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Design, Development and Evaluation of Gliclazide Tablets for Non-Insulin Dependent Diabetes Mellitus

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A B S T R A C T

The goal of the present work was to formulate the oral tablets of gliclazide for non-insulin dependent diabetes and provide a dosage form for prolonged period of time, in order to improve efficacy, reduce the frequency of total dose and better patient compliance. The powders were evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that powders showed excellent flow properties. The resulting tablets were evaluated for thickness, diameter, and uniformity of weight test, hardness, friability and drug content. In-vitro release of drug was performed using 7.4 pH phosphate buffers and dissolution was done. All the tablet formulations showed acceptable pharmacological properties and complied with pharmacopoeias standards.

Keywords: Gliclazide, Hausner's Ratio, Dissolution, Friability.

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INTRODUCTION:

Diabetes mellitus is a group of syndromes characterized by hyperglycaemia; altered metabolism of lipids, carbohydrates, and proteins and an increased risk of complication from vascular disease.[1] The two hormones mainly regulate the level of blood sugar are glucagon from the α-cells and insulin from the β-cells of the inlets of Langerhans. Deficiency of the insulin leads to diabetes mellitus.[2]

Most patients can be classified clinically as having either type-I diabetes mellitus (insulin-dependent diabetes mellitus or IDDM) or type-II diabetes mellitus (non- insulin dependent diabetes mellitus or NIDDM).[3] Non-insulin dependent diabetes mellitus (NIDDM) is much commoner than IDDM, accounting for 75% to 95% of all diabetics in most population. Type-II diabetes usually develops in people over age 40, and more likely in people who are overweight. Although this particular group of patients have sufficient or even excessive amounts of insulin in their systems, their bodies are unable to use the hormone effectively, called insulin resistance.[4]

Non-insulin-dependent diabetes mellitus is an inherited metabolic disorder characterized by hyperglycaemia with resistance to ketosis. Patients are variably symptomatic and frequently obese, hyperlipidaemia and hypertensive.

Clinical, pathological and biochemical evidence suggests that the disease is caused by a combined defect of insulin secretion and insulin resistance. [5]

Non-pharmacologic management includes meal planning to achieve a suitable weight, such that carbohydrates supply 50% to 60% of the daily energy intake, with limitation of saturated fats, cholesterol and salt when indicated, and physical activity appropriate to the patient's age and cardiovascular status. If unacceptably high plasma glucose levels (e.g., 8 mmol/L or more before meals) persist the use of orally given hypoglycaemic agents are indicated.[6]

Gliclazide is an oral hypoglycaemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It is considered a first-generation sulfonylurea due to the structural presence of a sulphonamide group able to release a proton and the presence of one aromatic group.[7] On the other hand, based on the pharmacological efficacy, Gliclazide is considered a second-generation sulfonylurea which presents a higher potency and a shorter half-life.

Gliclazide binds to the β cell sulfonylurea receptor (SUR1). This binding subsequently blocks the ATP sensitive potassium channels. The binding results in closure of the channels and leads to a resulting decrease in potassium efflux leads to depolarization of the β cells. This opens voltage-dependent calcium channels in the β cell resulting in calmodulin activation, which in turn leads to exocytosis of insulin containing secretary granules.[8]

Oral absorption of gliclazide is similar in patients and healthy volunteers, but there is intrasubject variation in time to reach peak plasma concentrations (tmax). Ages related differences in plasma peak concentrations (C-max) and t-max have been observed.

A single oral dose of 40 to 120 mg of gliclazide results in a C max of 2.2 to 8.0 μg/ml within 2 to 8 hours. T-max and C-max are increased after repeated gliclazide administration.[9]

Steady state concentration is achieved after 2 days administration of 40 to 120 mg of gliclazide. Gliclazide has low volume of distribution (13 to 24L) in both patients and healthy volunteers due to its high protein binding affinity (85 to 97%).[10]

The elimination half-life (t1/2) is about 8.1 to 20.5 hr. in healthy volunteers and patients after administration of 40 to 120 mg orally. Moreover, its plasma clearance is 0.78 L/h (13 ml/min). It is extensively metabolized to 7 metabolites and excreted in urine therefore renal insufficiency has no effect in pharmacokinetic of gliclazide.[11]

