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Research Article

FABRICATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF GLIPIZIDE

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ABSTRACT

The aim of this investigation is to style oral doubly a daily sustained unleash matrix tablets of Glipizide 10mg, used for the treatment of anti-diabetic drug from the antidiabetic drug category which might unharness the drug for ten hours. The tablets were ready by the Wet granulation technique mistreatment variable concentrations of sustained unharness polymers HPMC, Eudragit. The compatibility of the polymers was dominated out by FT-IR studies and located to be compatible. Total nine formulations were ready. The Glipizide powder and also the powder- blends of tablets were evaluated for their physical properties like angle of repose, bulk density and sponginess index and located to be smart and satisfactory. The manufactured tablets were evaluated for in method and finished product internal control tests as well as look, dimensions, weight variation, hardness, friability, drug content, and in vitro drug unleash. The dissolution medium used was hydrogen ion concentration half dozen.8. phosphate buffer. All formulations showed acceptable pharmaco-technical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated all formulations free up to 10hours and formulation containing HPMC: F3 was the foremost successful formulation with 99.38% drug unharness at the tip of ten hours.

Keywords: Glipizide; Sustained release polymers; sustained release; matrix tablets formulation; evaluation; in vitro release.

INTRODUCTION

The most employed method to modulate the sustained drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[1] Matrix system are also favored because of their simplicity, patient compliance than traditional drug delivery (TDS), which have many drawbacks like repeated administration and fluctuation in blood concentration level. In this type of drug delivery system, the drug is homogeneously dispersed throughout the matrix of crosslink of linear polymer chain.[2] It is assumed that from this type of drug delivery system, drug molecule come out from matrix by dissolution and then diffusion through the polymer structure.[3] As the drug is released, the distance for diffusion becomes greater and solid particles began to deplete. Most of the highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations of highly water soluble drugs.[4] As the dissolution medium or biological fluid penetrates the dosage form, the polymer swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology.[5]

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Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release(CR) drug delivery systems. Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Matrix type sustained delivery systems are popular because of their ease of manufactures. It Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release(CR) drug delivery systems. Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Matrix type sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pellitization during manufacturing and drug release from the dosage form. It is controlled mainly by the type and proportion of the polymers used in the preparation.[6]

Glipizide is a second generation sulphonylurea that is commonly used in the pharmacological treatment of type 2 diabetes mellitus[7]. It acts by increasing the release of endogenous insulin as well as its peripheral effectiveness; but it has been associated with gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy in the normal doses[8]. Accordingly, there is a strong clinical need and market potential for a dosage form that will deliver glipizide in a controlled manner to a patient needing this therapy which in turns could circumvent the aforementioned problems associated with oral administration of glipizide, thereby resulting in a better patient compliance. For the aforementioned reasons, the study was developed to formulate sustained release glipizide tablets.

METHODOLOGY:

STANDARD GRAPH FOR GLIPIZIDE

The UV scanning of drug sample was carried out using a solution of drug dissolved in methonolic 6.8 ph phosphate buffer solutions at concentration of 100 µg/ ml. The λmax was observed at 276nm. The calibration curve of Glipizide was obtained by dissolving the drug in buffer solutions and absorbance was measured at 276nm in methanolic buffer solution used as blank. Beer's law was obeyed the concentration range of 5-25 µg in 0.1 N HCL solution.

Procedure

Method of preparation of pH 6.8 Phosphate buffer solution:

224ml of 0.2M NaOH + 500ml of potassium dihydrogen orthophosphate (KH2PO4) and makeup the volume to one litres.

How to prepare 0.2M NaOH: Dissolve 8 gm of NaOH in 1000ml of distilled water.

How to prepare KH2PO4: Dissolve 27.2 gm of KH2PO4 in 1000ml of distilled water.

