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Formulation and Evaluation of Oral Controlled Release Osmotic Tablets of Glimepiride

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Abstract : *Glimepiride has a relatively short elimination half-life (5 h), thereby requiring twice or thrice daily dosing in patients, which may lead to non-compliance. Controlled release formulations of Glimepiride were developed based on osmotic technology. Formulation F9 was selected as optimized formulation. The effect of different formulation variable was studied to optimize release profile. The release rate increased significantly as the increase of osmogen ratio from 1:0.5 to 1:1. The release rate increased significantly with the increase of concentration of pore forming agent (PEG-400) as noticed from the dissolution profile of the formulations. Thus drug release was inversely proportional to the concentration of osmogen in the core and the amount of pore forming agents in the coated tablets. The drug release from developed formulations was independent of pH. The manufacturing procedure was standardized and found to be reproducible. Further studies are needed to investigate this formulation for its performance in vivo.*

Keywords: *controlled release, osmogen, osmotic technology, pore forming agent.*

I. INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective to manufacturing process. Oral route is the most commonly used route for drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. Even for sustained release systems the oral route of administration has been investigated the most because of flexibility in designing dosage forms.

Present controlled release drug delivery systems are for a maximum of 12 hours clinical effectiveness. Such systems are primarily used for the drugs with short elimination half life.

Oral controlled release dosage form

The treatment of acute diseases or chronic illnesses has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids, and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body[1].

Conventional drug therapy require periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems.

II. Review of Literature

Lee et al [17]

Developed the monolithic osmotic tablet system, which is composed of a monolithic tablet coated with cellulose acetate (CA) membrane drilled with two orifices on both side surfaces, has been described. The influences of tablet formulation variables including molecular weight (MW) and amount of polyethylene oxide (PEO), amount of potassium chloride (KCl), and amount of rice starch as well as nifedipine loading have been investigated. Orifice size and membrane variables including nature and amount of plasticizers as well as thickness on drug release have also been studied. It was found that PEO with MW of 300 000 g/mol was suitable to be thickening agent, both amount of KCl and amount of PEO had comparable and profoundly positive effects, while nifedipine loading had a strikingly negative influence on drug release.

Ritesh B. Patel et al [18]

Developed osmotic pump tablets (OPT) of Glimepiride (GLZ) and optimized the formulation using response surface methodology. The complex of GLZ and HP-β-CD were prepared and studied the effects of

different ratio of drug to HP-β-CD and preparation methods on complex formation. The release from the optimized formulations was independent of pH and agitation intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. The drug release from optimized formulation showed a controlled release pattern.

Vavia et al[19]

Studied a controlled porosity osmotic pump-based drug delivery system., pseudoephedrine was chosen as a model drug with an aim to develop a controlled release system for a period of 12 h. Sodium bicarbonate was used as the osmogent. The effect of different ratios of drug:osmogent on the in-vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane.

III. Materials & Methods

Preformulation studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance alone and when it combined with excipients.

FTIR spectrum interpretation

The infrared spectrum of the pure Glimepiride sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide. The pure drug and polymers were subjected to FTIR studies alone and in combination, to study the interference of polymer for drug analysis.

Determination of λ max

A 10mg of Glimepiride sample was accurately weighed and was first dissolved in 5 ml methanol and volume was made upto 10ml with 0.1N Hcl solution. From the standard stock solution, 1 ml was diluted to 10 ml with 0.1N Hcl solution. The resulting solution containing 10 mcg/ml was scanned between 200 to 400 nm.

Similar procedure was carried out for pH6.8 buffer solution and pH 7.4 buffer solution, absorbance was measured at 230 nm.

Preparation of osmotic tablets of Glimepiride

All the ingredients were blended thoroughly and directly compressed on tablet punching machine.

Evaluation of prepared tablets

The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time and percentage drug release.

IV. FIGURES AND TABLES

S.No	Ingredient (mg)	Core Tablet									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Glimepiride	8	8	8	8	8	8	8	8	8	8
2	Mannitol	4	4	4	4	4	4	8	8	8	8
3	PVP	15	15	15	15	15	15	15	15	15	15
4	MCC	120	120	120	120	120	120	116	116	116	116
5	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Coating composition										
7	CAP	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
8	Dibutyl phthalate(v/w)	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
9	PEG-400	5%	5%	5%	10%	10%	10%	5%	5%	5%	10%
	Weight gain (%)	2.5	5	10	2.5	5	10	2.5	5	10	2.5

Table 1: Formulation chart of osmotic tablets of Glimepiride

Drug/ Polymer	N-H Stretch	C-H Aromatic	C=O Amide	Methylene Cyclohexane	Sulfoxides
Glimepiride	3369.13	2930.39	1707.64	1673.89	1079.85
Glimepiride+ Mannitol	3414.86	2850.02	1729.18	1620.46	1074.46
Glimepiride+ MCC	3393.63	2917.75	1699.96	1657.13	1028.76
Glimepiride osmotic tablet	3410.10	2977.25	1704.35	1671.90	1072.41

Table 2: IR spectral peaks for Glimepiride and Superdisintegrants *All values expressed in cm^{-1}