The variability in absorption of gliclazide could be related to its early dissolution in the stomach leading to more variability in the absorption in the intestine. This process resulted in low bioavailability of the conventional dosage forms. The use of solubilizing agents like PEG 400 was reported to increase the bioavailability of gliclazide in its oral dosage forms.[12]

FORMULATION OF GLICLAZIDE TABLETS

Gliclazide was procured from Wellona Pharma, Surat Gujarat.Talcum, Methyl paraben sodium, Microcrystalline Cellulose., Propyl paraben sodium, Magnesium Stearate, Lactose, Gelatin, Maize Starch, Ethyl Cellulose, Empress DT, Cross Povidone, Sodium Starch Glycolatewere obtained from Heera Laxmi Pharma Agencies, Delhi.

All the ingredients were pre-weighed and passed through mesh #40 separately.

Table: 1 Formulations of Gliclazide Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gliclazide	8 kg	8 kg	8 kg	8 kg	8 kg	8 kg	8 kg	8 kg	8 kg
Talcum	1 kg	0.9 kg	0.8 kg	0.9 kg	0.8 kg	0.9 kg	1.0 kg	0.9 kg	0.9 kg
Methyl paraben sodium	0.04 kg	0.05 kg	0.04 kg	0.05 kg	0.06 kg	0.04 kg	0.04 kg	0.05 kg	0.05 kg
Microcrystalline Cellulose	3.4 kg	3.9 kg	3.5 kg	3.3 kg	3.3 kg	3.5 kg	3.4 kg	3.4 kg	3.4 kg
Propyl paraben sodium	0.04 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg
Magnesium Stearate	1.3 kg	1.8 kg	1.2 kg	1.0 kg	1.4 kg	1.2 kg	1.3 kg	1.3 kg	1.3 kg
Lactose	0.4 kg	0.4 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg
Gelatin	0.4 kg	0.4 kg	0.4 kg	0.4 kg	0.4 kg	0.4 kg	0.4 kg	0.4 kg	0.4 kg
Maize Starch	0.5 kg	0.4 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg	1.0 kg
Ethyl Cellulose	0.02 kg	0.04 kg	0.04 kg	0.06 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg	0.04 kg
Empress DT	1.4 kg	1.6 kg	1.4 kg	1.6 kg	1.4 kg	1.4 kg	1.4 kg	1.4 kg	1.4 kg
Cross Povidone	1.2 kg	0.9 kg	0.8 kg	0.9 kg	1.0 kg	0.8 kg	1.0 kg	1.0 kg	0.9 kg
Sodium Starch Glycolate	1.9 kg	1.7 kg	1.7 kg	1.7 kg	1.6 kg	1.7 kg	1.4 kg	1.5 kg	1.6 kg

Drug Binder Solution Preparation

Take purified water in SS vessel. Add gelatin and stir slowly until vortex is formed. Add starch in to the vortex followed, while stirring continuously till a homogenous dispersion is formed.

Granulation process

Transfer the weighted raw material into the Rapid mass mixture. Start the rapid mass mixture for 20 minutes to homogeneous mixing of raw material. After 20 minutes stop the RMG and wait for some time to settle down the powder. The transfer the paste into the RMG and mix for 10 to 15 minutes Take the sample for watching correct mixing. Transfer the material into fluid bed dryer to dry

Fluid Bed Granulation

Load the material into the trolly of fluid bed dryer. Pre warm the materials keeping product in between 40ºc at fluidization air of 300 750 m Spray the drug binder solution on the materials of above step.

Drying

Dry the wet granules at 50 º±5 ºc till LOD reaches NMT 2.0% w/w at 105ºc.

Sifting and milling

Set up the sifter. Set the desired granules through # 24 mesh, collect retentions and % 30 mesh granules separately into polythene bags. Mill the retention of above step and transfer it to double lined polythene HDPE container. Repeat the sifting and milling till all the materials passes through #24 mesh.

Blending and lubrication

Load # 24 mesh passed granules with sifted materials except Magnesium Stearate. Ensure that all granules are fully transferred into Bin blender. Start the blender & check the leakage of materials. Blend the loaded material for a specified time in a blender at specified rpm. Mix magnesium stearate with equal quantity of blend from blender in double polythene bag for appropriate time and add this back to the blender &blend or specified time at specified rpm. Unload the lubricated granules into tared HDPE container with double polythene bags.