PROCEDURE:

Accurately weighed quantity of Glipizide (100mg) was dissolved in Methanolic 6.8 buffer and the volume made up to 100ml with the same. **S.S I ⇒ 1000 mcg/ml.** 10ml of Stock solution I was further diluted with 100ml of pH 6.8 buffer to get a working standard **S.S I ⇒ 100mcg/ml** Aliquots of 5-25 mcg/ml of stock solution was pipetted into 10ml volumetric flask and diluted up to the volume with buffer. The absorbance was measured at 276nm against reagent blank (6.8ph buffer).As shown in the figure and table .Same procedure was employed to extract the standard graph for phosphate buffer 6.8.

PREPARATION OF GLIPIZIDE BY DIRECT COMPRESSION METHOD

Step 1: Weighing and Blending - the active ingredient, disintegration agents are Weighed and mixed.

Step 2: Sieving of the all mixture

Step3: Lubricate with aerosil

Step4: Compression in 6mm concave punch.

Formulation design:

Table-1: Table of formulation formula

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide	10	10	10	10	10	10	10	10	10
MCC 102	98	94.4	90.8	87.2	98	94.4	90.8	87.2	94.4
HPMC K100 CR	3.6	7.2	10.8	14.4	-	-	-	-	3.6
Eudragit L-100	-	-	-	-	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%) (free-flow agent)	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Total tab wt	120	120	120	120	120	120	120	120	120

Precompression Parameters:

FOURIER TRANSFORM INFRARED SPECTROSCOPY STUDIES:

Principle:

Electromagnetic radiation ranging between 500cm-1 and 4000cm-1 is passed through a sample and is absorbed by the bondes of the molecules in the sample causing them to stretch or bend.The wave length of the radiation absorbed is characteristic of the bond absorbing it.

Equipment Details Manufacture: Shimadzu Software: spectrum 100. The mid IR region of analytical importance. FT IR spectroscopy is used to determine the functional groups in the drug molecule. We can elucidate the structure of drugs. Mainly it is used for structural elucidation .Based on the drug given in figure 21 and the optimized formulation given in figure 25 ,comparing the spectrum in both we conclude that the spectrums are correlated with each other.

Procedure: In the present study, potassium bromide pellet technique was used .The sample area unit totally mixed with dry powdery K bromide .The mixture was compressed to create a disc mistreatment dies .The disc was placed within the photometer and also the spectrum was recorded.

PRE COMPRESSION PARAMETERS

Angle of Repose:

The frictional force within the powders can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powders are added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The powders were carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

The angle of repose (θ) was calculated using the following formula

$$\mathbf{Tan\ \theta = h/r}$$

Where; θ = Angle of repose h = Height of the cone in cms, r = Radius of the cone base in cms

Values for angle of repose ≤ 300 usually indicate a free flowing material and angles ≥ 400 suggest a poorly flowing material. 25- 30 showing excellent flow properties,31-35 showing good flow properties,36-40 showing fair flow properties,41-45 showing passable flow properties.

Bulk Density:

Density is defined as weight per unit volume. Bulk density (Db), is defined as the mass of the powders divided by the bulk volume and is expressed as gm/cm3. The bulk density of the powders primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. The bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the powders into a graduated cylinder. The bulk volume (Vb) and weight of the granules (M) was determined. The bulk density was calculated using the formula.

$$\mathbf{Db = M/Vb}$$

Where, M is the mass of the powders and Vb is bulk volume of the granules.

Tapped Density:

The measuring cylinder containing a known mass of powders was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the powders was measured. The tapped density was calculated using the formula.

$$\mathbf{Dt = M/Vt}$$

Where, M is the mass of the powders Vtis tapped volume of the powders

Compressibility Index:

The compressibility Index (Carr's Index) could be a live of the propensity of a powder/ granules to be compressed. it's determined from the majority and broached densities. In theory, the less compressible a fabric the additional flowable it's. during a free-flowing powder/ granules, such interactions ar typically diminished, and also the bulk and broached densities are going to be nearer in price. For poor flowing materials, there ar oftentimes bigger interparticulate interactions, and a bigger distinction between the majority and broached densities are going to be ascertained. These variations ar mirrored within the squeezability Index that is calculated exploitation the subsequent formulas.

$$\mathbf{CI\ (\%) = [(Tapped\ density - Bulk\ density) / Tapped\ density] \times 100}$$

Hausner's Ratio:

Hausner's ratio is an indirect index of ease of powder/granule flow. It is calculated by the following formula.

