WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 9, 1108-1122. Research Article ISSN 2277– 7105

FORMULATION AND *IN-VITRO* EVALUATION OF SOLID DISPERSION OF β-CYCLODEXTRIN COMPLEX OF GLIMEPIRIDE WITH POLOXAMER

Senthil Kumar Krishnan*, Pavan kumar, Dr.Mohammed Gulzar Ahmed

Department of Pharmaceutics, Sri Adhichunchanagiri College of Pharmacy, B.G.Nagara, Karnataka, Pin. Code: 571448, India.

Article Received on
30 June 2015,

Revised on 24 July 2015,
Accepted on 18 Aug 2015

***Correspondence for Author**
Senthil Kumar Krishnan
Department of Pharmaceutics, Sri Adhichunchanagiri College of Pharmacy, B.G.Nagara, Karnataka, Pin. Code: 571448, India.

ABSTRACT

The objective of the research project is to enhance of the solubility of Glimepiride by using solid dispersion technique and the production of GMP tablets showing prolonged effect. The polymers used were β-Cyclodextrin (β-CD) and Poloxamer 188 (PLX-188) and solid dispersions were prepared by physical mixture (PHY) and Solvent evaporation (SE) method. Solid dispersions with different ratios 1:1, 1:3, 1:5 (using physical mixture and solvent evaporation method were prepared). The prepared solid dispersions were characterized by Physical appearance, FT-IR, % Drug content were evaluated. F1 to F19 tablet formulations were prepared by dry granulation technique, lactose monohydrate used as a filler, HPMC as a binder, ethyl alcohol used as a granulating agent, ethyl cellulose used as a granules coating polymer and each formulation GMP containing; a) GMP alone, b) GMP : β-CD (1:1, 1:3,1:5) PHY and SE, c) GMP : PLX-188 (1:1, 1:3,1:5) PHY and SE and, d) GMP: β-CD: PLX-188 (1:1:1, 1:2:2,1:3:3) PHY and SE. The solvent evaporation method showed more enhancement of GMP solubility than the Physical mixture. Finally, optimized coated granules were evaluated for their micromeritic properties such as true density, tapped density, Carr's index, and flow properties show satisfactory results. Tablet formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, in-vitro dissolution profiles. The dissolution results revealed that formulations F12 showed 96.15%, F15 showed 94.93% and F18 showed 97.67% of drug release at the end of 12 hrs. The drug release follows mixed order kinetics and the mechanism was found to be diffusion and non-fickian release. Based on the results of in-vitro and

kinetics studies it was concluded that F12, F15 and F18 formulations shows sustained release action and solid dispersion technique by using β-CD and PLX-188 successfully used for enhancing the solubility of Glimepiride.

KEYWORDS: Glimepiride, β-Cyclodextrin (β-CD), Poloxamer 188 (PLX-188), Solid dispersion, Sustained release tablets.

INTRODUCTION

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs.[1] Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Over the years, a variety of solubilization techniques have been studied and widely used, and by many estimates up to 40 per cent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. There are various techniques available for enhancement of solubility. Solid dispersion is one of the most promising approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous.[2]

Glimepiride is the first, potent third generation oral hypoglycemic drug of sulfonyl urea class and is used in management of type II diabetes. Chemically it is 3 ethyl-4-methyl-N-(4-(N-((1r,4r)-4 methyl cyclo hexyl carbamoyl sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1H pyrrole-1-carboxamide.[3] Glimepiride suggested a number of potential benefits over other sulfonyl ureas currently available including lower dosage, rapid onset, longer duration of action and lower insulin c- peptide levels.[4] Glimepiride is practically insoluble in water; the slow absorption rate of drug usually originates from either poor dissolution of drug from the formulation or poor permeability of drug across GI membrane.[5]

MATERIALS AND METHODS

Preparation of standard curve

100mg of glimepiride was accurately weighed and dissolved in 100ml of 0.1N NaOH (SS-I), from this solution pipette out 10ml and added to another 100ml volumetric flask. The volume was made up with 0.1N NaOH to get a concentration of 100µg/ml (SS-II). From SS-II

aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml, 1.2ml, 1.4ml, 1.6ml, 1.8ml, 2ml were pipette into 10ml volumetric flasks and make up with 0.1N NaOH to get a concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml respectively. The absorbance of each concentration was measured at 228nm. The standard graph was drawn using the average values ten trails by plotting absorbance versus concentration of glimepiride.

