by Wolters Klwner Health Pvt. Ltd, New Delhi, 2007; 5: 553-559.
12. Jyothshna Devi K, Pavan Kumar B, Venkateswara Reddy B, Manubolu Sindhura. Pichika Madhavi. Asian J Pharm Clin Res 2013;7(1): 76-79.
13. Roni MA, Kibria G, Jalil R. Formulation and *in vitro* evaluation of Alfuzosin extended release tablets using directly Compressible Eudragit. Indian Journal of Pharmaceutical Sciences 2009; 71(3):252-258.
14. Mogili Vijaya Krishna, Venkateswara Rao. World Journal of Pharmacy and Pharmaceutical Sciences 2000; 3(11):1116-1135.
15. Kulkarni A, Bhatia M. Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iran. J Pharm Res 2009; 8: 15-25.
16. Kumar V B, Prasad G, Ganesh B, Swati C, Rashmi A, Reddy AG. Development and evaluation of guaifenesin bilayer tablet. Int J Pharm Sci Nanotech 2010; 3(3):1122-8.
17. Ankamma Chowdhary, Ramakrishna Raparla, Muramshetty Madhuri. Formulation and Evaluation of Multilayered Tablets of Pioglitazone Hydrochloride and Metformin Hydrochloride. Journal of Pharmaceutics 2014;4(1):14.

18. Seema Farheen, Abdul Saleem Mohammad, Nuha Rasheed, Shaik Zubair. International Journal of Pharmaceutical Sciences and Nanotechnology 2016;4(2):3512-3524.