Hausner's Ratio=Tapped density (ρt) / Bulk density (ρb)

Where ρt is the tapped density and ρb is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

Testing Procedure for Tablets:

Weight Variation:

To study the burden variation, twenty tablets were taken and their weight was firm singly and together on a digital scales. the typical weight of 1 pill was firm from the collective weight. the burden variation check would be a satisfactory methodology of determinative the drug content uniformity. The p.c deviation was calculated victimisation the subsequent formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Specifications of percentage weight variation allowed in tablets as per BP.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Twenty tablets were taken and their thickness was recorded using vernier caliper and the average thickness is calculated.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability by following procedure. Pre weighed tablets (20 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed loss in the weight of tablet is the measure of friability and is expressed in percentage by using below equation. 32

% Friability = [(W1 – W2) / W1] × 100

Where, W1=Initial weight, W2= Final weight. Limits for Friability are usually less than 1%

Tensile Strength

A non-compendial method of measuring the mechanical strength of tablets that is now widely used is the tensile strength. This is the force required to break a tablet in a diametral compression test. The radial tensile strength, T, of the tablets can be calculated from the equation

T or To = 2F/πDh

Where, T or To = tensile strength of tablet without or with centre hole respectively; F = diametric compression load needed to break the tablet; D = tablet diameter ; h = tablet thickness.

Drug Content:

Drug content was determined by accurately weighing 5 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 100 mg of drug was transferred to a 100 ml volumetric flask. 50 ml of Diluent was added and shaken. Volume was made up to 100 ml with Diluent. The solution was filtered through Whatmann filter paper. First few ml of the filtrate was discarded. 10 ml of the filtrate was diluted to 100 ml with Diluent. From the above solution 1ml was taken and diluted to 10 ml with Diluent. The absorbance of the resulting 10 µg/ml solution was recorded at 243nm and 273nm. Content uniformity was calculated using formula.

% Purity = 10 C (Au / As)

Where, C = concentration, Au and As are absorbance obtained from standard preparation and assay preparation respectively.

In vitro Dissolution Studies: The in vitro dissolution study was carried out in USP dissolution test apparatus type 2 (paddle)

Dissolution Medium: 900ml of 6.8 phosphate buffer

Temperature : 37 ± 0.5 C

RPM : 50

Volume withdrawn & replaced: 5 ml every 120 minutes.

λ max :276nm.

Stability Studies Introduction

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Objective of the Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA)

Long-Term Testing: 25 C ± 2 C / 60% RH ± 5% for 12 Months

Accelerated Testing: 40 C ± 2 C / 75% RH ± 5% for 6 Months

Method

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40 C / 75% RH for 3months and evaluated for their physical appearance, drug content and drug excipient compatibility at specified intervals of time.

Analytical Data Glipizide Drug % Release Dissolution

Dissolution Medium	:	900ml of 6.8 phosphate buffer
Number of baskets	:	8 baskets
Medium	:	6.8Phosphate buffer
Type	:	USP –II
RPM	:	50
Volume	:	900ml
Run time	:	10hr
Temp	:	37± 0.5º C.

RESULTS AND DISCUSSION:

FOURIER TRANSFORM INFRARED SPECTROSCOPY OF GLIPIZIDE

1.Glipizide

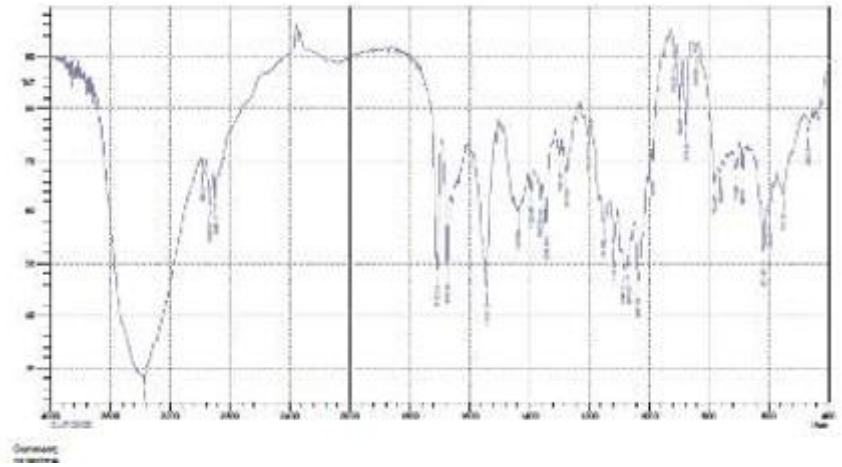

Figure-1: FTIR graph of Glipizide

2.Glipizide with HPMC

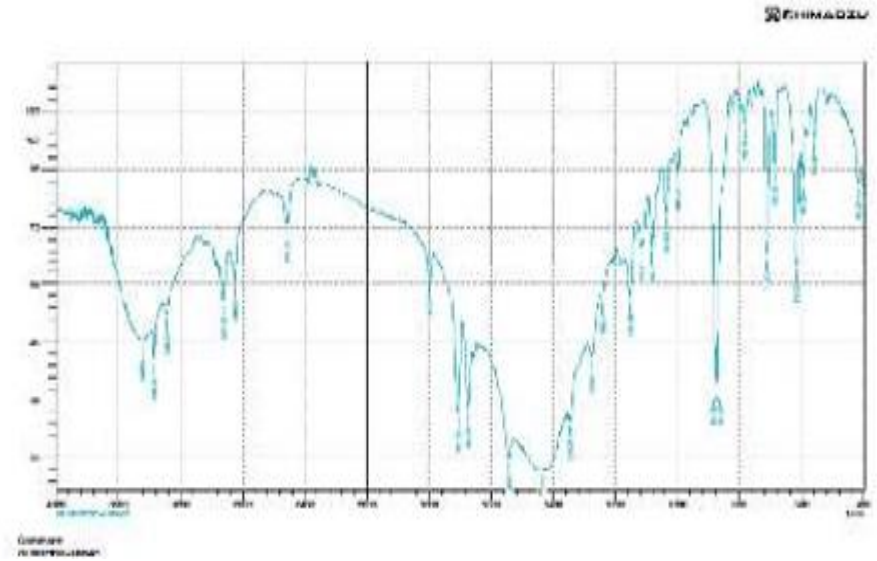

Figure-2: FTIR graph of Glipizide with HPMC

3.Glipizide with Eudragit

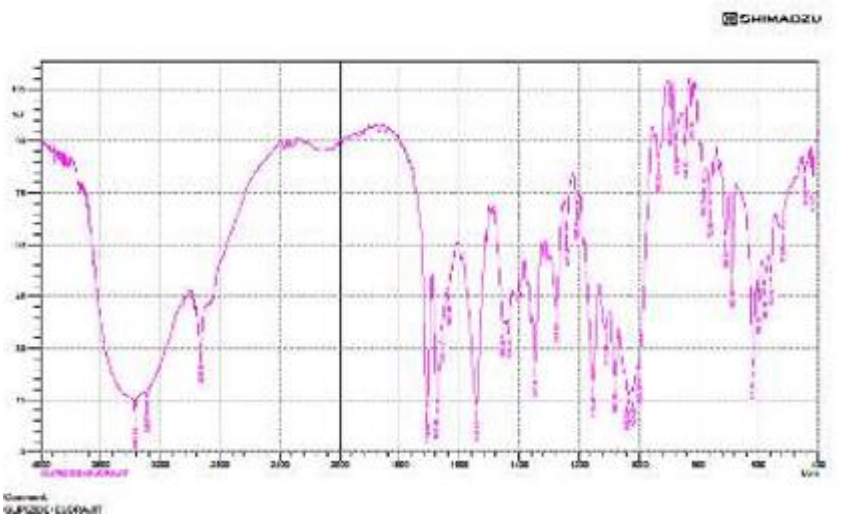

Figure-3: FTIR graph of Glipizide with Eudragit

4.Glipizide with MCCP

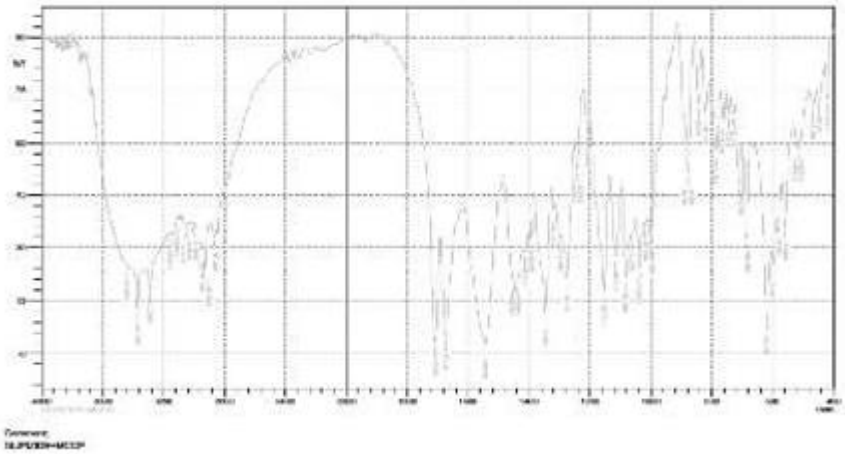

Figure-4: FTIR graph of Glipizide with MCCP

STANDARD GRAPH CALIBRATION CURVE OF GLIPIZIDE
STANDARD GRAPH RESULTS OF 6.8 Phosphate buffer

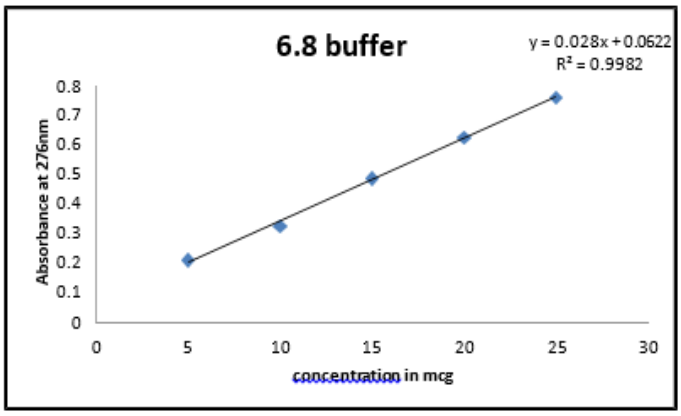

Figure-5: Standard graph of Glipizide

PRE AND POST FORMULATION STUDIES

Table-2: Table for PreCompression studies

Formulation	Bulk Density(gm\ml)	Tapped Density (gm\ml)	Compressibility Index (%)	Hausner Ratio	Angle of Repose