Composition of various solid dispersion of Glimepiride

Table 1: Composition of various solid dispersion of Glimepiride

Drug to Carrier Complex	Drug to Carrier ratio	Code for Complex
Physical Mixture		
GMP: β-CD	1:1	F1
GMP: β-CD	1:3	F2
GMP: β-CD	1:5	F3
GMP:PLX 188	1:1	F4
GMP:PLX 188	1:3	F5
GMP:PLX 188	1:5	F6
GMP: β-CD: PLX 188	1:1:1	F7
GMP: β-CD: PLX 188	1:2:2	F8
GMP: β-CD: PLX 188	1:3:3	F9
Solvent Evaporation		
GMP: β-CD	1:1	F10
GMP: β-CD	1:3	F11
GMP: β-CD	1:5	F12
PLX 188	1:1	F13
PLX 188	1:3	F14
PLX 188	1:5	F15
GMP: β-CD: PLX 188	1:1:1	F16
GMP: β-CD PLX 188	1:2:2	F17
GMP: β-CD PLX 188	1:3:3	F18
Pure Drug		F19

Phase solubility studies of pure drug

Phase solubility studies of pure drug (GMP) with different concentrations of β- cyclodextrins (3-15 millimoles) and Poloxamer 188 were performed by the method described by Higuchi and Connors. An excess of Glimepiride (200 mg) was added to 15ml of triple distilled water containing various concentrations of carrier such as 0, 1, 3, 6, 9, 12, and 15 x 10^{-3}moles/liter taken in a series of 25ml stopped conical flask and the mixture was shaken for 72 hours at room temperature on a rotary flask shaker. After 72 hrs of shaking to achieve equilibrium, 2ml aliquots are withdrawn at 1 hr interval and filtered through whatman no.1 filter paper.

The filtered samples are diluted suitably and assayed for the drug GMP content by specific UV method. Shaking is continued until the consecutive estimations are the same.

Preparation of Solid dispersion material[6]

Physical mixture

A physical mixture was used for the preparation of solid dispersion. Three different drugs: Carrier ratios (1:1, 1:3, 1:5) were used. F1 to F3 corresponds to preparations containing β-Cyclodextrin, F4 to F6 correspond to preparations containing Poloxamer 188 and F7 to F9 correspond to preparation containing combination of β-Cyclodextrin and Poloxamer 188. Accurately weighed quantity of drug and carrier mixed in a mortar for about 15min with contant trituration. This mixture was then subsequently passed through mesh no. 40 and stored in a dessicator for 48 h.

Solvent evaporation

The Solvent evaporation (SE) was used for the preparation of solid dispersion. Three different drugs: Carrier ratios (1:1, 1:3, 1:5) were used. F10 to F12 corresponds to preparations containing β-Cyclodextrin, F13 to F15 correspond to preparations containing Poloxamer 188 and F16 to F18 correspond to preparation containing combination of β-Cyclodextrin and Poloxamer 188. Glimepiride and carrier were triturated using a small volume of ethyl alcohol to give a thick paste; Solvent was removed by evaporation under reduced pressure. The dried mass was then pulverized, passed through mesh no. 80, stored in a vacuum desiccator (48 h) packaging in an airtight container.

Evaluation of solid dispersion material

Drug Content Estimation

50 mg of complex was accurately weighed and transferred to 50 ml of volumetric flask and volume was made up to the mark with 0.1N NaoH. From this 1ml was taken in 10 ml volumetric flask and the volume is adjusted up to the mark with same solution. The absorbance of the solution was measured at 228 nm. The drug content of GMP was calculated using calibration curve data.

Compatibility study using FT-IR

The IR spectrum of drug was recorded using Tensor 27, Bruker. The observations are shown in figure...

Formulation development of Glimepiride sustained release matrix tablets

Table 2: selected excipients for prototype formulation

Sl.no	Excipient	Function
1	Lactose monohydrate	Filler
2	Hydroxy propylmethyl cellulose	Binder
3	Ethyl alcohol	Dry granulating agent
4	Talc	Glidant
5	Magnesium stearate	Lubricant

Table 3: Selected excipients for preparation of coating solution

Sl. No	Excipient	Function
1	Ethyl Cellulose	Coating polymer
2	Acetone	Solvent
3	Isopropyl alcohol	Solvent

Table 4.1: Formulations containing various concentrations of excipients F1 to F9

Formulation code	Drug+ carrier ratio(mg)	Lactose monohydrate (mg)	HPMC (mg)	Ethyl Cellulose (6%)	Magnesium stearate (mg)	Talc (mg)	Total weight of tablet(mg)
F1	4	128	5	9	2	2	150
F2	8	124	5	9	2	2	150
F3	12	120	5	9	2	2	150
F4	4	128	5	9	2	2	150
F5	8	124	5	9	2	2	150
F6	12	120	5	9	2	2	150
F7	6	126	5	9	2	2	150
F8	10	122	5	9	2	2	150
F9	14	118	5	9	2	2	150

Table 4.2: Formulations containing various concentrations of excipients F10 to F19

Formulation code	Drug+carrier ratio(mg)	Lactose monohydrate(mg)	HPMC (mg)	Ethyl Cellulose (6%)	Magnesium stearate (mg)	Talc (mg)	Total weight of tablet(mg)
F10	4	128	5	9	2	2	150
F11	8	124	5	9	2	2	150
F12	12	120	5	9	2	2	150
F13	4	128	5	9	2	2	150
F14	8	124	5	9	2	2	150
F15	12	120	5	9	2	2	150
F16	6	126	5	9	2	2	150
F17	10	122	5	9	2	2	150
F18	14	118	5	9	2	2	150
F19	2	130	5	9	2	2	150

Preparation of Ethyl cellulose Coating Solution[7,8]

2.5 gms of ethyl cellulose (ETHOCEL) was dissolved in acetone: isopropyl alcohol (65:35). Polymer - solvent interactions are assumed to be at a maximum when the solubility parameter of the polymer and solvent are equal. Solubility parameters calculated for the solvent combinations acetone: IPA.