FTIR Spectral data

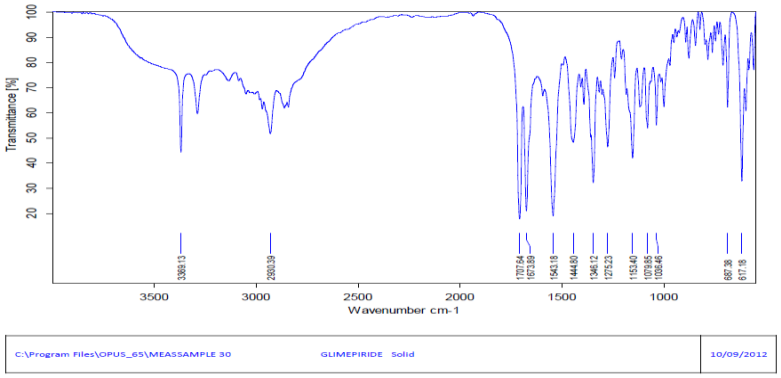

Fig 1: FTIR Spectra of Glimepiride solid

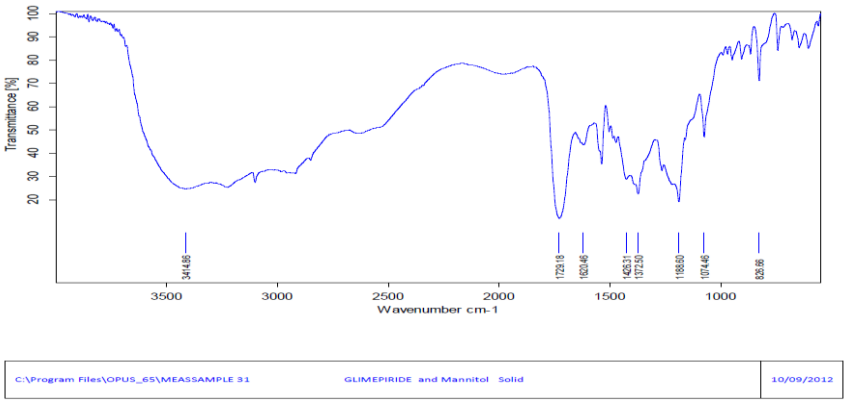

Fig 2: FTIR Spectra of Glimepiride and Mannitol solid

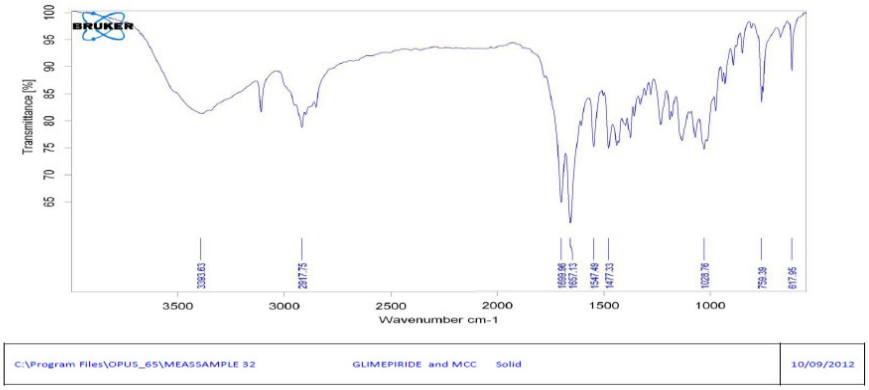

Fig 3: FTIR Spectra of Glimepiride and MCC solid

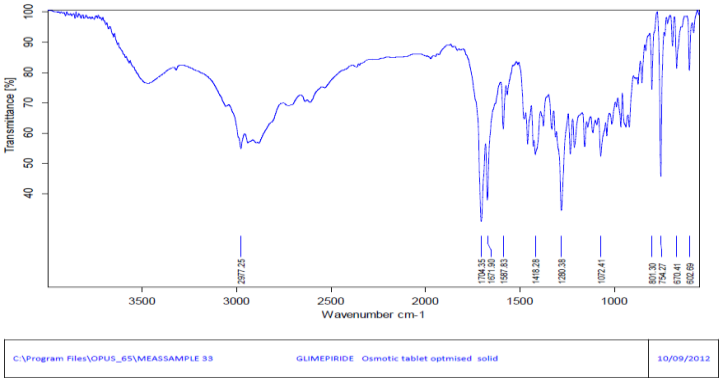

Fig 4: FTIR Spectra of Glimepiride optimized osmotic tablet solid

Table 3: Post compression parameters of Glimepiride osmotic tablets

S.No	Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
1	F1	151	3.33	1.59	0.43	97.23
2	F2	147	3.66	1.64	0.34	98.55
3	F3	148.5	3.66	1.59	0.49	98.16
4	F4	149	4.00	1.58	0.47	99.34
5	F5	148.5	3.66	1.59	0.49	98.16
6	F6	147	3.66	1.64	0.34	98.55
7	F7	148.5	3.66	1.59	0.49	98.16
8	F8	152.5	3.66	1.56	0.34	99.25
9	F9	152.5	3.66	1.56	0.34	99.25
10	F10	149	4.00	1.58	0.47	99.34

Table 4: Dissolution data of Glimepiride osmotic tablets

S.No	Formulation	0 min	1hr	2hr	3hr	4hr	5hr	6hr	8hr	12hr
1	F1	0	8.98	18.68	22.5	26.71	28.06	30.21	46.07	61.04
2	F2	0	10.51	21.39	26.02	31.32	33.5	45.09	56.08	72.06
3	F3	0	11.62	23.54	28.72	35.66	38.33	42.6	63.48	81.51
4	F4	0	9.85	21.09	27.75	31.62	34.72	40.25	54.93	76.73
5	F5	0	12.63	25.08	29.72	38.44	42.26	45.52	65.46	83.76
6	F6	0	14.46	30.87	36.54	48.32	52.31	56.72	69.53	76.58
7	F7	0	12.03	26.31	30.52	42.74	48.78	52.23	67.32	84.66
8	F8	0	14.69	36.37	42.35	51.79	55.74	60.1	77.44	88.25
9	F9	0	17.2	39.42	44.52	53.68	57.34	61.23	80.69	99.87
10	F10	0	21.39	30.87	36.54	42.74	56.72	69.53	97.63	-

Table 5: Release kinetics of Glimepiride osmotic tablets

S.No	Formulation	Korse Meyer Peppas			Zero Order		First Order		Higuchi	
		N	Kkp	R2	K0	R2	K	R2	KH	R2
1	F1	0.719	0.987	0.969	4.809	0.969	-0.032	0.973	17.26	0.937
2	F2	0.755	1.049	0.985	5.878	0.973	-0.045	0.987	21.25	0.954
3	F3	0.758	1.089	0.982	6.709	0.979	-0.061	0.950	23.97	0.937
4	F4	0.777	1.033	0.982	6.098	0.983	-0.049	0.963	21.78	0.941
5	F5	0.747	1.122	0.986	7.010	0.980	-0.071	0.937	25.14	0.945
6	F6	0.721	1.213	0.980	7.571	0.961	-0.109	0.870	27.79	0.971
7	F7	0.788	1.124	0.985	7.397	0.975	-0.083	0.930	26.78	0.959
8	F8	0.712	1.254	0.954	7.818	0.940	-0.155	0.820	29.09	0.977
9	F9	0.656	1.310	0.956	7.790	0.928	-0.207	0.767	29.23	0.980
10	F10	0.703	1.279	0.944	11.17	0.977	-0.165	0.726	31.75	0.899

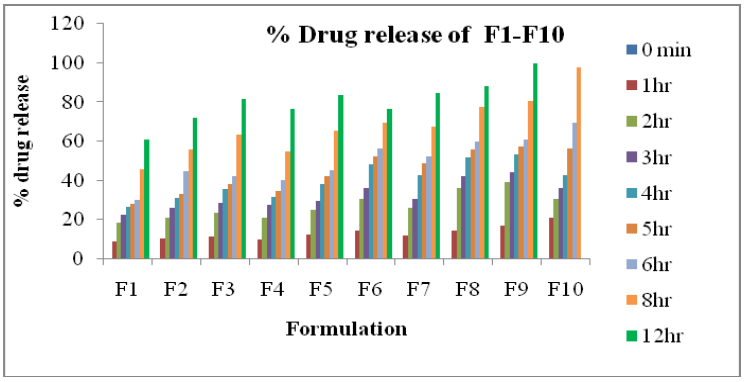

Fig.5: Dissolution profile of Glimepiride osmotic tablets F1-F10

V. DISCUSSION

Standard Calibration Curve of Glimepiride

It was found that the estimation of Glimepiride by UV spectrophotometric method at λ_{max} 230.0 nm in 0.1N Hydrochloric acid, λ_{max} 228.0 nm in 6.8pH buffer, λ_{max} 228.0 nm in 7.4pH buffer all of them had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1 in all the media.

Fourier Transform Infrared spectroscopy

The present study was carried out to develop osmotic tablets of Glimepiride by direct compression of core tablets followed by spray coating with polymers and pore formimg agent. Hence it was necessary to find suitable excipients with good compatibility.

The IR spectrum of Glimepiride is shown in Table 2, Fig 1, reveals characteristic shoulders in the Glimepiride IR spectrum that occur These bands were also observed for the physical mixture of excipients and Glimepiride with the same absorbance as shown in Fig 2, 3, 4. From these results, it can be confirmed that there is no interaction between Glimepiride and excipients in the physical mixture.

Tablet formulation

Formulation of Glimepiride Osmotic Tablets by Direct Compression

The present study of Glimepiride by direct compression method reveals that the flow properties of the powder blend is showing the good flow property. (Table 1)

Evaluation Parameters for osmotic Tablets of Glimepiride

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 3. The average weight of the tablet is approximately in range 147 to 152.5, so the permissible limit is ±10% (135-165mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using monsanto hardness tester and the data's were shown in Table 3. The results showed that the hardness of the tablets is in range of 3.00 to 4.00 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table 3. The result showed that thickness of the tablet is raging from 2.16 to 2.75 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 3. The average friability of all the formulations lies in the range of 0.34 to 0.43% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro dissolution studies

Finally, the tablets were evaluated for *in vitro* dissolution studies in acid buffer (pH-1.2) for 2 hours followed by pH 6.8 buffers for 3 hours and finally for 7 hrs in pH 7.4 pH buffer. The results were shown in the Table 4. Formulations F1- F5 could not release maximum amount of drug from formulations till 12 hrs of dissolution study. Formulations F6-F9 showed a sustained drug release till 12 hours of dissolution study of which Formulation F9 has showed maximum amount of drug released with drug release of 9.87% at the end of 12^{th} hour, so it is choosen as an optimized formulation. On the other end formulations F10-F12 complete release of drug within 8 hours of dissolution study. The reason may be due to increase in concentration of pore forming agent (10%). The results are shown in Fig 5.

Assay

The percentage drug content of all the tablets was found to be between 97.23±0.280% and 99.25±0.670% of Glimepiride, which was within the acceptable limits. This result indicates that there was uniform distribution of the drug throughout the batch.

VI. CONCLUSION

Glimepiride has a relatively short elimination half-life (5 h), thereby requiring twice or thrice daily dosing in patients, which may lead to non-compliance. Controlled release formulations of Glimepiride were developed based on osmotic technology. Formulations F1- F5 could not release maximum amount of drug from formulations till 12 hrs of dissolution study. Formulations F6-F9 showed a sustained drug release till 12 hours of dissolution study of which Formulation F9 has showed maximum amount of drug released with drug release of 9.87% at the end of 12^{th} hour, so it is choosen as an optimized formulation. The effect of different formulation variable was studied to optimize release profile. The release rate increased significantly as the increase of osmogen ratio from 1:0.5 to 1:1. The release rate increased significantly with the increase of concentration of pore forming agent (PEG-400) as noticed from the dissolution profie of the formulations. Thus Drug release was inversely proportional to the concentration of osmogen in the core and the amount of pore forming agents in the coated tablets. The release from developed formulations was independent of pH. The manufacturing procedure was standardized and found to be reproducible. Further studies are needed to investigate this formulation for its performance in vivo.

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