F1	0.510gm/ml	0.598gm/ ml	15.81%	1.17	26.28
F2	0.512gm/ml	0.597gm/ ml	15.38%	1.18	26.85
F3	0.512gm/ml	0.60gm/ml	14.87%	1.17	27.14
F4	0.505gm/ml	0.591gm/ ml	14.64%	1.17	27.75
F5	0.507gm/ml	0.595gm/ ml	14.72%	1.17	28.07
F6	0.5076gm/ml	0.597gm/ ml	14.97%	1.176	28.07
F7	0.512gm/ml	0.595gm/ ml	13.846%	1.16	29.39
F8	0.515gm/ml	0.598gm/ ml	13.91%	1.161	29.74
F9	0.515gm/ml	0.602gm/ ml	14.43%	1.168	29.02

POST COMPRESSION PARAMETER

Table -3: Post compression parameters of Glipizide

Formulation	Avg.Wt (mg)	Diameter(mm)	Hardness (Kg\cm^2)	Friability	Thickness
F1	121	6	5.5	0.11	4.60
F2	122	6	5.4	0.06	4.71
F3	119	6	5.6	0.14	4.80
F4	124	6	6	0.04	4.10
F5	120	6	5.1	0.14	4.9
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	4.7
F9	122	6	5.4	0.02	4.9