Table no 5: Selected Physical Properties of EC and Solvents used in this Study

Ingredients	Dielectric constant	Solubility parameter (δ)	Boiling point (^{0}C)
Ethyl cellulose	3.2-4.0	21.1	-
Iso propyl alcohol	19.9	23.5	82.5
Acetone	20.7	20.3	56.5

Preparation of Sustained Release Matrix Granules

The granules are prepared by using dry granulation technique. Different batches of granules (F1 to F19) were prepared according to the composition mentioned in Table. Accurately weighed quantities of each component were mixed in a mortar. The powder mix was wetted with ethyl alcohol. The granules obtained after passing through sieve (16 mesh size) were then dried adequately at 45°C for 15–20 min. The dried granules were sifted manually through 16 mesh screen. The matrix granules in particle size range of 14–20 mesh had been selected. These batches of granules were put under physical characterization and drug release study.

Coating of Sustained Release Matrix Granules

The granules F1 to F19 exhibited sustained release up to 12 hrs. Matrix granules (14-20 mesh size) were coated stepwise in a conventional coating pan. Granules were spray coated with an ethyl cellulose coating solution to form intermediate layer. This layer makes 3–6% weight gain to the initial granules to prevent any incompatibility between drug and carrier.

Evaluation of Glimepiride matrix tablets

The matrix tablets prepared were evaluated for the following parameters:

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Table 6: IP standards of Uniformity of weight

Sl.No	Avg Wt of Tablet	% of Deviation
1	≤ 80mg	10
2	>80 mg – 250 mg	7.5
3	≥ 250 mg	5

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India) respectively.

$$\%\ Friability = \frac{Weight_{initial} - Weight_{final}}{Weight_{initial}} \times 100$$

Drug Content

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder**.** 50 mg of powder was accurately weighed and transferred to 50 ml of volumetric flask and volume was made up to the mark with 0.1N NaOH. From this 1ml was taken in 10 ml volumetric flask and the volume is adjusted up to the mark with same solution. The absorbance of the solution was measured at 228 nm. The drug content of GMP was calculated using calibration curve data.

***In-vitro* dissolution studies**

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm in a 900ml of 0.1N NaoH as a dissolution medium. Medium is maintained at 37±0.5^{0}C. At every 1 hour samples of 5ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant and maintain sink conditions. After filtration and appropriate dilution, the sample solution were analyzed at 228nm by using double beam U.V-Visible spectrophotometer (SHIMADZU-1700) and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from standard.

Kinetic Analysis of *In-Vitro* release rates of Glimepiride matrix tablets

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero- order Kinetic model – Cumulative % drug released versus Time.
2. First- order Kinetic model – Log cumulative % drug remaining versus Time.
3. Higuchi's model- Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model- Log cumulative percent drug released versus log time.

Stability Studies[9]

The optimized formulation was subjected for two month stability study according to ICH guidelines**.** The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at 25ºC / 60% RH, 30ºC / 65% RH, 40ºC / 75% RH for 2 months and evaluated for their permeation study.

RESULTS AND DISCUSSION

Calibration Curve of Glimepiride in 0.1N NaOH

The absorbance was measured in a UV spectrophotometer at 228 nm against 0.1N NaOH. The absorbance's so obtained and graph was plotted and shown in the Figure no.1

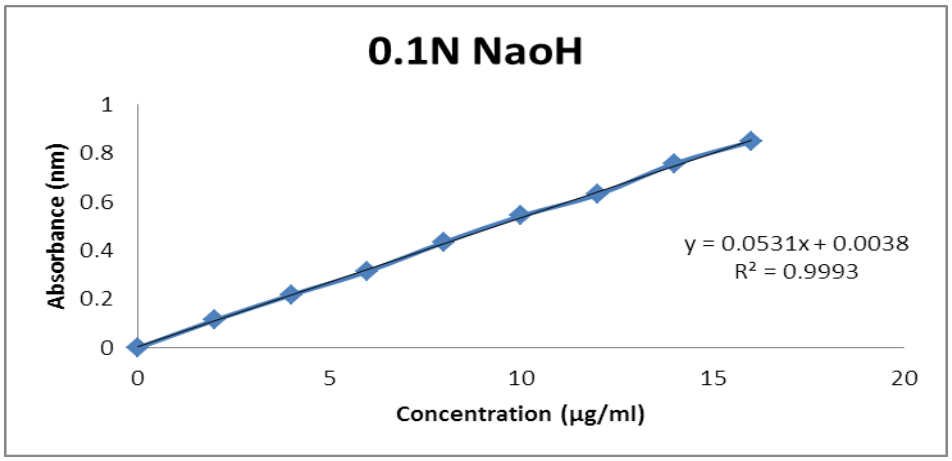

Fig no 1: Calibration Curve of Glimepiride in 0.1 N NaOH

Compatibility study using FT-IR

Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. Drug and polymers were identified and conformed from the peak values by performing FT-IR studies.