RESULTS AND DISCUSSION

Evaluation of powder blends:

The blended powders of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows:

Table: 2 Flow characteristics of powder blends

Formulation code	Angle of repose (^{0})*	Loose bulk density(g/ml)*	Tapped bulk density(g/ml)*	Hausner ratio*	Carr's index (%)*
GF1	24.17±0.97	0.635±0.00	0.730±0.00	1.13±0.00	12.147±0.30
GF2	24.48±0.17	0.534±0.00	0.616±0.06	1.07±0.02	10.333±0.33
GF3	23.36±0.98	0.491±0.01	0.547±0.04	1.10±0.00	9.736±1.14
GF4	23.44±0.73	0.547±0.00	0.724±0.02	1.28±0.10	14.505±2.20
GF5	24.05±0.19	0.572±0.00	0.682±0.00	1.22±0.03	16.253±0.61
GF6	23.30±0.17	0.616±0.00	0.775±0.00	1.21±0.00	16.582±0.09
GF7	23.93±0.77	0.561±0.01	0.691±0.00	1.20±0.06	13.586±2.66
GF8	23.20±0.61	0.590±0.01	0.646±0.00	1.11±0.00	12.038±1.50
GF9	24.49±0.36	0.602±0.01	0.636±0.00	1.16±0.17	15.236±0.47

Angle of repose:

Angle of repose ranged from 23.20°± 0.61 to 24.49°± 0.36. The results were found to be below 25o and hence the blend was found to have excellent flow ability.

Loose bulk density and tapped bulk density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.481 ± 0.01 to 0.638 ± 0.00 g/ml; and 0.547 ± 0.04 to 0.778 ± 0.00 g/ml respectively.

Hausner ratio:

The Hausner ratio ranged from 1.09 ± 0.02 to 1.24 ± 0.10. The result indicates the free flowing properties of the powders.

Identification by FTIR spectroscopy:

The FTIR spectrum of gliclazide was shown in Figure and the interpretations of FTIR frequencies were showed in Table

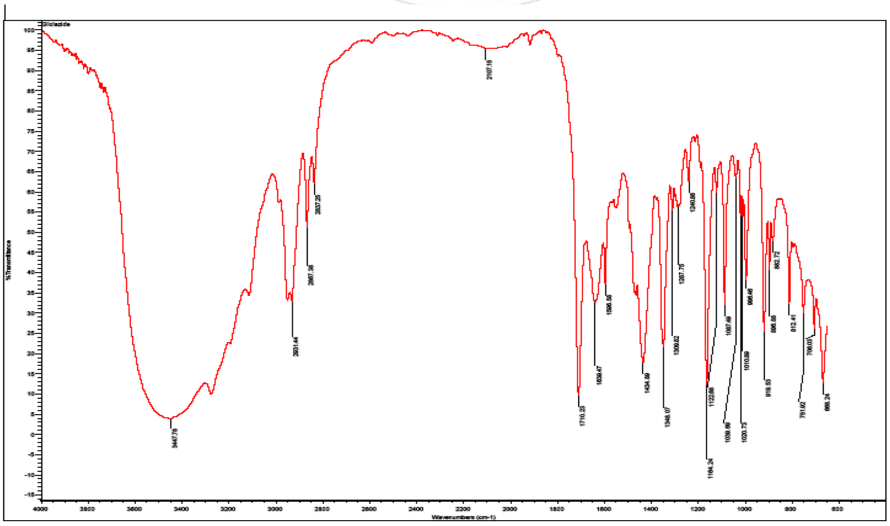

Figure: 1 FTIR spectrum of gliclazide

Interpretation of FTIR Spectrum:

Major functional groups present in gliclazide shows characteristic peaks in FTIR spectrum. Table shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of gliclazide. Hence, the sample was confirmed as gliclazide.

Table: 3 Characteristic frequencies in FTIR spectrum of gliclazide

Wave No.(cm $^{-1}$)	Functional group
3447.78	N-H stretching
2931.44	CH3 asymmetric stretching
2867.38	CH3 absorption
1710.23	C-O stretching
1639.47	NH2 deformation
1596.58	C=C stretching
1348.07	C-C stretching
1164.24	C-N stretching

Melting point:

Melting point of gliclazide sample was found to be 180.4^{0}C. The reported melting point for gliclazide was in range of 18^0 to 182^{0}C. Hence, experimental values are in good agreement with official values.

Table: 4 Solubility of gliclazide in different solvents

Name of solvents	Solubility
Distilled water	Insoluble
Methanol	Sparingly soluble
0.1N HCl	Freely Soluble
Dichloro methane (or) methylene chloride	Freely Soluble
Phosphate buffer (pH 7.4)	Freely Soluble
Acetone	Soluble

Percentage purity of drug:

The percentage purity of drug was calculated by using calibration curve method. The percentage purity of drug was found in official limits.

Table: 5 Percentage purity of gliclazide in pure drug

S. No.	Percentage purity (%)	Average percentage purity (%)
1.	**99.75**	**100.13 $\pm$ 0.30**
2.	**100.22**	
3.	**100.31**	

The reported percentage purity for gliclazide in IP 2007 is 97 to 102%.

Differential scanning calorimetry:

The compatibility and interactions between drug and polymers were checked using differential scanning calorimetry and the results were shown in Figures

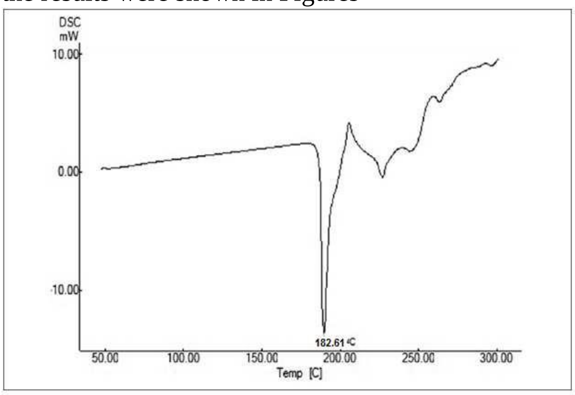

Figure: 2 DSC thermal analysis of gliclazide

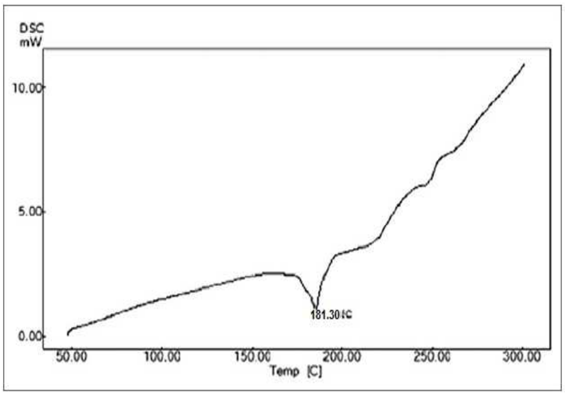

Figure: 3 DSC thermal analysis of gliclazide

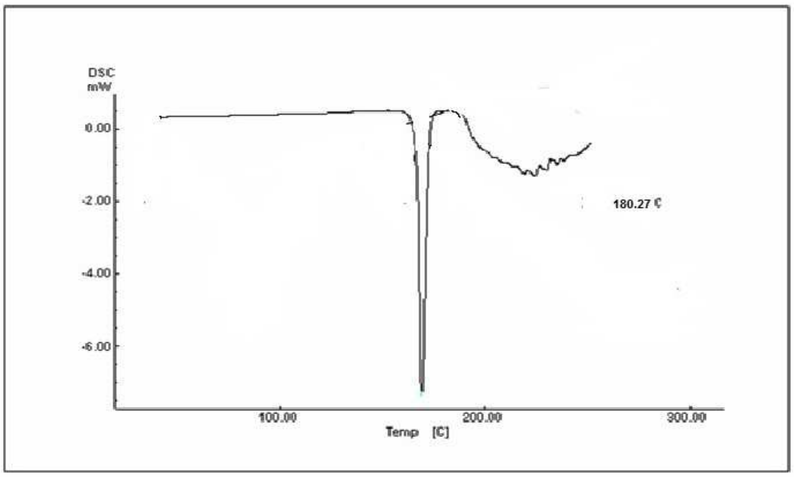

Figure: 4 DSC thermal analysis of gliclazide + ethyl cellulose

Evaluation of tablets:

Appearance:

Surface nature of tablets was observed visually, and it was concluded they did not show any defects such as capping, chipping and lamination.

Physio-chemical characteristics:

The physical characteristics of gliclazide tablets (GF1 to GF9) such as thickness, diameter, hardness, friability, uniformity of weight and drug content were determined, and the results were shown in table.

Dimension (Thickness and Diameter):

The size (diameter) of the tablets was found to be in the range from 11.17±0.01 mm to 11.20 ± 0.01 and thickness between 4.32 ± 0.06 to 4.58 ± 0.04 mm.

Tablet hardness:

The hardness of tablets was found to be in the range from 5 kg/cm2 to 6 kg/cm2. This indicates good mechanical strength of tablet.

Uniformity of weight:

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 200 mg, the pharmacopoeial limit for percentage deviation is ± 7.5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for uniformity of weight according to the pharmacopoeial specifications IP 2007.

Drug content:

The drug content of all the formulation was found to be in the range from 98.50 ± 1.55 to 102 ± 2.20 % w/w, which was within the specified limit as per IP 2007.

Stability study:

After exposure to accelerated stability conditions the formulation was analysed for various evaluation parameters;

Table: 6 Stability studies

Stability Chamber	Time	Appearance	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	% drug release
40± 2°C with 75± 5 % RH	Initial	White	6-7	0.63	98.50	98.2
	1st month	No change	6- 7	0.62	98.38	97.8
	2nd month	No change	5-6	0.62	97.99	97.3
	3rd month	No change	5-6	0.70	97.36	96.9

In vitro drug release studies

Table: 7 In vitro drug release studies

Gliclazide Tablet F1							
Time	% of gliclazide dissolved of the label claim						
	1	2	3	4	5	6	Mean
15 min.	65.26	63.51	66.88	65.65	62.93	64.13	65.79
30 min.	86.28	82.39	85.45	88.03	88.42	84.30	85.29
45 min.	92.91	92.64	96.81	95.19	90.62	91.55	92.48

Gliclazide Tablet F2							
Time	% of gliclazide dissolved of the label claim						
	1	2	3	4	5	6	Mean
15 min.	63.42	64.82	63.98	63.62	63.88	63.35	63.84
30 min.	83.76	83.95	82.72	83.57	82.54	83.82	83.39
45 min.	91.75	90.42	92.84	96.07	92.81	95.59	93.24

Gliclazide Tablet F3							
Time	% of gliclazide dissolved of the label claim						
	1	2	3	4	5	6	Mean
15 min.	60.48	61.42	60.86	60.54	61.94	62.32	61.26
30 min.	88.82	83.37	86.58	84.35	87.24	85.10	85.91
45 min.	90.12	90.54	91.49	90.17	89.55	90.49	90.39

Gliclazide Tablet F4							
Time	% of gliclazide dissolved of the label claim						
	1	2	3	4	5	6	Mean
15 min.	67.59	66.15	67.98	67.54	67.87	66.39	67.25
30 min.	88.52	88.51	88.79	87.74	88.38	86.94	88.14
45 min.	93.82	91.57	93.94	94.48	93.87	96.45	94.02

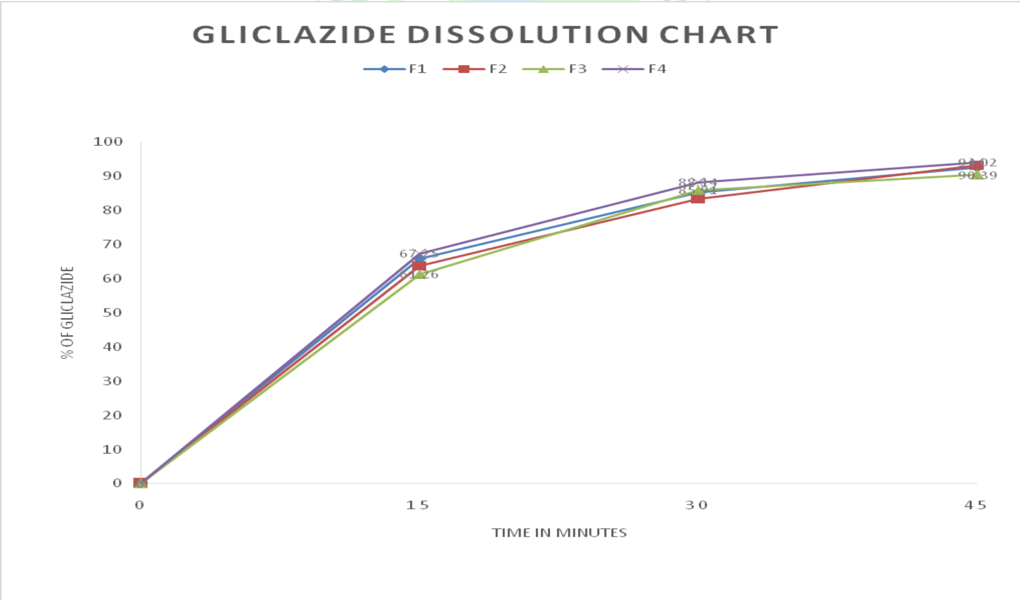

Figure: 5 Dissolution study of Gliclazide

CONCLUSION

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes.

Gliclazide was chosen as a drug having soluble in intestinal pH. Gliclazide plays a major role in treatment of Diabetic mellitus type2. The drug half-life in plasma is 10.4 hours. It is bound to plasma proteins 85 to 95%. Gliclazide is rapidly absorbed with a bioavailability of over 97% following oral ingestion, hence it was considered as a good candidate for the design of oral release dosage form.

In the present study, Infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction. The powders and resulting tablets were evaluated for different parameters. All showed excellent flow properties and complied with pharmacopoeial standards. The *in vitro* release profiles from tablets of drug and different polymer ratio were applied on various kinetic models. It shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation F4 as best formulation among all the nine formulations. Based on release exponent (n) values, it was concluded that mechanism of drug release was found to be diffusion coupled with erosion (anomalous transport mechanism).

From the stability studies, there was no significance difference in hardness, friability, drug content and *in vitro* release profile for the best formulation.

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REFERENCES:

1. AnanyaSarkar, Ajay Tiwari "Pharmacological & Pharmaceutical Profile of Gliclazide: A Review" Jaipur National University, Jaipur.Journal of Applied Pharmaceutical Science, 2011; 01(09)11-19
2. Walker R., C. Edwards, "Diabetes Mellitus", Chapter 43 in Clinical pharmacy and Therapeutic, 2nd edition, Churchill Livingstone: 633-637.
3. Rathbone M.J., G. Ponchel, F.A. Ghazali"Systemic Oral Mucosal Drug Delivery and Delivery Systems", Chapter 11 in Oral Mucosal Drug Delivery, Marcel Dekker,2010; 63:243-245.
4. Zhang H. J.R. Robinson, "Routtes of Drug Transport Across Oral Mucosa". Chapter 3 in Oral Mucosal Drug Delivery, Marcel Dekker, 2012; 63:52-53.
5. KellawayI.W. ,S.J. Warren. "Mucoadhesive hydrogels for Buccal Delivery", Chapter 10 in Oral Mucosal Drug Delivery, Marcel Dekker, 63:231-232.
6. Perioli L, Ambrogi V, Giovagnoli S, Blassi P, Rossi C, Mucoadhesivebilayered tablets For buccal sustained release of flurbiprofen, AAPS Pharm Sci Tech,2007; 8(3):54.
7. AndrzejCzyrski, MatyldaResztak, Tadeusz Hermann Determination of Gliclazide Minimum Concentration in Type 2 Diabetes Mellitus Patients 2018 ;106:1267-1270.
8. Arti Banerjee , P R P Verma, Subhash Gore Controlled Porosity Solubility Modulated Osmotic Pump Tablets of Gliclazide 2015 ;16(3):554-68
9. Jamadar, Snehal P. Mulye, Poonam S. Karekar , Yogesh V, Pore, Kishor B and Burade.Development and validation of UV spectrophotometric method for the determination of gliclazide in tablet dosage form, *Der Pharma Chemica,* **2011**; 3(4):38-343.
10. SeemaPushkar and Nikhil K. Sachan. Pharmaceutical characterization and assessment of drug release behaviour of diclofenac sodium extended release matrix devices, *Int. J. Pharm. Sci. Tech*., **2009**; 2(1):14-21.
11. Shalin A. Modi, Gaikwad P.D., Bankar V.H. and Pawar S.P. Sustained release drug delivery system: A Review, *International Journal of Pharma Research and Development*, **2011**; 2(12):147-160.
12. Sundaramoorthy K., Kavimani S. and Swaminathan S. Development and evaluation of extended release metformin hydrochloride matrix tablets: Rate of *In-Vitro* and *In-Vivo* Release Studies, *Journal of Pharmacy Research,* **2011**; 4(3):884-885.