DISSOLUTION STUDIES

Table -4: Dissolution table of formulations in 6.8 Phosphate buffer

Time in hr	1hr	2hr	4hr	6hr	8hr	10hr
F1	22.36	34.23	59.63	71.77	95.52	96.07
F2	23.46	33.12	60.73	77.02	96.9	96.9
F3	21.53	36.44	67.63	87.51	94.41	99.38
F4	23.74	30.92	54.66	68.74	81.71	89.44
F5	25.39	35.88	59.35	73.71	96.62	97.17
F6	24.29	36.99	58.25	70.39	93.31	98.28
F7	26.22	34.23	61.01	70.67	77.57	83.92
F8	20.7	39.75	54.93	75.09	91.38	99.11
F9	17.94	34.23	45.82	64.32	85.3	96.62

GRAPHS OF DISSOLUTION STUDIES

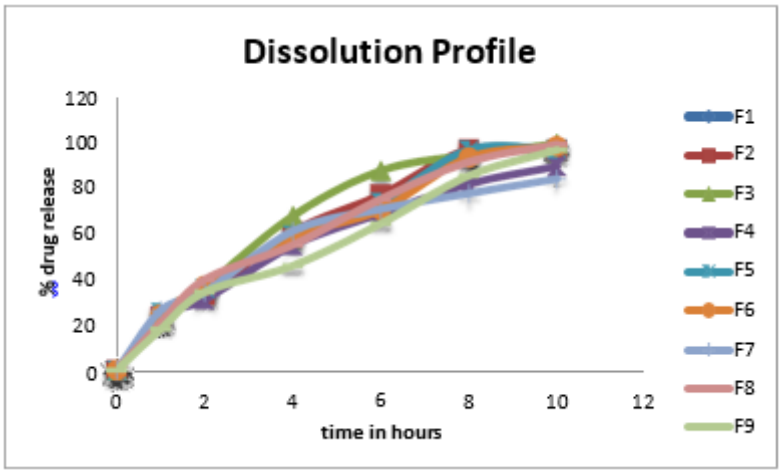

Figure-6: Graph of Dissolution profile of Glipizide tablets

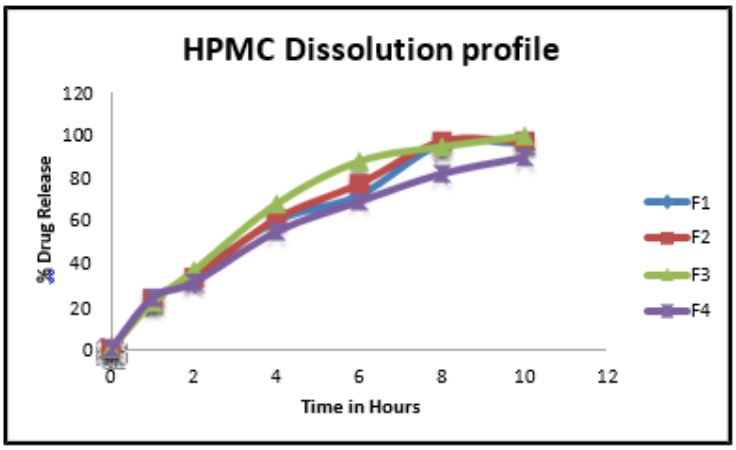

Figure-7: Graph Dissolution profile of HPMC

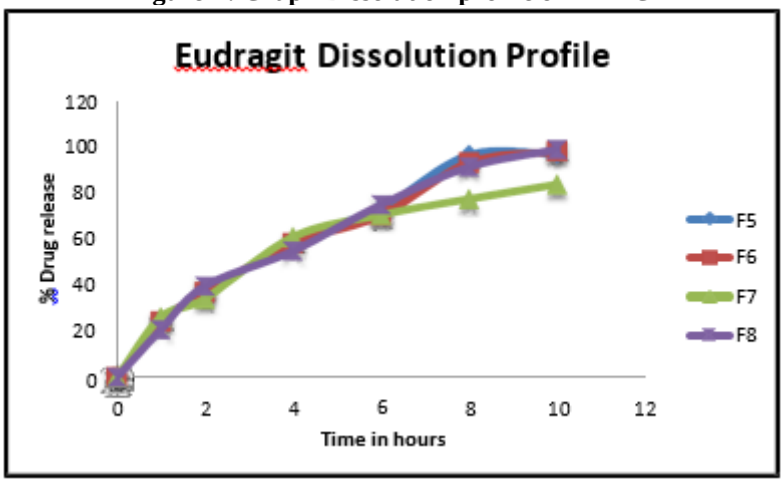

Figure-8: Graph for Dissolution profile of Eudragit

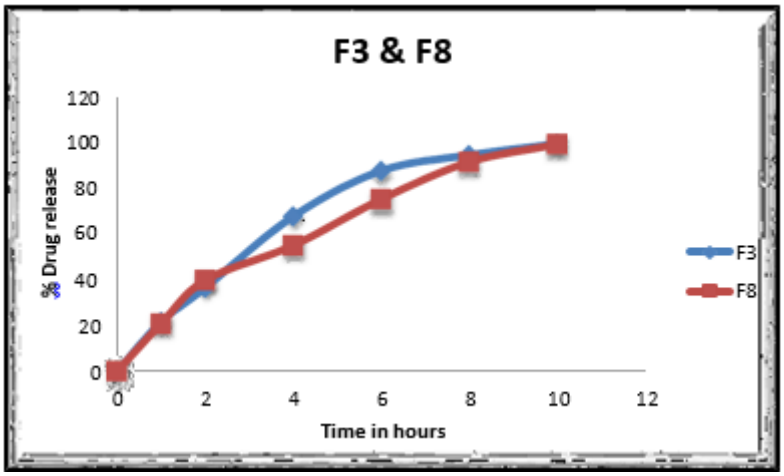

Figure-9: Graph for Dissolution profile of F3 & F8

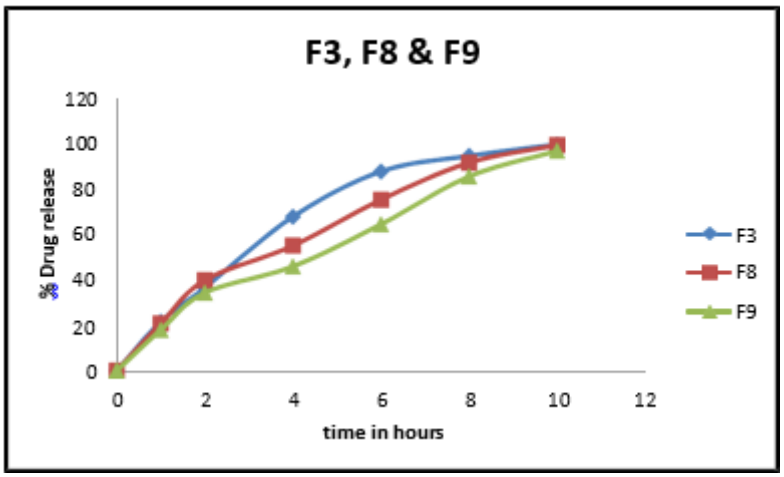

Figure-10: Graph for Dissolution profile of F3, F8 and F9