FT-IR spectra of pure drug and with the excipients are identical and do not show any incompatibility, thus the excipients are compatable with the drug.

Table no: 7

Functional group	FT-IR Range (cm^{-1})
S-O	762
S=O	1079
N-H	3369

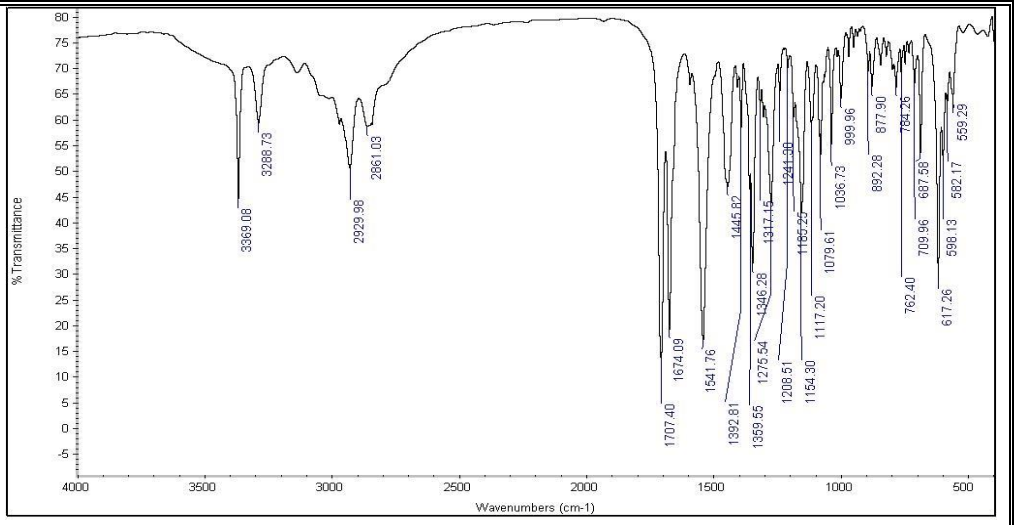

Fig no 2: FT-IR spectra of Glimepiride

Table no: 8

Functional group	FT-IR Range (cm^{-1})
S=O	1079
C-O-H	1407
N-H	3369

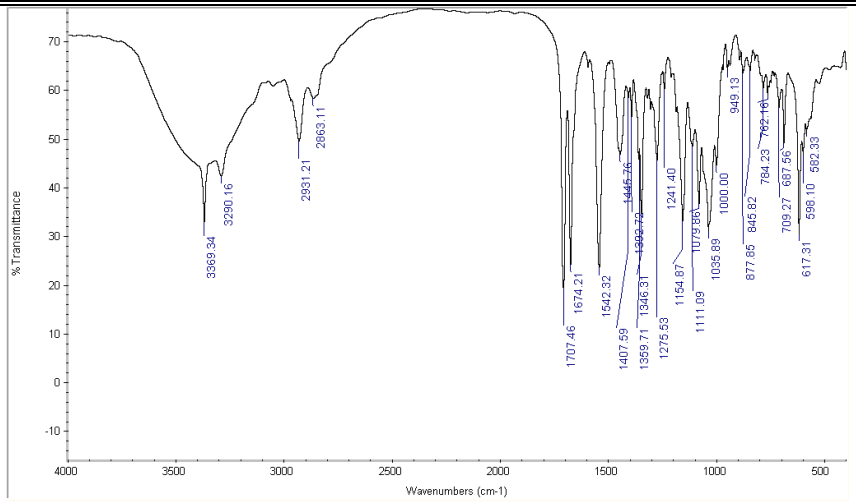

Fig no 3: FT-IR spectra of Glimepiride with β-Cyclodextrin

Table no: 9

Functional group	FT-IR Range (cm^{-1})
S=O	1079
C-O-H	1407
N-H	3369
CH_3	1343

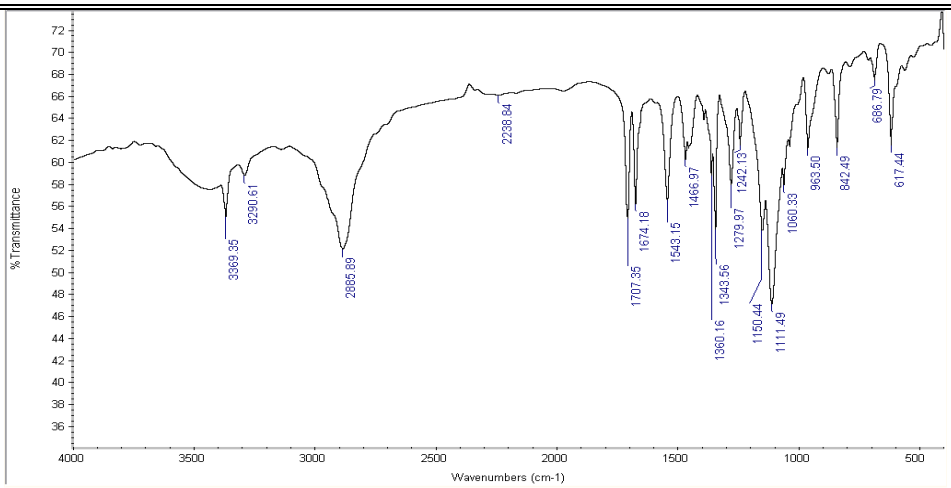

Fig no 4: FT-IR spectra of Glimepiride with Poloxamer 188

Table no: 10	
Functional group	**FT-IR Range (cm^{-1})**
C-O	1335
C-O-H	1407
N-H	3369
O-H	2887