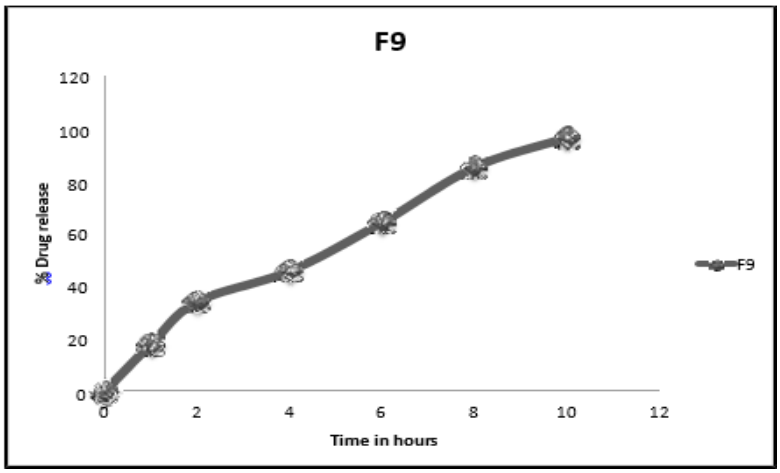

Figure-11: Graph for Dissolution profile of F9

STABILITY STUDIES

Table -5: Table for Stability Data of Formulation 3 at 40 ±20C / 75 ± 5% RH.

Sl. No	Time in days	Physical changes	Percentage of drug content* ±SD	Moisture content	Percentage of drug release *±SD (99.5% of release label claim in 10 min).
1.	**1st day (initial)**	Round, yellow 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%

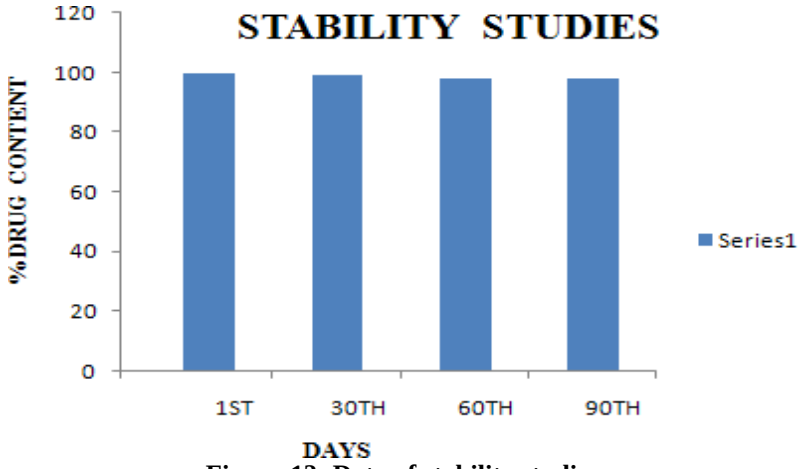

Figure-12: Data of stability studies

ASSAY OF GLIPIZIDE

Table-6: Table for assay

		FE1	FE2	FE3	FE4	FE5	FE6	FE7	FE8	FE9
std.wt	10	-	-	-	-	-	-	-	-	-
std.abs	0.326	-	-	-	-	-	-	-	-	-
stl.wt	-	120	123	124	125	120	119	121	123	122
spl.abs	-	0.033	0.033	0.035	0.033	0.032	0.034	0.035	0.032	0.033
std.dil.f	0.02	-	-	-	-	-	-	-	-	-
spl.dil.f	0.002	-	-	-	-	-	-	-	-	-
std.purity	99.8	-	-	-	-	-	-	-	-	-
avg.wt	120	-	-	-	-	-	-	-	-	-
amt/tab	-	10.10	9.86	10.37	9.70	9.80	10.50	10.63	9.56	9.94
%Assay	-	101.00	98.60	103.70	97.00	98.00	105.00	106.30	95.60	99.40

Discussion: Short-term stability studies on the above promising formulations (at 400C/ 75% RH for 3 months) have shown no significant changes in physical appearance, drug content data of the promising formulation.

CONCLUSION

Various solid matrix formulations were prepared with swellable and non-swellable polymers (HPMC k100m, Eudragit L-100) in solid matrix using direct compression method. Increasing the amount of HPMC and Eudragit in solid matrix tablet decreased the release rate of the drug. The formulation 3, drug release profile is 99%, rest of 9 formulations. In the formulation 3 having swellable polymer as HPMC k100CR showing better drug release profile than non-swellable polymer (Eudragit L-100). Hence the swellable polymer HPMC k100 CR is better suitable for sustained release delivery.

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