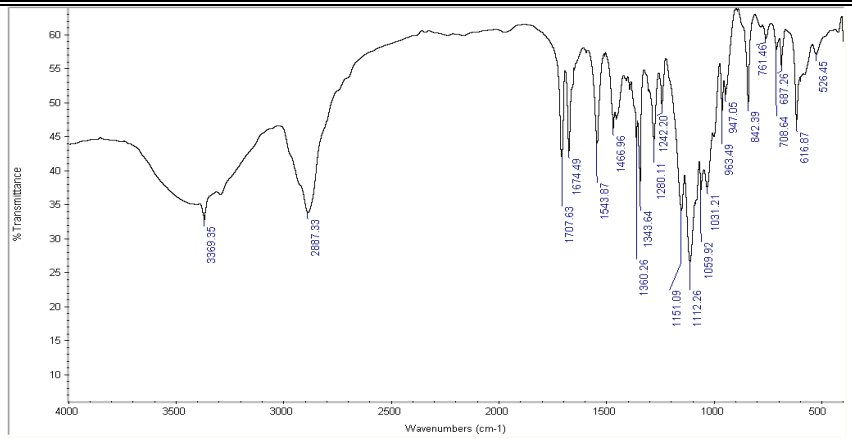

Fig no 5: FT-IR spectra of Glimepiride with combination (PLX 188 & β-CD)

Phase solubility Studies

- Phase Solubility Studies of glimepiride : β-Cyclodextrin Complexes has shown that increase in the concentration of β-Cyclodextrin increases the solubility of glimepiride.
- Phase Solubility Studies of glimepiride : Poloxamer 188 Complexes has shown that increase in the concentration of Poloxamer 188 increases the solubility of glimepiride.

Table no 11: Phase Solubility Studies of glimepiride: β-Cyclodextrin complexes

Sr.no	Conc. of : β-CD (mM)	Conc. of GMP
1	0	0.040
2	3	0.043
3	6	0.047
4	9	0.051
5	12	0.055
6	15	0.061

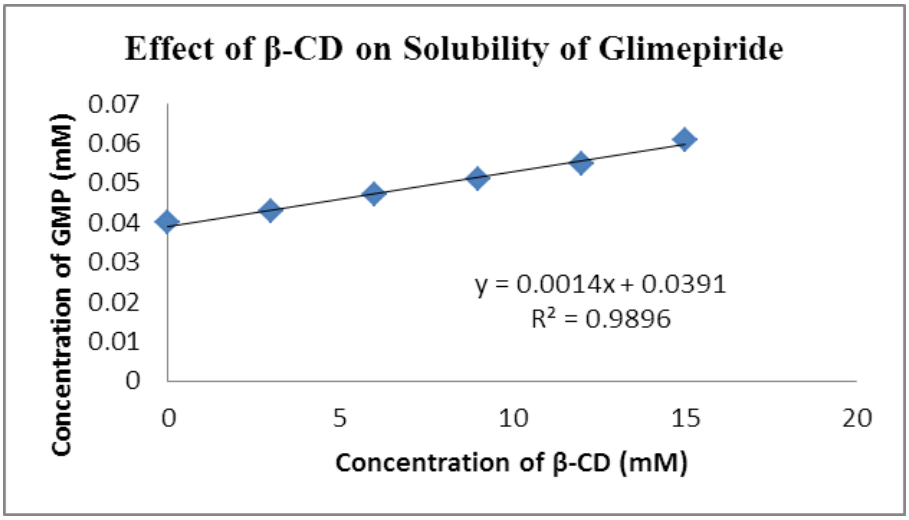

Fig no 6: Effect of β-CD on Solubility of Glimepiride

Table no 12: Phase Solubility Studies of glimepiride: Poloxamer 188 Complexes

Sl.no	Conc. of : PLX 188 (mM)	Conc. of GMP
1	0	0.040
2	3	0.042
3	6	0.045
4	9	0.048
5	12	0.050
6	15	0.059

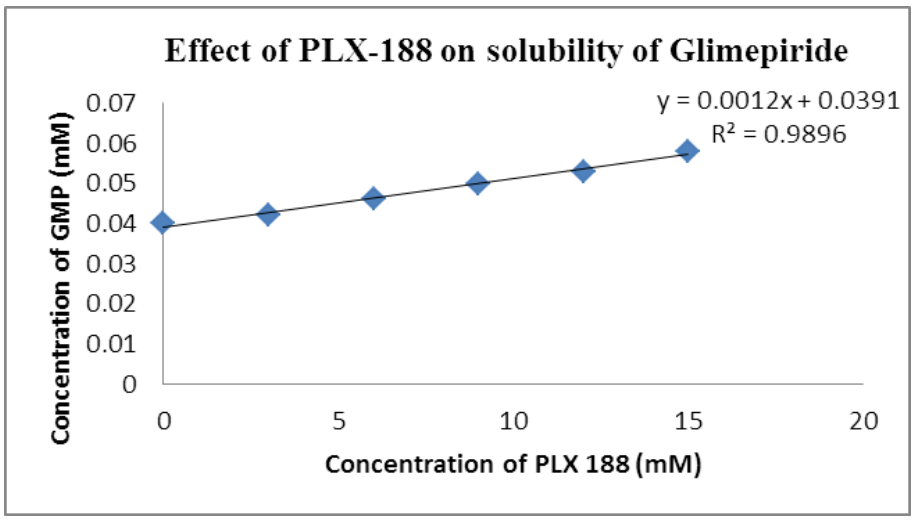

Fig no 7: Effect of PLX 188 on Solubility of Glimepiride

Drug Content Estimation

The complexes prepared by Solvent Evaporation method showed nearly 99.77 % (β-CD), 98.82 % (PLX 188) and 98.61% (Combination) drug content was observed. But the complexes prepared by physical mixture method were found to be slightly less shown in figure.

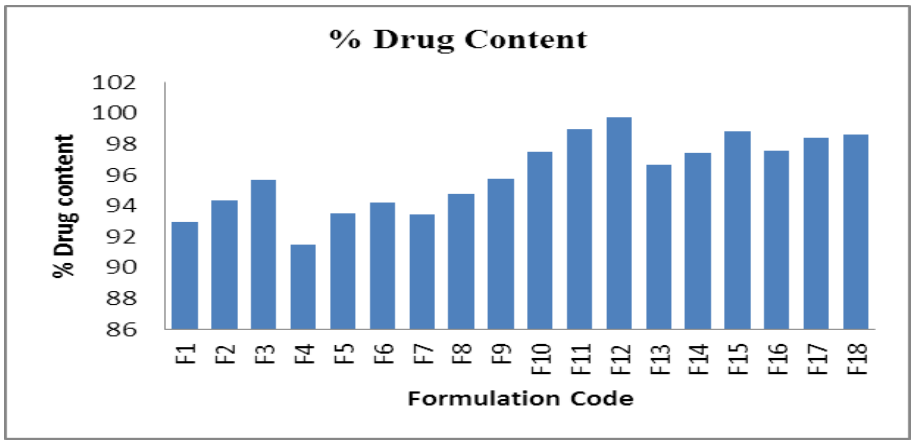

Fig no 8: Drug Content Estimation of F1 to F18

Table no 13: Post Compression Evaluation Parameters of F1 to F19

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	149.8±0.45	5.8±0.20	0.792±0.027	92.82±0.76
F2	150.1±0.58	5.9±0.15	0.752±0.030	94.26±0.63
F3	150.3±0.75	4.9±0.15	0.930±0.046	95.58±0.60
F4	149.9±0.35	4.8±0.11	0.953±0.037	91.35±0.80
F5	149.7±0.66	6.4±0.05	0.374±0.041	93.54±0.48
F6	150.1±0.70	6.5±0.15	0.444±0.055	94.23±0.52
F7	150.3±0.87	4.7±0.15	0.834±0.039	93.47±0.57
F8	149.8±0.85	4.6±0.23	0.966±0.028	94.76±0.45
F9	149.7±0.37	6.3±0.15	0.392±0.042	95.75±0.75
F10	150.3±0.43	6.5±0.25	0.371±0.046	97.53±0.61
F11	150.6±0.23	5.7±0.15	0.902±0.066	98.97±0.28
F12	149.9±0.78	5.9±0.28	0.950±0.032	99.77±0.82
F13	150.5±0.17	5.6±0.14	0.915±0.057	96.68±0.39
F14	148.7±0.67	5.4±0.05	0.367±0.032	97.43±0.38
F15	150.4±0.34	5.2±0.14	0.912±0.046	98.82±0.22
F16	150.5±0.46	5.1±0.16	0.932±0.069	97.57±0.29
F17	149.6±0.72	6.0±0.15	0.274±0.032	98.41±0.38
F18	150.6±0.24	5.7±0.14	0.912±0.073	98.61±0.28

Table no 14: *In-vitro* drug release profiles of Formulation F1 to F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	16.2	11.7	15.3	18.9	12.6	15.3	16.2	18	15.3
2	17.91	20.765	25.915	22.065	20.77	21.685	22.59	24.4	23.485
3	19.899	26.28	29.9285	25.877	25.385	28.105	28.115	29.935	29.915
4	20.2785	32.725	36.4835	30.0695	30.025	34.56	34.57	33.34	36.38
5	25.2495	36.505	40.194	37.4345	38.29	36.46	39.26	36.583	44.68
6	30.5175	44.805	46.894	44.8395	43.9	41.5195	45.775	43.713	50.325
7	45.624	51.35	52.37	48.2345	48.64	51.916	50.525	55.0215	59.6
8	50.4635	56.13	66.155	51.647	54.305	63.359	55.3	60.2715	65.325
9	56.3185	61.835	69.575	61.827	60	65.414	59.2	65.189	70.18
10	63.1945	66.67	74.182	66.752	64.825	68.5585	65.91	71.212	74.16
11	67.947	70.63	75.4825	69.0925	69.675	74.3285	72.4755	75.3765	79.06
12	71.284	73.98	78.948	72.704	73.65	77.2485	75.7455	79.292	83.085

Table no 15: *In-vitro* drug release profiles of Formulation F1 to F9

Time	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19
0	0	0	0	0	0	0	0	0	0	0
1	16.2	12.6	18.9	12.6	15.3	23.4	29.7	17.1	17.1	9.99
2	25.29	20.77	26.205	18.07	24.385	30.73	33.015	26.195	28.895	14.4555
3	32.63	25.385	34.45	26.27	33.52	38.1	43.5475	34.44	37.155	19.0355
4	36.41	35.425	42.74	43.515	40.905	51.81	48.2875	41.83	51.76	22.7405
5	43.81	52.72	51.075	47.355	44.73	56.595	52.1525	50.61	57.445	27.2755

6	49.45	57.51	63.055	53.015	59.375	64.105	61.4375	55.0275	64.69	28.415
7	56.92	68.625	69.7	62.305	69.6	66.975	65.4625	58.568	70.7135	31.63
8	64.43	76.2	74.49	68.045	73.58	74.629	68.428	65.4565	74.6085	33.242
9	74.68	80.215	78.1345	71.115	78.48	78.2735	74.198	75.7115	82.213	35.942
10	80.485	83.35	83.507	75.1	82.505	81.846	79.098	79.7215	89.0475	36.316
11	85.42	86.5	92.057	79.105	86.55	92.186	83.123	85.6415	93.1275	38.401
12	88.58	93.265	96.152	86.73	91.515	94.931	90.768	94.562	97.6775	44.8165

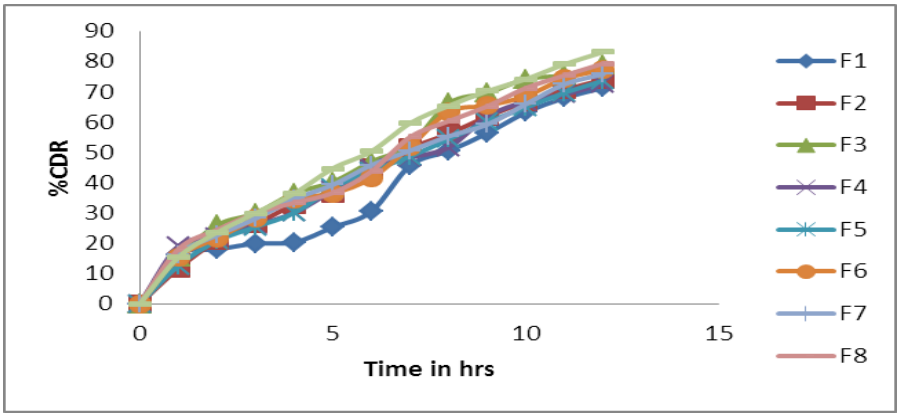

Fig no 9: Cumulative percentage release Vs Time profile of formulations F1 to F9

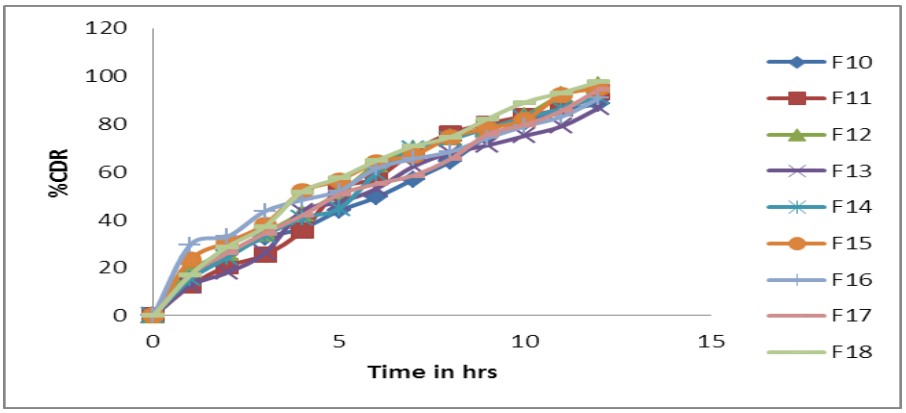

Fig no 10: Cumulative percentage release Vs Time profile of formulations F10 to F18

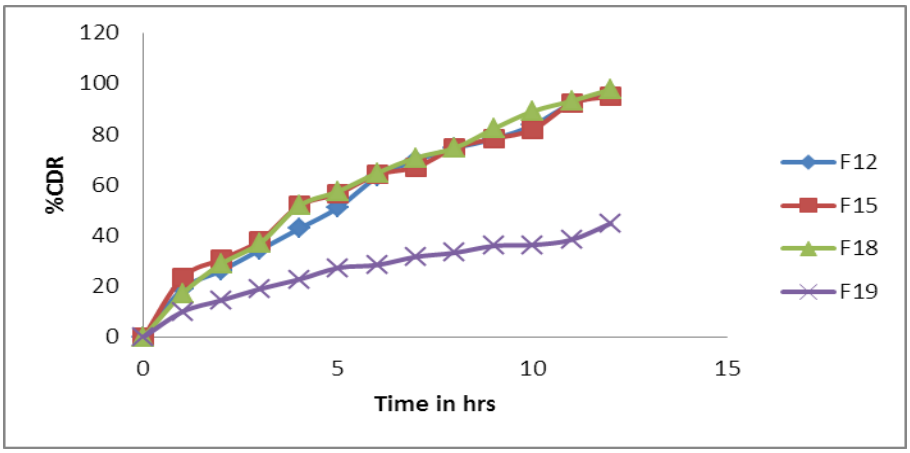

Fig no 11: Cumulative percentage release Vs Time profile of formulations F12, F15, F18, F19

Release Kinetics

All the formulations show linearity with respect to zero order and first order kinetics.

Table no 16: Mathematical modelling and drug release kinetics of formulation F1 to F19

FORMULATION CODE	KINETIC MODELS					
	Zero order	First order	Higuchi	Hixson	Korsmeyer-pappas	
	R^2	R^2	R^2	R^2	n	R^2
F1	0.9565	0.9350	0.8912	0.9647	0.6893	0.8508
F2	0.9920	0.9625	0.9526	0.9448	0.7457	0.9974
F3	0.9797	0.9727	0.9732	0.9495	0.6725	0.9857
F4	0.9902	0.9573	0.9608	0.9812	0.6012	0.9501
F5	0.9961	0.9868	0.9866	0.9584	0.720	0.9952
F6	0.9837	0.9713	0.9670	0.9627	0.6855	0.9794
F7	0.9978	0.9746	0.9829	0.971	0.6372	0.9911
F8	0.9899	0.9673	0.9623	0.9783	0.6290	0.9658
F9	0.9892	0.9857	0.9905	0.948	0.7061	0.9958
F10	0.9943	0.9437	0.9734	0.9706	0.6994	0.9888
F11	0.9657	0.9623	0.9786	0.9145	0.8589	0.982
F12	0.9853	0.9013	0.9675	0.9276	0.6901	0.991
F13	0.9675	0.9756	0.9871	0.9012	0.8151	0.9806
F14	0.9749	0.9709	0.9853	0.9276	0.7463	0.9922
F15	0.9804	0.9068	0.9904	0.9379	0.5856	0.9895
F16	0.9912	0.9317	0.984	0.9685	0.4696	0.9732
F17	0.9937	0.8713	0.9839	0.956	0.6808	0.9961
F18	0.9749	0.8904	0.9966	0.9085	0.7006	0.9941
F19	0.9665	0.9749	0.9859	0.9164	0.5824	0.9933

Stability studies

The best formulations F12, F15 and F18 were subjected to stability studies at room temperature and 45 RH for 2 months. Then the tablets were analyzed for physical change, drug content estimation and *in-vitro* dissolution studies at an interval of 15 days. Results show that after analyzing there was no change in case of physical appearance, no significant differences in the drug content and dissolution study.

Bibliography

1. Dhirendra K, Lewis S, Udupa N and Atin K. Solid Dispersions: A Review. Pak J Pharm Sci., 2009; 22(2): 234-46.
2. http://www.pharmainfo.net/reviews/solid-dispersions-overview

3. Prameela RA, Siva TP, Archana N, Bala SC. Phase Solubility Studies on Oral Antibiotic Drugs with β-Cyclodextrin and HP-β Cyclodextrin. International Journal of Pharm Tech Research., 2009; 1(4): 1632-37.
4. Abd-elgawad MR, Shimaa HE. Electrochemical study of glimepiride and its complexation with β-cyclodextrin. Collect. Czech. Chem. Commun., 2011; 76(1): 13-25.
5. Baliar Singh OP, Biswal S, Sahoo J, Murthy PN. Physicochemical Properties of Glimepiride in Solid Dispersions with Polyethylene Glycol 20000. International Journal of Pharmaceutical Sciences and Nanotechnology., 2009; 2(2): 537-43.
6. Sanjoy Kumar D, Sudipta Roy,Yuvaraja Kalimuthu, Jasmina K, Arunabha Nanda. Solid Dispersions: An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs. International Journal of Pharmacology and Pharmaceutical Technology., 2010; 1(1): 37-46.
7. http://www.colorcon.com/literature/marketing/mr/Extended%20Release/Surelease/English/ads influ coat sys type.pdf.
8. Golam Kibria and Reza-ul Jalil. *In- vitro* Release Kinetics Study of Diltiazem Hydrochloride from Pellets using an Ethylcellulose Pseudolatex Coating System. Dhaka Univ J Pharm Sci., 2007; 6(2): 87-92.
9. ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products.[online]. [Cited 2008 Nov 10]; Available from: URL:http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdf.