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Comparitive Evaluation of Three Granulation Processes for Antidiabetic Drug of Gliclazide by Using Design of Experiment

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ABSTRACT

In the present study compared and evaluated the three granulation process for controlled release antidiabetic drug of Gliclazide. The effect of three different polymers on the *in-vitro* dissolution profiles of Gliclazide controlled release tablet was studied. Later combinations of polymers were used and the tablets were prepared by using wet, dry and MADG (Moisture Activated Dry Granulation) process. The study was carried out using full factorial designs of experiments. The release rate of 5 to 6 mg%/ hour was targeted and the effect of the polymers on drug release over 24 hours was evaluated. The DOE experiments have shown that when the combination of polymer is used, the total polymer concentration should be in a narrow range of 32.4% w/w to 37.5% w/w in order to achieve the target dissolution profile for Gliclazide. The effect of three granulation process on the tablet properties and drug release were studied. Wet granulation and MADG process were compared. Finally MADG process is showing better results when compared with other process.

Keywords: Gliclazide, MADG (Moisture Activated Dry Granulation), Design of Experiments (DOE).

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INTRODUCTION

"A dosage form compressed in to a single unit mass'' containing a unit dose of one or more medicaments. They are intended for oral administration is tablet. A tablet consist of active medicament along with excipients which are in powder form are compressed or pressed into a solid dosage form[1].

Granulation may be defined as a size enlargement process which converts fine or coarse particles into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity. The art and science for process and production of granules are known as Granulation Technology.

Granulation process has been widely used in the pharmaceutical industry for the preparation of material for tableting. Other process which involves the granule formation includes microencapsulation, multi-particulate system for modified release mechanism and to prepare granules to be used by patient directly. Primarily granules are prepared to improve flow and compression characteristics of the blend but there are many other reasons and sometimes multiple reasons for granulation such as-

- Improving flow properties of the mix and hence the uniformity of the dose;
- Increasing the bulk density of a product;
- Facilitating metering or volumetric dispensing;
- Controlling the rate of drug release;
- Decrease dust generation and reduce employee exposure to drug product;
- Improving product appearance;

Granulation is the process in which primary powder particles are made to adhere to form larger, multi particle aggregates called granules**.** After granulation process the granules will either be packed (when used as a dosage form - powder), or they may be mixed with other excipients prior to tablet compaction or capsule filling. Granulation is used mainly to improve flow, compressibility of powders, and to prevent segregation of the blend components improve content uniformity, and eliminate excessive amounts of fine particles. Particle size of the granulate is mainly affected by the quantity and feeding rate of granulating liquid. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use[2,3].

Methods used in preparation of tablets.

a) Direct compression
b) Wet granulation
c) Dry granulation

Advanced Granulation Techniques: [4]

Over a period of time, due to technological advancements and in an urge to improve commercial output various, newer granulation technologies have been evolved such as-

- Steam Granulation
- Melt/Thermoplastic Granulation
- Moisture Activated Dry Granulation (MADG)
- Moist Granulation Technique (MGT)
- Thermal Adhesion Granulation Process (TAGP)
- Foam Granulation

Moisture Activated Dry Granulation Technique (MADG) [5, 6-13]

Wet granulation, dry granulation and direct blending are the most popular granulation processes for solid dosage form manufacture in the pharmaceutical industry, but they each have distinct drawbacks.

MADG is a process in which moisture is used to activate granule formation, without the need to apply heat to dry the granules. During this process, the generation of moist agglomerates is followed by the stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute the moisture, which results in a uniform, free-flowing and compactable granulation. This process is a single pot process.

There are two major stages in MADG: agglomeration and moisture distribution/absorption. During agglomeration, all or part of the Drug is mixed with an agglomerating binder, such as Povidone to obtain a uniform mixture. While mixing, a small amount of water is sprayed onto the powder blend, which moistens the binder and makes it tacky. The binder facilitates the binding of the drug and excipients during the kneading stage. The resulting agglomerates are small and spherical because the amount of water used in MADG is much lower than in conventional wet granulation; thus preventing the agglomerates from forming large wet lumps. The particle size of the agglomerates generally falls in the range of 150–500 μm.

In moisture distribution/absorption, the balance amount of formula is added and mixed. When they come into contact, the moisture absorbents pick up moisture from the moist agglomerates, resulting in moisture redistribution within the mixture. When this happens, the entire mixture becomes relatively dry. While some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact and some usually the larger particles may break up. This process results in granulation with more uniform particle size distribution. Then, while mixing, lubricant(s), such as Magnesium Stearate are added and blended for sufficient time to achieve adequate lubricity.

This completes the MADG granulation process.

Table 1: Moisture Activated Dry Granulation Process

Raw materials dispensing and sifting
Dry mixing (5 minutes) (grn)
Agglomeration with small amount of water (7 to 10 minutes) (grn)
Moisture distribution with remaining ingredients (8 to 10 minutes) (grn)
Lubricant mixing (3 minutes) (grn)
Compression

Advantages

- Applicable to more than 90% of the granulation need for pharmaceutical, food and Nutritional industry.
- Time efficient
- Very few variables involved in the process.
- Suitable for continuous processing
- Less energy involved during processing.

Disadvantages

- Moisture sensitive and high moisture absorbing API are poor candidates.
- Formulations with high drug loading are difficult to develop.

Design of Experiments[14]

This section introduces the basic concepts, terminology, goals and procedures underlying the proper statistical design of experiments. Design of experiments is abbreviated as DOE.

Topics covered are

- What is experimental design or DOE?
- What are the goals or uses of DOE?
- What are the steps in DOE?

What is experimental design?

Experimental Design (or DOE) economically maximizes information. In an experiment, we deliberately change one or more process variables (or factors) in order to observe the effect the changes have on one or more response variables. The (statistical) design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions.

What are the uses of DOE?

DOE is multipurpose tools that can help in many situations. Below are seven examples illustrating situations in which experimental design can be used effectively?

- Choosing Between Alternatives
- Selecting the Key Factors Affecting a Response
- Response Surface Modeling to:
    - Hit a Target
    - Reduce Variability
    - Maximize or Minimize a Response
    - Make a Process Robust (i.e., the process gets the "right" results even though there are uncontrollable "noise" factors)
    - Seek Multiple Goals

What are the steps of DOE?

Obtaining good results from a DOE involves these seven steps:

1. Set objectives
2. Select process variables
3. Select an experimental design
4. Execute the design
5. Check that the data are consistent with the experimental assumptions
6. Analyze and interpret the results
7. Use/present the results (may lead to further runs or DOE's).

FULL FACTORIAL DESIGNS: [14]

Full factorial designs in two levels:

A common experimental design is one with all input factors set at two levels each. These levels are called `high' and `low' or `+1' and `-1', respectively. A design with all possible high/low combinations of all the input factors is called a full factorial design in two levels. If there are k factors, each at 2 levels, a full factorial design has 2^k runs and is shown in the table 2.

Table 2: Number of Runs for a 2^k Full Factorial

Number Factors	Number of Runs
2	4
3	8
4	16
5	32
6	64
7	128

➢ ***Two-level full factorial designs:***

Description:

Consider the two-level, full factorial design for three factors, namely the 2^3 design. This implies eight runs (not counting replications or centre point runs). Graphically, we can represent the 2^3 design by the cube shown in Figure: 3 .The arrows show the direction of increase of the factors. The numbers '1' through '8' at the corners of the design box reference the 'Standard Order' of runs.

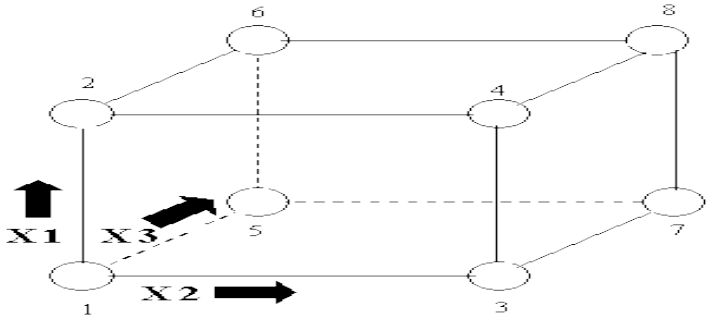

Fig 1: A 2^3 two-level, full factorial design; factors X1, X2, X3

Table 3: A 2^3 two-level, full factorial design table showing runs in 'Standard Order'

Run	X1	X2	X3
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1

Diabetes Mellitus: [15, 16, 17]

Diabetes mellitus is a group of syndromes characterized by hyperglycemia, glycosuria, hyperlipedimia, negative nitrogen balance, and sometimes ketonemia. A wide spread pathological changes are, thickening of capillary basement membrane, increasing in vessel wall matrix, and cellular proliferation resulting in vascular complications like lumen narrowing , early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy, and peripheral vascular insufficiency. Diabetes is not a disease, but a disorder which requires continuous use of drugs for its maintenance.

Two major types of diabetes mellitus are

Type I: Insulin dependent diabetes mellitus(IDDM), juvenile onset diabetes there are 'β' cell destruction in pancreatic islets, majority of the cases are autoimmune(type IA) antibodies that destroy 'β' cell are detectable in blood, but some are idiopathic(type IIB) –no 'β' cell antibodies is

found. In all type I cases, circulating insulin levels are low or very low and patients are more prone to ketosis. This type is less common and has low degree of genetic predisposition.

Type II: Non insulin dependent diabetes mellitus (NIDDM), maturity onset diabetes. This typically involves abnormal 'β' cell function that result in relative insulin deficiency, insulin resistance is accompanied by decreased glucose transport into muscles and fat cells, and increased hepatic glucose output, all of which contribute to hyperglycemia. Type II diabetes characteristically comprises of pathophysiologic abnormalities like insulin deficiency, insulin resistance involves myocytes, and adipocytes, and hepatic insulin resistance (resulting in increased glyconeogenesis and impaired glycogen synthesis.

Following classes of oral hypoglycaemic agents are used in the treatment of type II diabetes. Sulfonylurea's derivatives, first generation include Tolbutamide and Chlorpropamide, while second generation includes Glibenclamide, Gliclazide, Gliclazide and Glimepiride. Biguanides are Phenformin and Metformin. Meglitinide analogues are Repaglinide and Nateglinide. Thiazolidinediones derivatives are Rosiglitazone and Pioglitazone. Glycosidase inhibitors are acarbose and miglitol. These drugs must be administered repeatedly to the diabetic patients. Sustained release provides the most desirable dosing regimens with effective pharmacokinetic profile and Pharmacodynamic response in diabetes treatment. This approach help the patient to low blood sugar and help body to use insulin more efficiently through maintenance of consistent drug input and it may ease the variability involved in the administration of multiple doses per day. Thus sustained released dosage form of anti-diabetic drug like MetforminHCl tablet improves patient compliance.

Diabetes mellitus (DM) is fast expanding throughout the world and particularly in developing countries like India. MetforminHCl is a biguanide-type drug used along with a diet and exercise program to control high blood sugar in patient with type II diabetes. Gliclazide binds to the β cell sulfonyl urea 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.

Gliclazide is administrated for the treatment of NIDDM which know as type two in patient who failed to respond to dietary restriction. The drug is administered in doses range from 40 to 320

mg/day as tablets once to three times daily. Recently, modified release formulations containing 60 mg of gliclazide has been developed to obtain a better predictable release of active principle.

MATERIALS AND METHOD

Gliclazide USP was gift sample from EMCO industries, HPMC K4M USP, HPMC K15M USP and Guargum USP were obtained from DOW Chemicals USA, Magnesium Stearate, Lactose, Colloidal Silicon Dioxide (Aerosil 200 Pharma), Maltodextrin were obtained from locals chemical distributors

Experimental methods for Gliclazide:

Analytical Method Development:

The field of pharmaceutical analysis includes a wide range of analysis, varying in structure from very simple compounds to complex bio molecules. As such, a host of approaches have been and continue to be used in developing reliable analytical methodology for these analytes. In the broadest sense, there are two types of procedures: those that are designed as simple, reliable means of monitoring formulated products in terms of their identity, strength and quality and those that are used during the drug discovery and development stages to answer numerous and fundamentally more challenging questions related to safety, therapeutic effectiveness, drug stability and purity, as well as in helping to develop better understanding of the bio mechanisms and kinetics.

Procedure:

Preparation of buffers:

Potassium dihydrogen phosphate 0.2M:

Dissolve 27.218 g of potassium dihydrogen phosphate in water and dilute with water to 1000 ml.

Sodium hydroxide 0.2M:

Dissolve 8gm of sodium hydroxide in 1000ml of distilled water.

Phosphate buffer pH 7.4:

Place 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200 ml volumetric flask, add 39.1 ml of 0.2 M sodium hydroxide and then add water to volume.

Preparation of standard graph of Gliclazide:

Stock solution:

Weigh accurately 100mg of Gliclazide in 100ml of volumetric flask and make up the volume with phosphate buffer pH 7.4 to form a stock solution (1000µg per ml).

Working standard solution:

1ml of the stock solution was further diluted to 100ml with phosphate buffer pH 7.4 to obtain a working standard solution containing 10µg/ml.

Determination of λ_{max}:

The aliquots of working standard solution was diluted serially with sufficient phosphate buffer pH 7.4 to obtain 0, 1, 2, 3, 4, 5 µg/ml concentrations. The above solutions were subjected to scanning between 200 – 400 nm and absorption maximum was determined. A calibration curve of Gliclazide was obtained by measuring the absorbance at the λ_{max} of 226 nm. **Effect of hydrophilic polymers on drug release for Gliclazide:**

Formulation development:

The effect of individual polymers on the *in vitro* dissolution of Gliclazide was evaluated at 10%, 15%, 30% and 45% w/w of each of HPMC K4M, HPMC K15M and Guargum. The unit composition formula is given in Table 4.

Table 4: Composition Chart (Individual polymer) for Gliclazide

		HPMC K4M				HPMC K15 M				GUARGUM							
FORMULATION	**GLICLAZIDE (mg)**	**10 %**	**15 %**	**30 %**	**45%**	**10 %**	**15 %**	**30 %**	**45 %**	**10 %**	**15 %**	**30 %**	**45 %**	**MALTRODEXTRIN(mg)**	**AEROSIL (mg)**	**Mg STREARATE mg**	**LACTOSE (mg)**
F1	**60**	**30**												**80**	**3**	**3**	**124**
F2	**60**		**45**											**80**	**3**	**3**	**109**
F3	**60**			**90**										**80**	**3**	**3**	**64**
F4	**60**				**135**									**80**	**3**	**3**	**19**
F5	**60**					**30**								**80**	**3**	**3**	**124**
F6	**60**						**45**							**80**	**3**	**3**	**109**
F7	**60**							**90**						**80**	**3**	**3**	**64**
F8	**60**								**135**					**80**	**3**	**3**	**19**
F9	**60**									**30**				**80**	**3**	**3**	**124**
F10	**60**										**45**			**80**	**3**	**3**	**109**
F11	**60**											**90**		**80**	**3**	**3**	**64**
F12	**60**												**135**	**80**	**3**	**3**	**19**

Procedure:

The mixing and direct compression method was followed for HPMC Matrix and Guar gum tablets.

Methodology:

A hydrophilic matrix is a homogeneous dispersion of the drug molecules within a skeleton in which one or several of the excipients incorporated are a hydrophilic polymer, such as cellulose derivatives, sodium alginate, Guargum, Xantham gum, polyethylene oxide, or Carbopol among others, that swells upon contact with water. Hydrophilic polymer selected in the present work was

HPMC of two viscosity grades (K4M, K15M) and Guar gum. These polymers are well characterized and most widely used and hence were selected for this study.

Blending and compression technique:

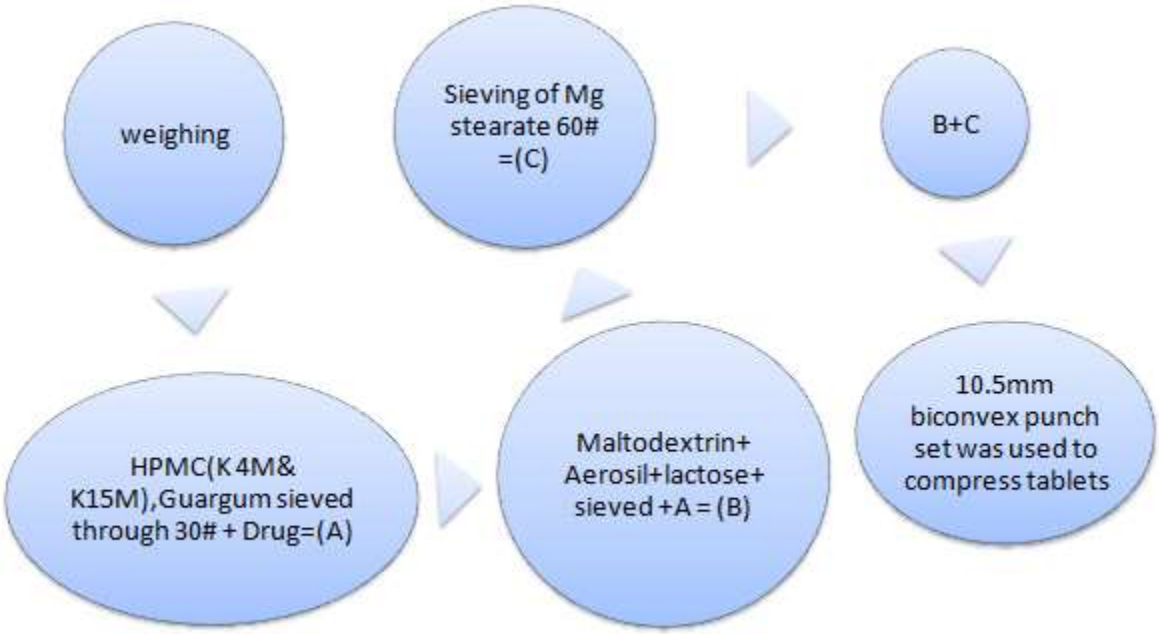

Figure 2: Flow Chart for Process of Direct Compression

The method followed to obtain tablet is direct compression, the process is as follows:

All the tablets of HPMC matrix and Guar gum were compressed on 10.5 mm circular biconvex punch set on Rimex Rotary Tablet Compression Machine at Average Weight of 300mg, Thickness 4.8-5.2 mm, Hardness 4 kg /cm^2.

Pre-compression and Post-compression studies:

For all the batches Pre-compression studies such as Bulk density, Tapped density, Angle repose, %compressibility (or) Carr's index, Hausner ratio and Post-compression studies such as Weight Variation Test, Hardness, Friability, Thickness, and Drug Content were performed.

Bulk density:

Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method:

Weigh accurately 25 g of powder blend sifted through 20 mesh sieve and transferred to 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the appearance bulk density in g/ml by the following formula**:**

Bulk density = Weight of the powder / Volume of the packing

Tapped density:

Weigh accurately 25 g of powder blend shifted through 20 mesh sieve and transfer to 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2 % then the final tapped volume is V_2. If the difference between the two volume is more than 2 % then repeat the tapping an additional 1250 times and measure the tapped volume (V_3) to the nearest graduated units.

Tapped density = Weight of the powder / Tapped volume of the packing

Hausner's Ratio:

Hausner's Ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density. Hausner's ratio was calculated as**:**

Hausner's ratio = Tapped density / Bulk density

Table 5: Relationship between Hausner's Ratio and Flowability

Hausner's ratio	Flow
Less than 1.25	Good
1.25-1.5	Moderate
Greater 1.5	Poor

Compressibility Index:

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indicated as Carr's compressibility index (CI) and can be calculated as follows:

CI% = (Tapped density – Bulk density) 100 /Tapped density

Table 6: Relationship between Compressibility Index and Flowability

Compressibility index	Flow
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
35-38	Very poor
40 +	Extremely poor

Flow properties (Angle of Repose):

Irregular flow of powders from the hopper produces tablets with non-uniform weights. As a result content uniformity and dose precision cannot be achieved in production of Tablets & capsules. The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane.

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

Where,

h = height of pile.

r = radius of the base of pile.

θ = angle of repose.

Table 7: Relationship between Angle of Repose and Flowability

Angle of Repose	Flow
$<25^0$	Excellent
$25\text{-}30^0$	Good
$30\text{-}40^0$	Passable
$>40^0$	Poor

Method:

A funnel was held with a clamp such that the stem of the funnel is 2 cm above the graph paper that is placed on a horizontal surface. Weighed amount of powder (5g) was taken and poured in to the funnel keeping the orifice of funnel blocked. The powder was allowed to flow by removing the blockage until the apex of the conical pile just touches the tip of the funnel. Height of pile (h) and average of six diameters formed by the pile of the powder was measured with the help of a ruler and the angle of repose was determined.

Post-Compression studies:

Uniformity of weight (Weight variation test):

To study weight variation individual weights (W_I) of 20 tablets of each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated. % weight variation = $(W_A–W_I)/W_A$ x100

Hardness Test:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. "Hardness factor", the average of the six determinations, was determined and reported. The force is measured in kg/cm^2. Hardness was measured using Monsanto hardness tester.

Friability:

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This IPQC test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. The permitted friability limit is 1.0 %.

Ten tablets were weighed correctly and placed in a Roche friabilator and rotated for 100 times at 25 rpm and tablets were removed dedusted and weighed again. The % friability was measured using the below formula.

$$\% \text{ Friability} = \frac{W1-W2}{W1} \text{ X } 100$$

Where, W_1 = Initial weight of the tablets

W_2 = Weight of tablets after test

Thickness:

Three samples were selected randomly from each batch and thickness was measured using Vernier calipers**.**

Drug content:

Twenty tablets were randomly selected and average weight was calculated and powdered in a mortar. Powder equivalent to 100 mg of drug was weighed accurately and transferred to 100 ml volumetric flask, added 50 ml of pH 6.8 phosphate buffer and sonicated for 20 min. Then, the volume was made up to 100 ml. The solution was filtered through 0.45 µ nylon membrane filter. The filtrate was diluted suitably using pH 6.8 phosphate buffer and the drug content was estimated by UV spectrophotometer at λ_{max} against blank and reported. The content uniformity should be not less than 90% and not more than 110% of the labelled value.

***In-Vitro* Dissolution testing method:**

- The *In-vitro* dissolution studies were performed using USP type 1 dissolution apparatus (Basket type).

- Dissolution test was carried out for a total period of 24hours using 0.1 N HCl (900 ml) as dissolution medium at 37 ± 0.5°c.
- An aliquot (5ml) sample was withdrawn at specific time intervals and replaced with fresh medium to maintain a constant volume.
- The samples were filtered, and analyzed by UV spectrophotometer at respective wavelength (226 nm).
- The concentration was calculated using standard calibration curve.

The *In-vitro* dissolution profile test was carried out as per the following parameters (Table 8):

Table 8: Dissolution Parameters of Gliclazide

Drug	**Gliclazide**
USP dissolution apparatus	Type I (Basket)
Dissolution medium	pH 7.4 phosphate buffer
Dissolution volume	900 ml
RPM	100
Temperature	37±0.5°C
Wavelength	226 nm

Effect of combination of polymers on drug release for Gliclazide:

Design of experiment for optimizing hydrophilic matrix and guargum:

The effect of a combination of K4M, K15M and Guargum on the *in vitro* drug release for Gliclazide was evaluated using full factorial 3^3 design of experiments (Table). The three levels as fixed by the DOE Pro XL software are shown in Table 9.

Table 9 : DOE Levels

POLYMERS	**LOW LEVEL – L (30% OF TABLET WT)**	**MEDIUM LEVEL – M (37.5% OF TABLET WT)**	**HIGH LEVEL - H (45% OF TABLET WT)**
HPMC-K4M	10%	12.5%	15%
HPMC-K15M	10%	12.5%	15%
GUARGUM	10%	12.5%	15%

Table 10 : Template for Full Factorial 3^3 DOE

	POLYMERS		
S.NO	**K4M**	**K15M**	**Guargum**
1	H	H	H
2	H	H	M
3	H	H	L
4	H	M	H
5	H	M	M
6	H	M	L
7	H	L	H
8	H	L	M
9	H	L	L

10	M	H	H
11	M	H	M
12	M	H	L
13	M	M	H
14	M	M	M
15	M	M	L
16	M	L	H
17	M	L	M
18	M	L	L
19	L	H	H
20	L	H	M
21	L	H	L
22	L	M	H
23	L	M	M
24	L	M	L
25	L	L	H
26	L	L	M
27	L	L	L

Table 11: Formulation chart for Gliclazide in combination of polymers

Formulation	Gliclazide (mg)	HPMC K4M (mg)	HPMC K15M(mg)	Guargum(mg)	Maltodextrin (mg)	Aerosil(mg)	Mg stearate(mg)	Lactose(mg)
F1(HHH)	60	45	45	45	35	3	3	64
F2(HHM)	60	45	45	37.5	35	3	3	71.5
F3(HHL)	60	45	45	30	35	3	3	79
F4(HMH)	60	45	37.5	45	35	3	3	71.5
F5(HMM)	60	45	37.5	37.5	35	3	3	79
F6(HML)	60	45	37.5	30	35	3	3	86.5
F7(HLH)	60	45	30	45	35	3	3	79
F8(HLM)	60	45	30	37.5	35	3	3	86.5
F9(HLL)	60	45	30	30	35	3	3	94
F10(MHH)	60	37.5	45	45	35	3	3	71.5
F11(MHM)	60	37.5	45	37.5	35	3	3	79
F12(MHL)	60	37.5	45	30	35	3	3	86.5
F13(MMH)	60	37.5	37.5	45	35	3	3	79
F14(MMM)	60	37.5	37.5	37.5	35	3	3	86.5
F15(MML)	60	37.5	37.5	30	35	3	3	94
F16(MLH)	60	37.5	30	45	35	3	3	86.5
F17(MLM)	60	37.5	30	37.5	35	3	3	94
F18(MLL)	60	37.5	30	30	35	3	3	101.5
F19(LHH)	60	30	45	45	35	3	3	79
F20(LHM)	60	30	45	37.5	35	3	3	86.5
F21(LHL)	60	30	45	30	35	3	3	94
F22(LMH)	60	30	37.5	45	35	3	3	86.5
F23(LMM)	60	30	37.5	37.5	35	3	3	94
F24(LML)	60	30	37.5	30	35	3	3	101.5
F25(LLH)	60	30	30	45	35	3	3	94
F26(LLM)	60	30	30	37.5	35	3	3	101.5
F27(LLL)	60	30	30	30	35	3	3	109

The tablets were prepared by using WET GRANULATION and DRY GRANULATION and compressed on 10.5 mm circular biconvex die/punch set using Rimek MiniPress rotary compression machine. The compression force was set in such a way that all formulations were compressed at hardness of 4 to 6 kg/cm^2. All batches were subjected to 24 hours dissolution profile in pH 7.4 phosphate buffer using USP Type I apparatus at 100 rpm. Samples were withdrawn at 1, 2, 4, 8, 12, 16 and 20 hours interval at 226nm and analyzed for % drug dissolved using UV Spectrophotometric method.

DOE for Gliclazide :

The D1, D8 and D20 values were fed into the DOE PROXL software. Interaction plots and the surface response plots were obtained. The design space was evaluated from output of the software.

(A) DOE For 1st Hour Release (D1):

The first hour dissolution value is crucial and decides the release rates for the controlled release formulation. The D1 values for all 27 formulations were fed into the DOE PROXL Software and the interaction of polymer was evaluated.

(B) DOE of 8th Hour (D8): The 8th hour time point defines whether the formulation will be a 12hour release formulation (greater than 80% release) or a 24 hour formulation (less than 70% release) and the values for this time point were fed into this software and interaction was evaluated.

(C) DOE of 20th Hour (D20): The 20th hour time point defines the extent of drug release and indicates which of the formulation would ensure complete release of drug (greater than 80%) from the formulation is very critical for the entire profile.

MOISTURE ACTIVATED DRY GRANULATION (MADG) PROCESS:

Formulation Development of Gliclazide Sustained release tablets:

Among all granulating techniques, MADG technology is widely used in granulation of active pharmaceutical ingredients. The present study will be carried out with the Gliclazide as ideal drug candidate for the preparation of granules by innovative MADG technology & optimization of water content, concentration of granulating binder and along with other excipients.

Moisture content of drugs, excipients combined to manufacture a final dosage form and processing manipulations involving moisture may have a significant impact on a wide range of chemical and physical properties of the finished product. Moisture activated dry granulation technique used to decrease the moisture content in the granulation and reduce the drying time. Moisture activated dry

granulation technique is more advantageous because it takes less time for preparation of granules and the fines produced during granulation are less which results in more drug content in tablets.

The present work describes the process optimization trials for Gliclazide 60mg immediate release tablets by using the MADG method.

Formulation and development of Gliclazide CR tablets by using MADG process:

Matrix tablets are prepared by MADG process .The API and ingredients accurately weighed and mix according to the method used. API, Polymer Mix (obtained from the DOE results of the wet granulation 11%), binder, whole or part of them are taken for agglomeration stage mix them for 5-7 min with mortar and pestle and pour small amount of water to moist the blend mix for 10 min and add balanced amounts of ingredients for drying step at last add the lubricants mix it for 3min of each addition. The unit composition formula was given in table 12.

Table 12: General Formulae of Gliclazide in MADG

Ingredients	Quantity/tablet(mg)
Gliclazide	60
Maltodextrin	35
Polymer Mix	33
Magnesium stearate	3

Formulation and evaluation parameters of controlled release Gliclazide tablets by MADG process

As per the process of MADG there are two major stages: agglomeration and moisture distribution/absorption.

Levels of critical formula ingredients in the 2^3 designs of experiments for controlled release tablets

A full 2^3 factorial design was introduced to optimize the agglomeration stage of the MADG process. The process was optimized with respect to the % drug, % Polymer Mix and % fluid uptake to be used in the agglomeration stage of the MADG process using the 2^3 full factorial design of experiments.

The three factors for optimization of agglomeration stage are:

(a) API (Gliclazide)

(b) Polymer Mix

(c) Fluid uptake

Table 13 : Levels of critical formula ingredients in the 2^3 designs of experiments

S.NO.	Critical formula ingredients	Low level(L) (%w/w)	High level(H) (%w/w)
1	GLICLAZIDE	25	50
2	MALTODEXTRIN	------	----
3	Polymer Mix	3.33	8.3
4	Fluid uptake	1	2

So, a 2^3 full factorial design in a tablet press was developed to study the interdependency of the 3 factors, API (Gliclazide), Polymer Mix and Fluid Uptake on the percentage dissolution of Gliclazide tablets in 7.4 pH phosphate buffer.

Design of Experiment:

Optimization of Gliclazide formulation using 2^3 full factorial designs. In order to get a statistically relevant data and remove experimental bias, the 2^3 design was formulated and run thrice (R1, R2, and R3).

Table 14: 2^3 Design of Gliclazide CR formulations

Formulation code	Gliclazide	Polymer mix	Fluid uptake
F1	L	L	L
F2	L	L	H
F3	L	H	L
F4	H	L	L
F5	H	L	H
F6	L	H	H
F7	H	H	L
F8	H	H	H

Formulation of MADG process of Gliclazide 60 mg tablets

Controlled release formulations of Gliclazde is given in table

Table 15: Formulation of MADG process of Gliclazide 60mg tablets

	Agglomeration stage				Moisture distribution stage		Lubrication mixing stage (mg)		
Formulations	API (mg)	Maltodextrin (mg)	Polymer Mix (mg)	Fluid uptake	API(mg)	Polymer Mix (mg)	Aerosil (mg)	Latose (mg)	Mg stearate (mg)
GF1	15	50	10	1	45	23	3	151	3
GF2	15	50	10	2	45	23	3	151	3
GF3	15	50	25	1	45	8	3	151	3
GF4	15	50	25	2	45	8	3	151	3
GF5	42	50	10	1	18	23	3	151	3
GF6	42	50	10	2	18	23	3	151	3
GF7	42	50	25	1	18	8	3	151	3
GF8	42	50	25	2	18	8	3	151	3

- As a part of process simplification project, an attempt was made to convert the existing process for Gliclazide to a MADG process.
- To speed up the process.
- To make the process single pot and reduce the cleaning times
- To make it amenable to site transfer to different plants
- To optimize the % of formula which goes for agglomeration step and which can be used for moisture distribution step.

Pre-compression and Post-compression studies:

For all the batches Pre-compression studies such as Bulk density, Tapped density, Angle repose, %compressibility (or) Carr's index, Hausner ratio and Post-compression studies such as Weight Variation Test, Hardness, Friability, Thickness, Drug Content were performed. The *in-vitro* dissolution studies were performed as per given below.

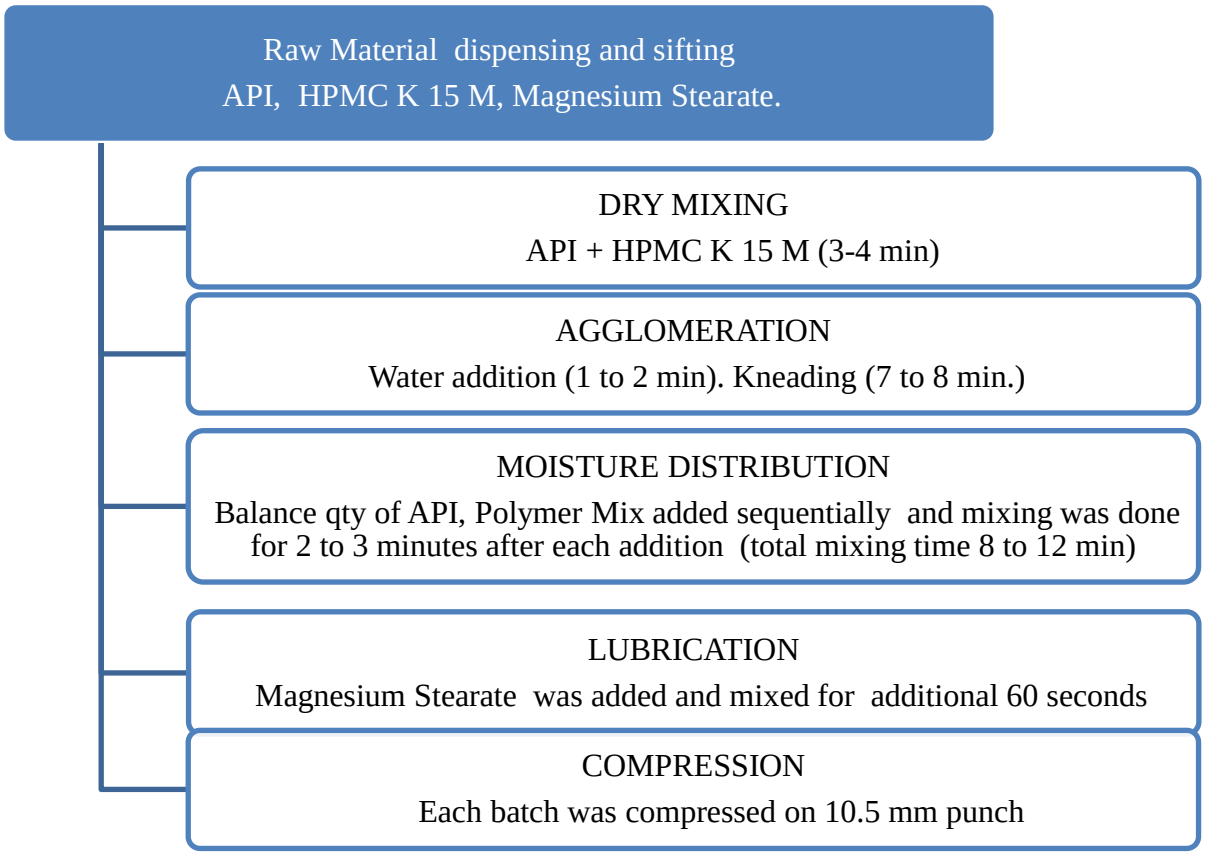

Figure 3: MADG process flow chart with Polymer Mix

In vitro Drug Release Studies [18]

The in vitro drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus under the following conditions.

✓ **Dissolution test parameters:**

Medium	:	900ml pH 7.4 phosphate buffer
Rotation speed	:	100 rpm
Temperature	:	37±0.5ºC
Sampling Volume	:	5ml

Sampling time points **:** *0 ,1,2,4,8, 10 hours*

At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer. The sample absorbance was measured at 226nm in pH 7.4. The % drug dissolved was calculated from the absorbance value of a standard solution which was prepared in pH 7.4.

After getting the dissolution profiles of all the formulations, the mean of triplicate of each formulation is taken and these similarity factors were considered as the response values and incorporated into the DOE software to get the optimized range.

Mechanism of drug release:

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted.

RESULTS AND DISCUSSION:

STANDARD CALIBRATION CURVE OF GLICLAZIDE IN pH7.4 PHOSPHATE BUFFER:

Table 16: Standard calibration curve of Gliclazide in pH7.4 Phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
1	0.124
2	0.249
3	0.362
4	0.485
5	0.543

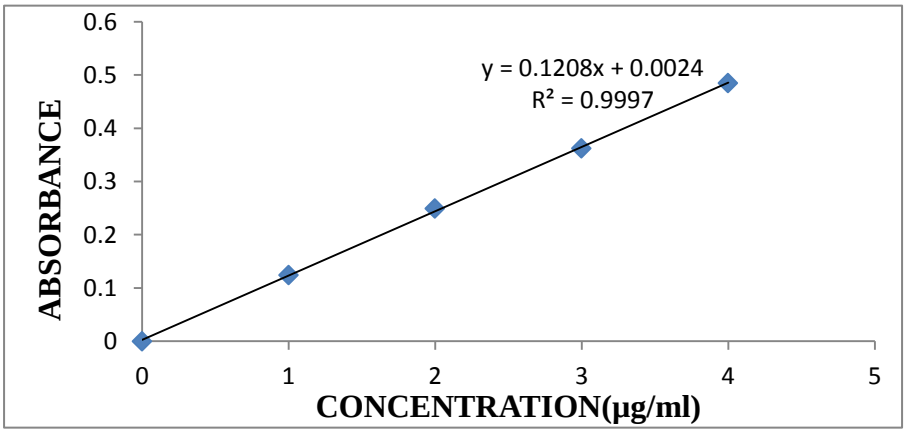

Figure 4: Calibration curve of Gliclazide in pH7.4 Phosphate buffer

Effect of hydrophilic polymers on drug release for Gliclazide:

Pre-compression studies:

The Pre-compression studies of the all batches were determined and the data is reported in the Table 17.

Table 17: Pre-Compression Parameters of Gliclazide in individual polymers

Formulation cod	Angle of repose	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index(%)	Hausner ratio
K4M 10%	29.14	0.45	0.54	16	1.21
K4M 15%	28.66	0.48	0.54	11.11	1.13
K4M 30%	25.04	0.49	0.55	10.90	1.12
K4M 45%	27.99	0.51	0.58	12.06	1.15
K15M 10%	28.16	0.46	0.53	13.20	1.15
K15M 15%	26.67	0.49	0.58	15.51	1.18
K15M 30%	27.53	0.46	0.54	14.81	1.17
K15M 45%	25.98	0.45	0.54	16	1.21
Guargum10%	27.81	0.48	0.55	12.72	1.14
Guargum15%	26.64	0.51	0.57	10.52	1.11
Guargum 30%	27.01	0.46	0.53	13.20	1.15
Guargum 45%	25.55	0.48	0.54	11.11	1.13

Pre-Compression parameters of all formulations are satisfactory. Bulk density, Tapped density, Angle repose, %compressibility (or) Carr's index, Hausner ratio are within the limits.

Bulk density (gm/ml) : 0.45 to 0.51

Tapped density (gm/ml) : 0.54 to 0.58

Angle of repose : 25.04 to 29.14

%compressibility : 10.90 to 16

Hausner's ratio : 1.11 to 1.21

From the Pre-Compression Studies it is observed that, the flow properties of the blend for all the formulations were found to be good on the basis of compressibility index Hausner ratio and Angle of repose.

Post-compression studies: The Post-compression studies of the all batches were determined and the data is reported in the Table 18

Table 18: Post-compression studies of Gliclazide Tablets in individual polymers

Formulations	Average Weight(mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm2)	Assay (%)
K4M 10%	302	3.13	0.162	7.62	97.9
K4M 15%	300	3.11	0.159	7.59	98.2
K4M 30%	298	3.08	0.154	7.31	97.7
K4M 45%	302	3.126	0.160	7.59	97.6
K15M 10%	302	3.09	0.152	7.32	98.6

K15M 15%	299	3.124	0.161	7.56	98.5
K15M 30%	298	3.11	0.159	7.59	98.1
K15M 45%	300	3.09	0.152	7.32	98.7
Guargum10%	296	3.104	0.158	7.41	98.3
Guargum15%	300	3.085	0.156	7.30	97.8
Guargum30%	301	3.126	0.161	7.58	97.9
Guargum45%	304	3.092	0.157	7.34	98.3

The parameters of all formulations were found to be satisfactory and all were within pharmacopeias limits.

The Hardness for all formulations found to be 7.3kg/cm^2 to 7.6 kg/cm^2

The Thickness of tablet was found to be between 3.081mm to 3.13 mm.

The Friability was found to be between 0.152% and 0.165 %.

The Weight variation was found to be between 296 mg and 302mg.

Assay values of the formulations were observed in the range of 97.5% to 98.7%.

***In-Vitro* Dissolution studies for wet granulation:**

The Dissolution profile values for formulations using K4M are recorded shown in Fig 5

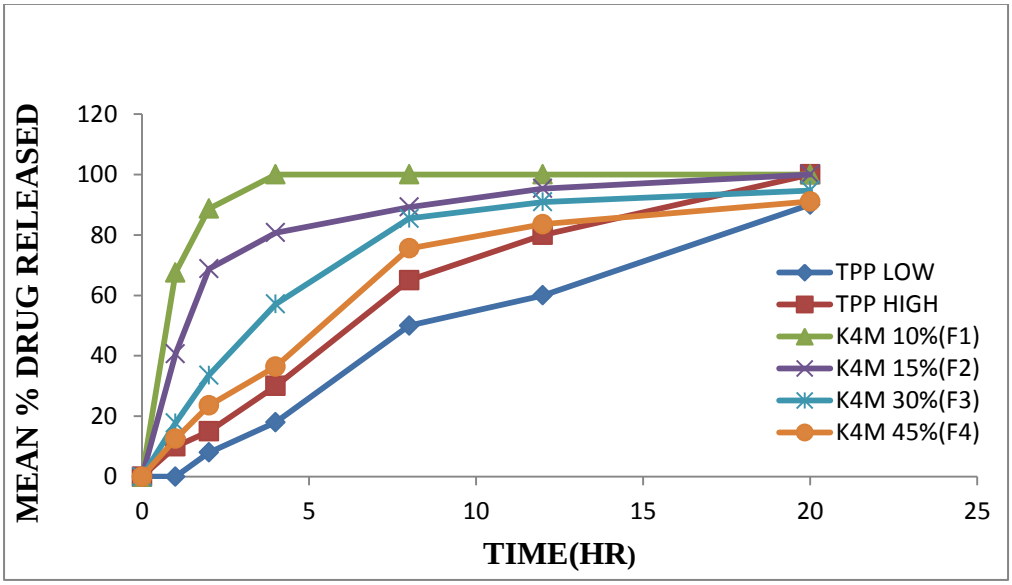

Figure 5: Comparative Dissolution Profiles Of Gliclazide Using HPMC K4M Polymer

This study indicates that when K4M is used all formulations are significantly faster than TPP. The low viscosity grades of HPMC K4M polymer may not be providing a formidable to diffusion of Gliclazide even at high use levels. The Dissolution profile values for formulations using K15M are recorded shown in Figure 6

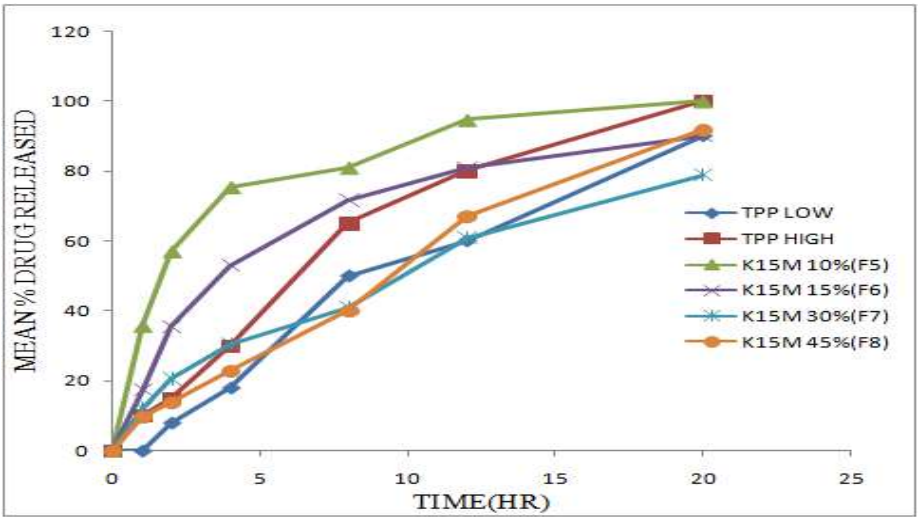

Figure 6: Comparative Dissolution Profiles Of Gliclazide Using HPMC K15M Polymer

- This study indicates that for Gliclazide the minimum concentration of K15M required to control drug release is 30%
- When used singly, formulation with 45% K15M is within the target product profile, whereas all other formulations are outside the TPP.
- The release rate kinetics forF8- 45% K15M was calculated (Table 19 and Table 20). The Peppas model defines the release rate kinetics and is shown in Figure 7

Table 19: Release Rate Kinetics For F8-45% K15M

Cumulative(%)Release Q	Time(T)	Root(T)	Log(%) Release	Log(T)	Log(%)Remaing	Release Rate(Cumulative % Release/T)	1/Cum%Release	Peppas Log Q/100	%Drug Remaining	Q0 1/3	Qt 1/3	Q0 1/3-Qt 1/3
0	0	0			2.000				100	4.642	4.642	0.000
9.57	1	1.000	0.981	0.000	1.956	9.570	0.1045	-1.019	90.43	4.642	4.489	0.153
13.89	2	1.414	1.143	0.301	1.935	6.945	0.0720	-0.857	86.11	4.642	4.416	0.226
22.68	4	2.000	1.356	0.602	1.888	5.670	0.0441	-0.644	77.32	4.642	4.260	0.382
40.1	8	2.828	1.603	0.903	1.777	5.013	0.0249	-0.397	59.9	4.642	3.913	0.729
67.07	12	3.464	1.827	1.079	1.518	5.589	0.0149	-0.173	32.93	4.642	3.205	1.436
91.71	20	4.472	1.962	1.301	0.919	4.586	0.0109	-0.038	8.29		2.024	

Table 20: Release Rate Kinetic Model For F8-45% K15M

	RELEASE KINEITCS				
	ZERO	HIGUCHI	PEPPAS	FIRST	Hixson Crowell
	1	2	3	4	5
	R(CvT)	R(CvRoot(T))	Log T vs Log C	TIME vs LOG % REMAINING	TIME Vs (Q1/3-Qt1/3)
Slope	4.603	21.239	0.782	-0.011	0.112
Correlation	0.9927	0.9710	0.9938	-0.9758	0.9851
R 2	0.9854	0.9428	0.9877	0.9523	0.9705

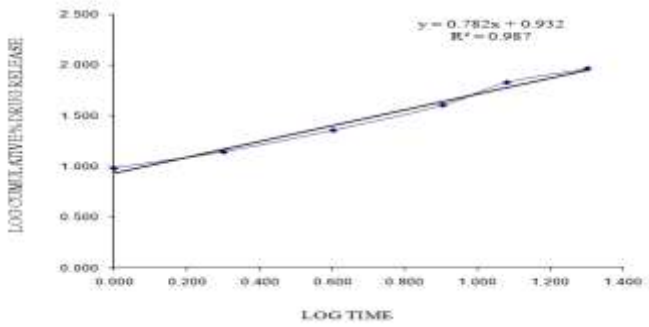

Figure 7: Peppas Model Plot

The Dissolution profile values for formulations using Guargum are recorded in Table 21 and shown in Fig 8

Table 21: Dissolution Profile Values For Formulations Using Guargum (n=3) with Gliclazide

TIME(HR)	MEAN % DRUG RELEASED					
	TPP LOW	TPP HIGH	Guar gum 10% (F9)	Guar gum 15%(F10)	Guar gum 30%(F11)	Guar gum 45%(F12)
0	0	0	0	0	0	0
1	0	10	30.71	10.67	8.67	5.17
2	8	15	49.077	33.5	12.34	8.21
4	18	30	68.91	45.68	16.89	10.18
8	50	65	77.65	58.27	20.67	14.3
12	60	80	85.99	68.19	22.54	18.54
20	90	100	93.76	73.46	44.78	34.17

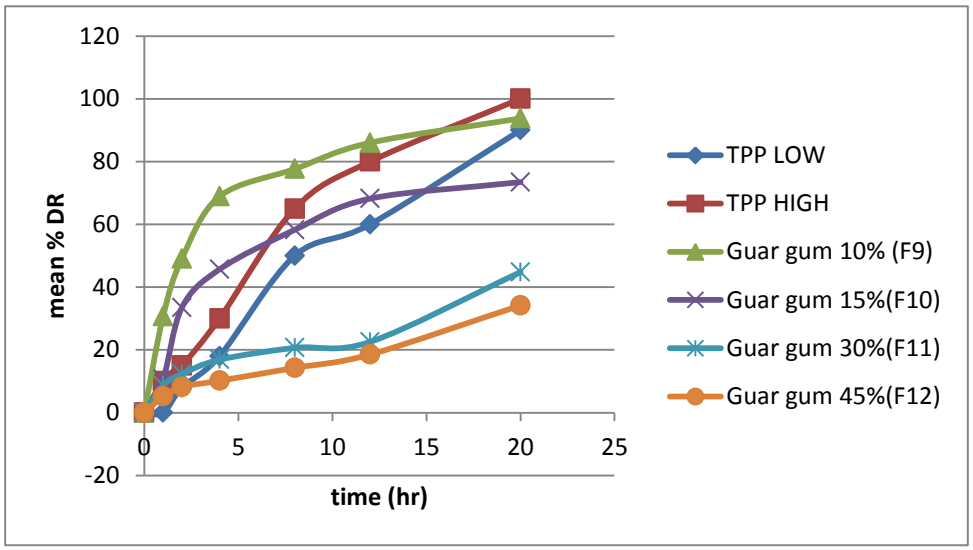

Figure 8: Comparative Dissolution Profiles Of Gliclazide Using Guargum Polymer

- This study indicates that for Gliclazide the minimum concentration of Guargum required to control drug release is 15%
- When Guargum is used, all formulations are significantly slower than the TPP.
- This may be due to the fact that the drug is practically insoluble in water. Hence the natural polymer Guargum may be providing a formidable barrier to diffusion of the drug even at low use levels.

The dissolution profile experiment indicates that when polymers are used alone, each polymer results in an acceptable dissolution profile only for a very narrow range. The concentration of the polymer in case of K15M is 45% w/w. Higher and lower concentrations do not pass the TPP range.It was thought worthwhile to evaluate how these polymers modulate the dissolution profile when

used in combination. The experiments were designed using full factorial 3^3 DOE. The levels of each polymer were selected in such a way that the total polymer concentration range was between a low of 30%,medium of 37.5% and high of 45%.

Effect of combination of polymers on drug release for Gliclazide using wet and dry granulation:

For wet granulation and dry granulation processes the effect of a combination of K4M, K15M and Guargum on the Pre-compression, post-compression studies and *in vitro* drug release for Metformin Hydrochloride was evaluated using full factorial 3^3 design of experiments.

Pre-compression studies: The Pre-compression studies of the all batches were determined and the data is reported in the Table 22

Table 24: Pre-compression studies of combination of polymers on Gliclazide

Formulation code	Angle of repose(θ)*	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Carr's index (CI)*	Hausner's ratio(HR)*
F1	31.6	0.422	0.511	17.41	1.21
F2	35.9	0.435	0.522	16.66	1.2
F3	34.4	0.419	0.509	17.68	1.21
F4	36.7	0.428	0.514	16.73	1.20
F5	29.5	0.431	0.519	16.95	1.204
F6	31.1	0.425	0.513	17.15	1.207
F7	36.3	0.411	0.496	17.13	1.206
F8	33.9	0.428	0.514	16.73	1.20
F9	36.5	0.426	0.512	16.79	1.20
F10	34.6	0.418	0.508	17.71	1.21
F11	32.8	0.436	0.523	16.63	1.199
F12	35.4	0.421	0.509	17.28	1.209
F13	29.3	0.432	0.52	16.92	1.203
F14	34.7	0.428	0.515	16.89	1.203
F15	35.2	0.414	0.506	18.18	1.222
F16	29.8	0.426	0.512	16.79	1.201
F17	35.8	0.418	0.508	17.71	1.215
F18	28.9	0.428	0.515	16.89	1.203
F19	33.8	0.433	0.521	16.89	1.203
F20	35.5	0.429	0.516	16.86	1.202
F21	33.8	0.432	0.52	16.92	1.203
F22	33.5	0.429	0.516	16.86	1.202
F23	36.3	0.43	0.518	16.98	1.204
F24	33.9	0.432	0.521	17.08	1.2
F25	35.9	0.428	0.515	16.89	1.203
F26	36.7	0.429	0.517	17.02	1.205
F27	33.4	0.431	0.52	17.11	1.206

Post-compression studies: The Post-compression studies of the all batches were determined and the data is reported in the Table 23

Table 23: Post-compression studies of combination of polymers on Gliclazide

Formulation code	A. weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	302	3.126	0.160	7.59	97.9
F2	302	3.09	0.152	7.32	98.2
F3	299	3.124	0.161	7.56	97.7
F4	298	3.11	0.159	7.59	97.6
F5	300	3.09	0.152	7.32	98.6
F6	296	3.104	0.158	7.41	98.5
F7	299	3.124	0.161	7.56	98.1
F8	298	3.11	0.159	7.59	98.7
F9	300	3.09	0.152	7.32	98.3
F10	296	3.104	0.158	7.41	97.8
F11	300	3.085	0.156	7.30	97.9
F12	301	3.126	0.161	7.58	98.3
F13	304	3.092	0.157	7.34	98.6
F14	302	3.13	0.162	7.62	98.7
F15	300	3.11	0.159	7.59	97.6
F16	298	3.08	0.154	7.31	97.9
F17	302	3.126	0.160	7.59	98.9
F18	302	3.09	0.152	7.32	99.6
F19	299	3.124	0.161	7.56	98.7
F20	298	3.11	0.159	7.59	99.8
F21	300	3.09	0.152	7.32	99.7
F22	296	3.104	0.158	7.41	98.5
F23	300	3.085	0.156	7.30	98.6
F24	301	3.126	0.161	7.58	98.4
F25	304	3.092	0.157	7.34	99.1
F26	298	3.08	0.154	7.31	98.4
F27	302	3.126	0.160	7.59	98.6

- In Dry granulation content uniformity problems were arise, because of the micronized particles of the drug and polymer particle size. Hardness of the tablet is within the range same like wet granulation formulations.
- *In-Vitro* Dissolution studies: All batches of wet granulation were subjected to 24 hours dissolution profile in pH 7.4 phosphate buffer using USP Type I apparatus at 100 rpm. . The Dissolution profiles and comparative values of dissolution are shown in Figure 9

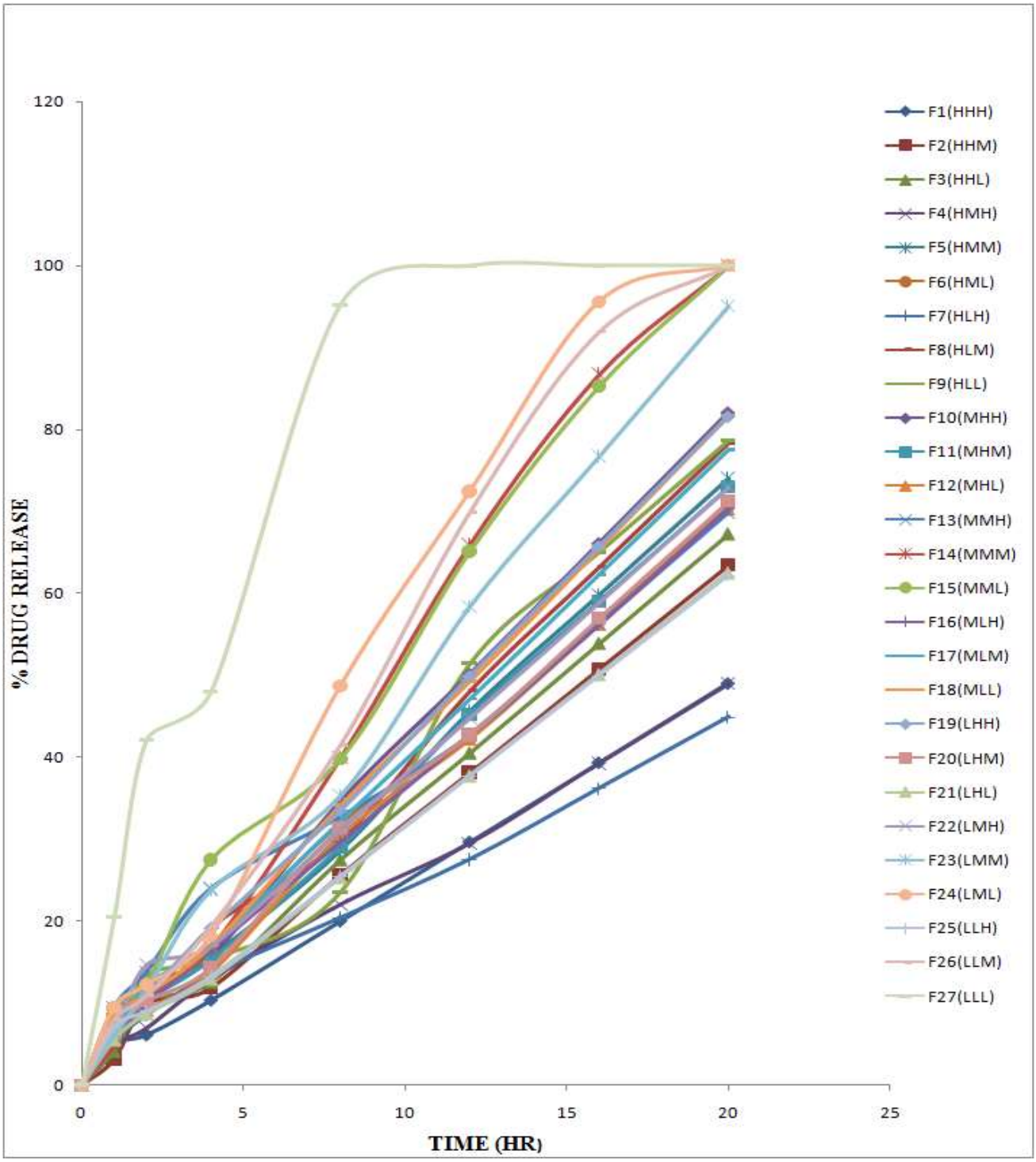

Figure 10: Dissolution Profiles Of All 27 Formulations

This study indicates that 1hr,8 hr and 20 hr time points are very significant and determines the rate and extent of drug release.

DOE for Gliclazide:

The D1,D8 and D20 values for all 27 formulations were fed into the DOE PROXL Software and the interaction of polymer was evaluated.

(A) DOE For 1st Hour Release (D1):1 hr design chart was shown in Table 24 Interaction plots and Surface response plots were shown in Fig 11 to 16

Table 24: 1 HR Design chart of Gliclazide

Factor Row #	A K4m	B K15m	C Guargum	1 HOUR Y1	Y bar
1	15	15	15	4.9	4.9
2	15	15	12.5	3.1	3.1
3	15	15	10	4.1	4.1
4	15	12.5	15	4.8	4.8
5	15	12.5	12.5	5.8	5.8
6	15	12.5	10	7.5	7.5
7	15	10	15	5.3	5.3
8	15	10	12.5	7	7
9	15	10	10	5.5	5.5
10	12.5	15	15	8.7	8.7
11	12.5	15	12.5	7	7
12	12.5	15	10	5.6	5.6
13	12.5	12.5	15	9.5	9.5
14	12.5	12.5	12.5	4.9	4.9
15	12.5	12.5	10	9.4	9.4
16	12.5	10	15	5.7	5.7
17	12.5	10	12.5	6	6
18	12.5	10	10	8.5	8.5
19	10	15	15	6	6
20	10	15	12.5	6.4	6.4
21	10	15	10	5.56	5.56
22	10	12.5	15	6.5	6.5
23	10	12.5	12.5	6.2	6.2
24	10	12.5	10	9.55	9.55
25	10	10	15	7.08	7.08
26	10	10	12.5	7.97	7.97
27	10	10	10	20.5	20.5

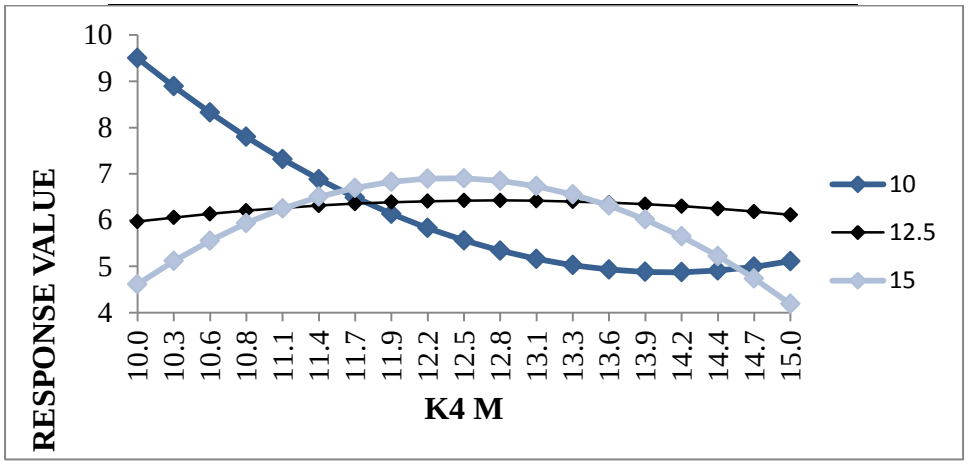

Figure 11: Y-Hat Interaction Plot K4M Vs K15M For D1(Constant Guargum=12.5)

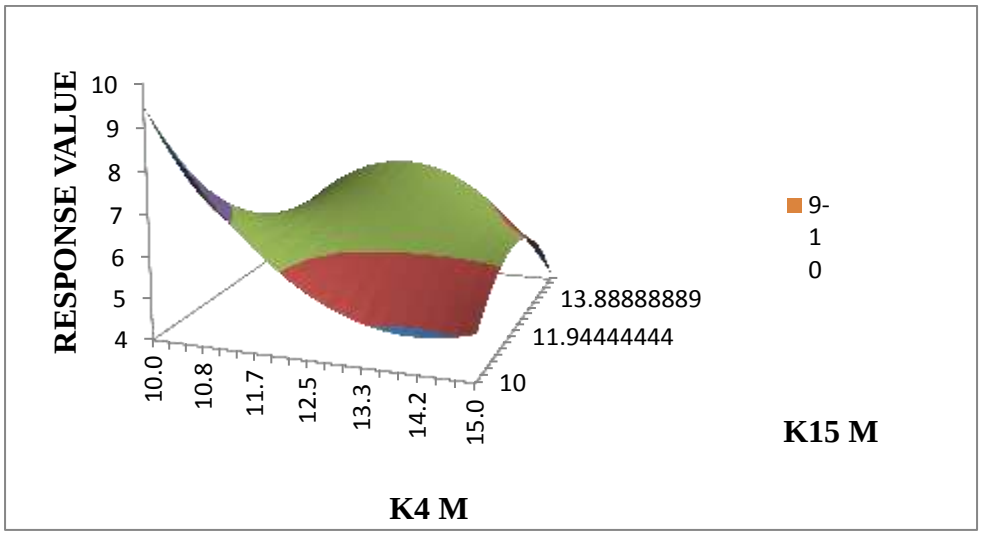

Figure 12: Y-Hat Contour Plot K4M Vs K15M For D1(Constant Guargum=12.5)

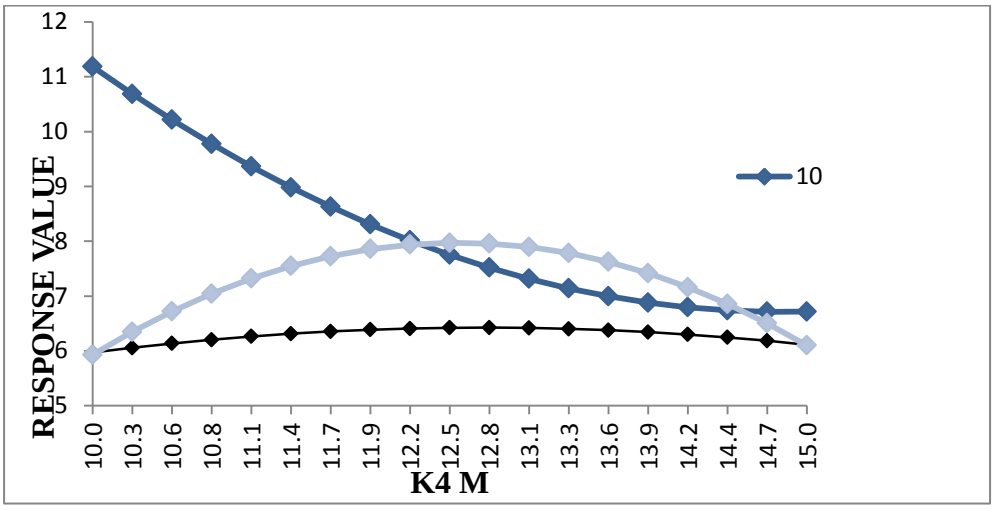

Figure 13: Y-Hat Interaction Plot K4M Vs Guargum For D1(Constant K15M=12.5)

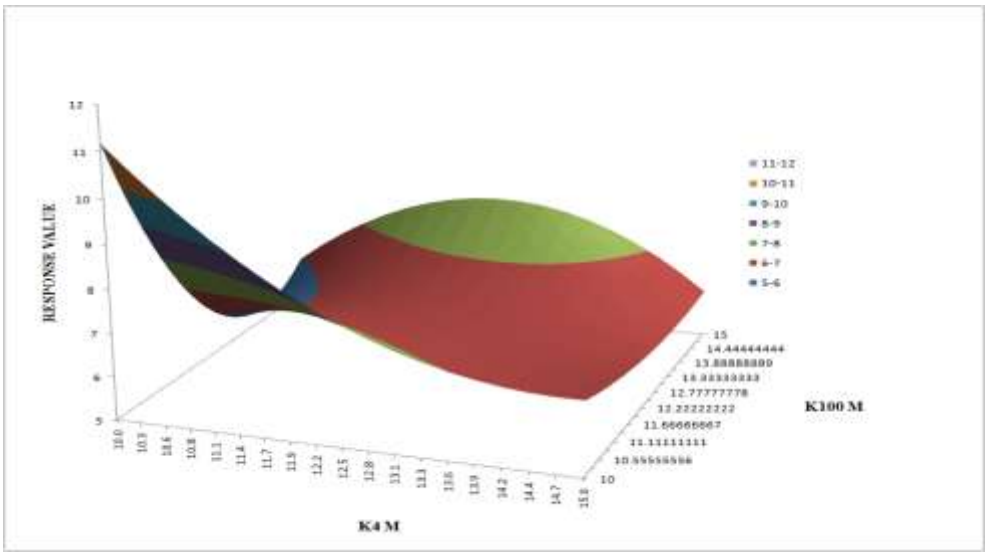

Figure 14: Y-Hat Contour Plot For K4m Vs Guargum For D1(Constant K15M=12.5)

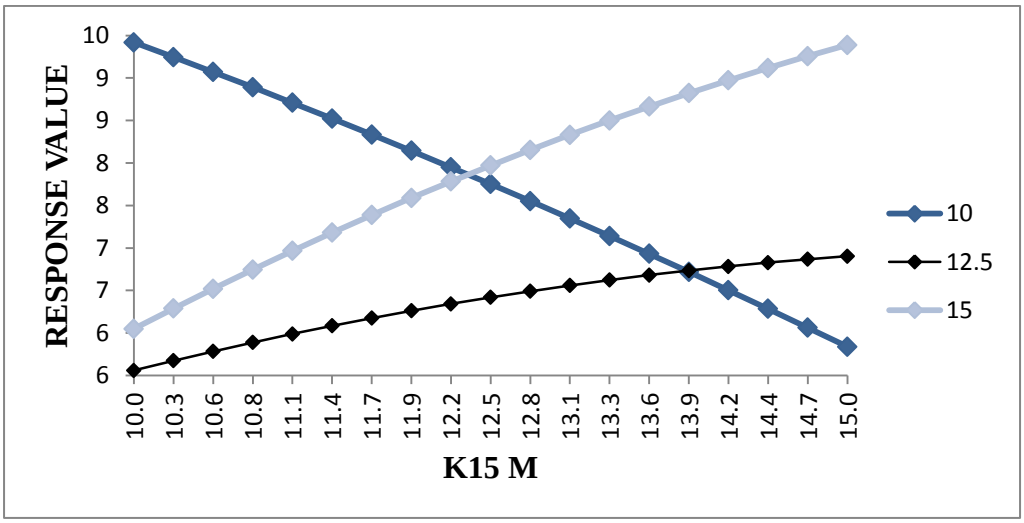

Figure 15 : Y-Hat Interaction Plot K15M Vs Guargum For D1(Constant K4M=12.5)

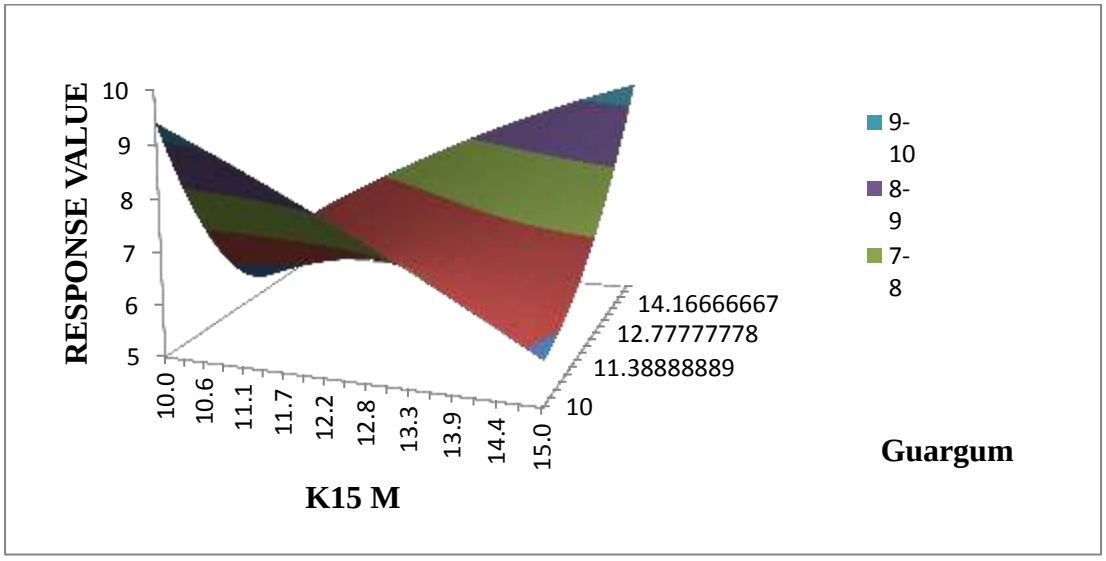

Figure 16: Y-Hat Contour Plot For K15m Vs GuargumFor D1(Constant K15M=12.5)

(B) DOE of 8th Hour (D8): 8 Th hour design sheet was shown in Table 25 Interaction plots and Surface response plots were shown in Fig 17 to 22.

Table 25: HR Design chart of Gliclazide

Factor Row #	A K4m	B K15m	C Guargum	8 HOUR Y1	Y bar
1	15	15	15	20	20
2	15	15	12.5	25.62	25.62
3	15	15	10	27.51	27.51
4	15	12.5	15	22.01	22.01
5	15	12.5	12.5	28.66	28.66
6	15	12.5	10	31.95	31.95
7	15	10	15	20.43	20.43
8	15	10	12.5	29.86	29.86

9	15	10	10	23.53	23.53
10	12.5	15	15	34.67	34.67
11	12.5	15	12.5	29.1	29.1
12	12.5	15	10	30.49	30.49
13	12.5	12.5	15	32.77	32.77
14	12.5	12.5	12.5	39.96	39.96
15	12.5	12.5	10	39.85	39.85
16	12.5	10	15	29.67	29.67
17	12.5	10	12.5	32.2	32.2
18	12.5	10	10	34.16	34.16
19	10	15	15	33.53	33.53
20	10	15	12.5	31.38	31.38
21	10	15	10	25.36	25.36
22	10	12.5	15	31.12	31.12
23	10	12.5	12.5	35.36	35.36
24	10	12.5	10	48.78	48.78
25	10	10	15	25.52	25.52
26	10	10	12.5	41.56	41.56
27	10	10	10	95.26	95.26

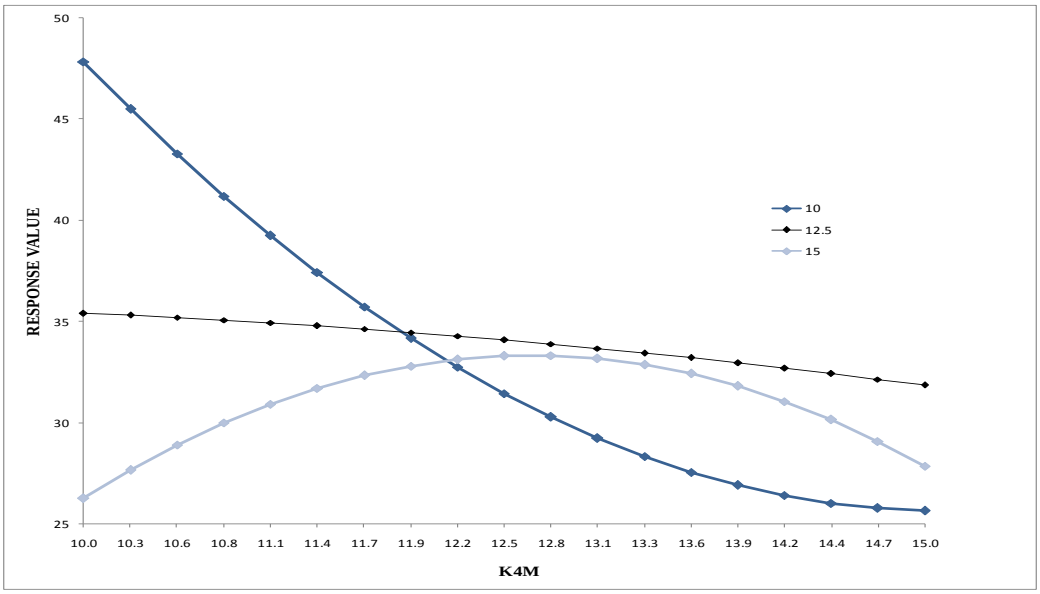

Figure 17: Y-Hat Interaction Plot K4M Vs K15M For D8(Constant Guargum=12.5)

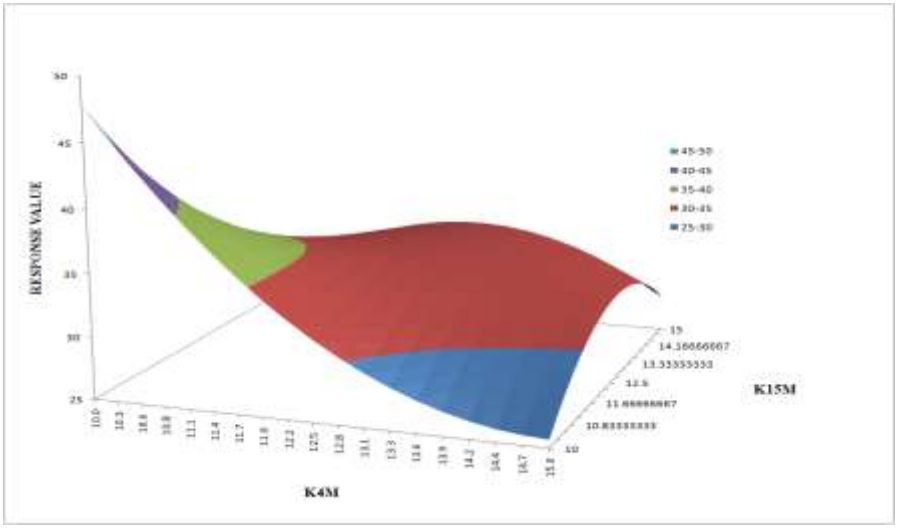

Figure 18: Y-Hat Contour Plot For K4m Vs K15m For D8(Constant Guargum=12.5)

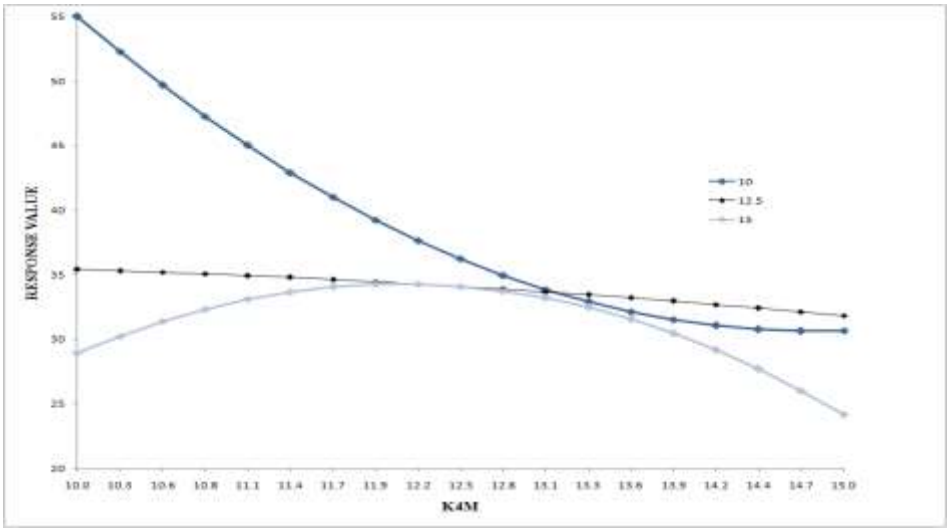

Figure 19: Y-Hat Interaction Plot K4M Vs Guargum For D8(Constant K15M=12.5)

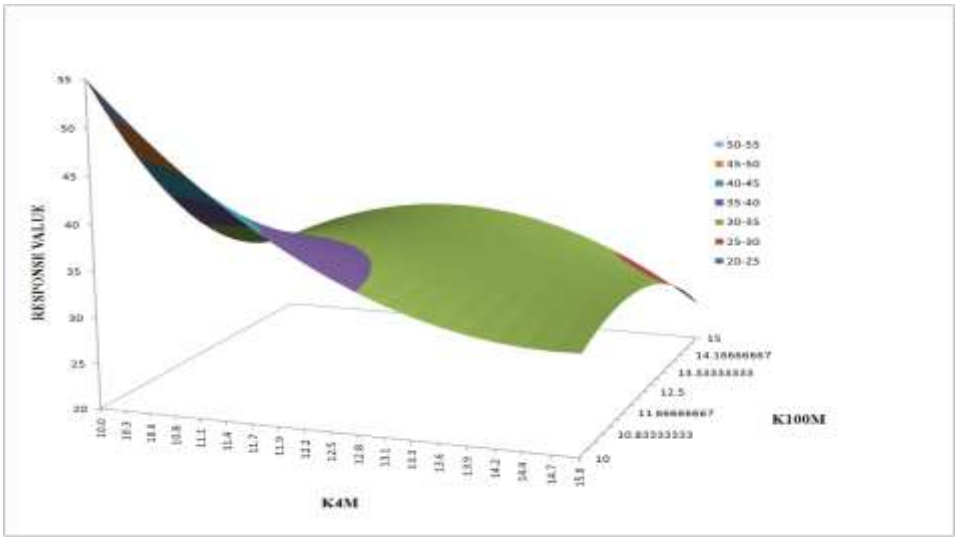

Figure 20: Y-Hat Contour Plot For K4m Vs Guargum For D8(Constant K15M=12.5)

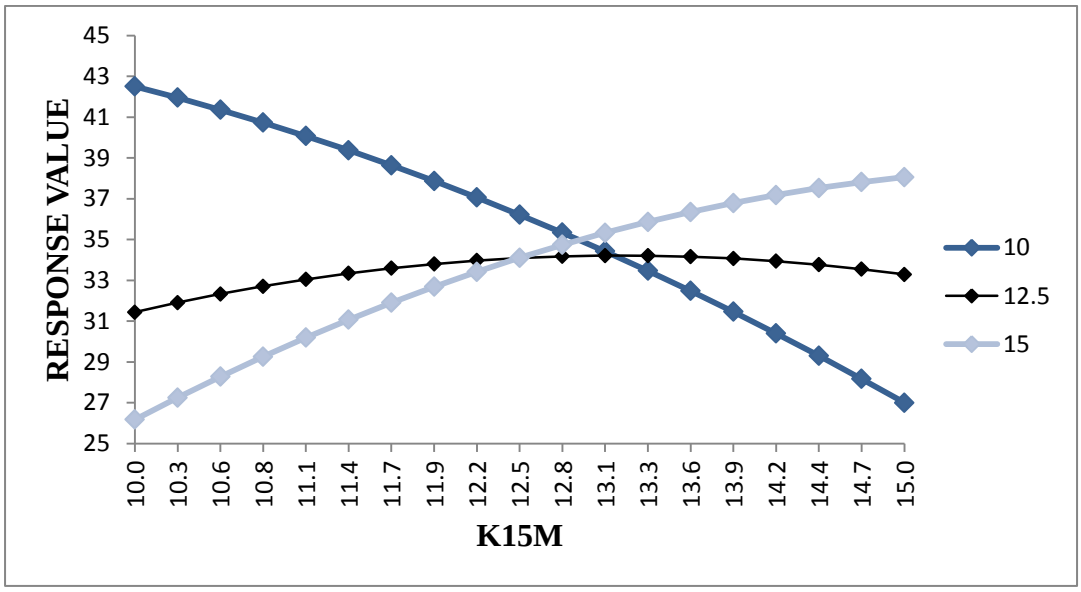

Figure 21: Y-Hat Interaction Plot K15M Vs Guargum For D8(Constant K4M=12.5)

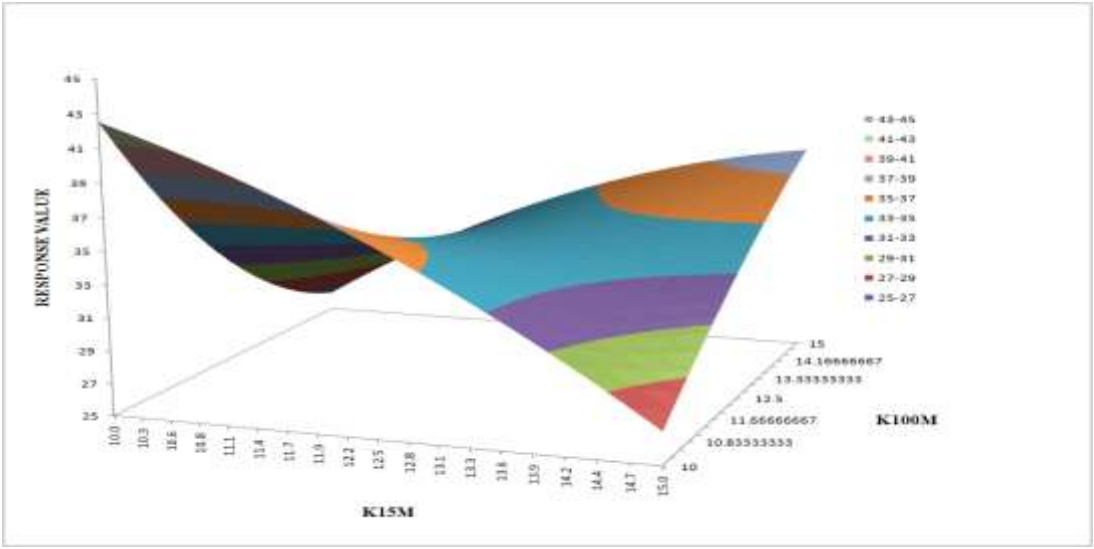

Figure 22: Y-Hat Contour Plot For K15m Vs K100m For D8(Constant K4M=12.5)

(C) DOE of 20th Hour (D20):. 20 th hour design chart was shown in Table 26 Interaction plots and Surface response plots were shown in Fig 23 to 28

Table 26: HR Design chart of Gliclazide

Factor Row #	A K4M	B K15M	C Guargum	1Hour Y1	Y bar
1	15	15	15	48.3	48.3
2	15	15	12.5	63.3	63.3
3	15	15	10	67.2	67.2
4	15	12.5	15	49	49
5	15	12.5	12.5	74	74
6	15	12.5	10	70.52	70.52
7	15	10	15	44.9	44.9
8	15	10	12.5	78.2	78.2

9	15	10	10	78.58	78.58
10	12.5	15	15	82.1	82.1
11	12.5	15	12.5	72.9	72.9
12	12.5	15	10	70.24	70.24
13	12.5	12.5	15	69.8	69.8
14	12.5	12.5	12.5	100	100
15	12.5	12.5	10	100	100
16	12.5	10	15	70.3	70.3
17	12.5	10	12.5	77.4	77.4
18	12.5	10	10	81.68	81.68
19	10	15	15	81.6	81.6
20	10	15	12.5	71.2	71.2
21	10	15	10	62.56	62.56
22	10	12.5	15	72.9	72.9
23	10	12.5	12.5	95	95
24	10	12.5	10	100	100
25	10	10	15	62.24	62.24
26	10	10	12.5	100	100
27	10	10	10	100	100

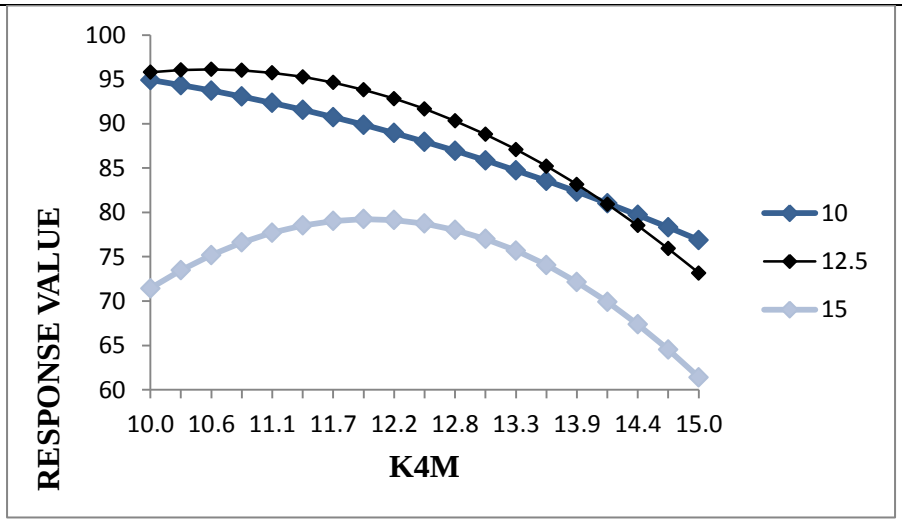

Figure 23: Y-Hat Interaction Plot K4M Vs K15M For D20(Constant Guargum=12.5)

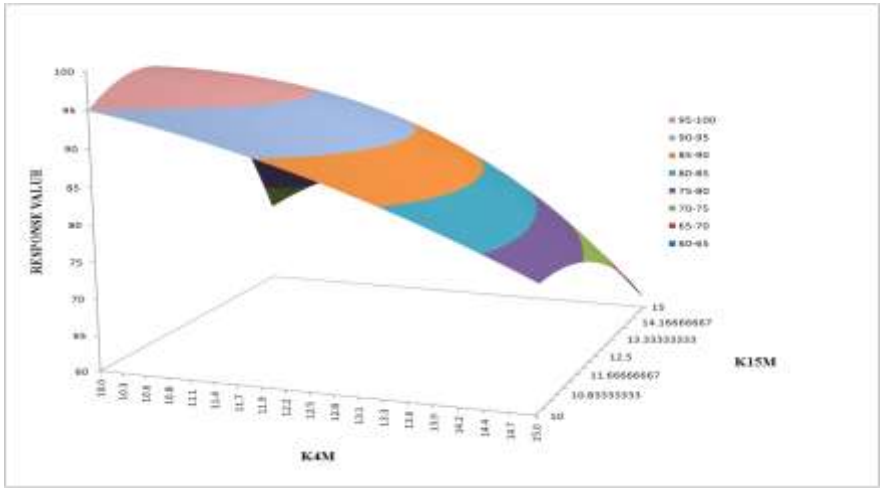

Figure 24: Y-Hat Contour Plot For K4m Vs K15m For D20(Constant Guargum=12.5)

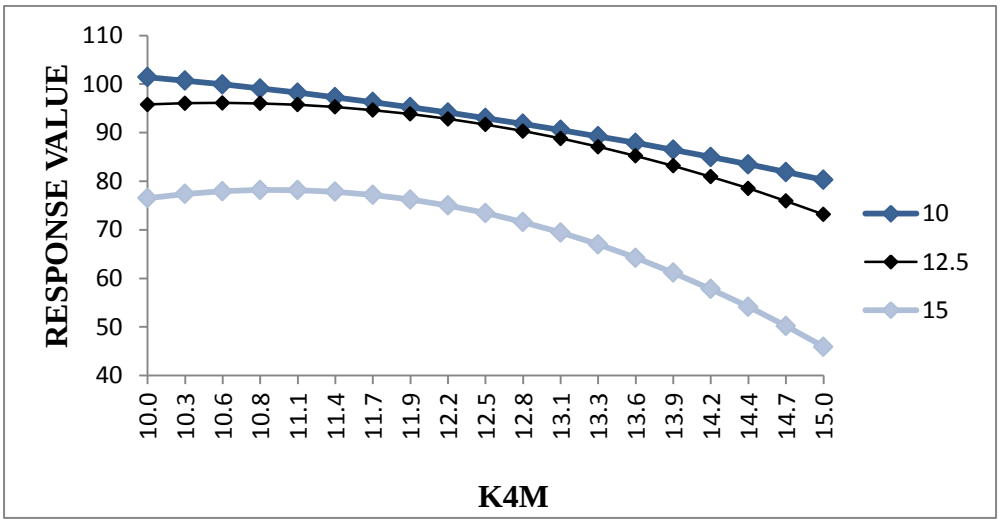

Figure 25: Y-Hat Interaction Plot K4M Vs Guargum For D20(Constant K15M=12.5)

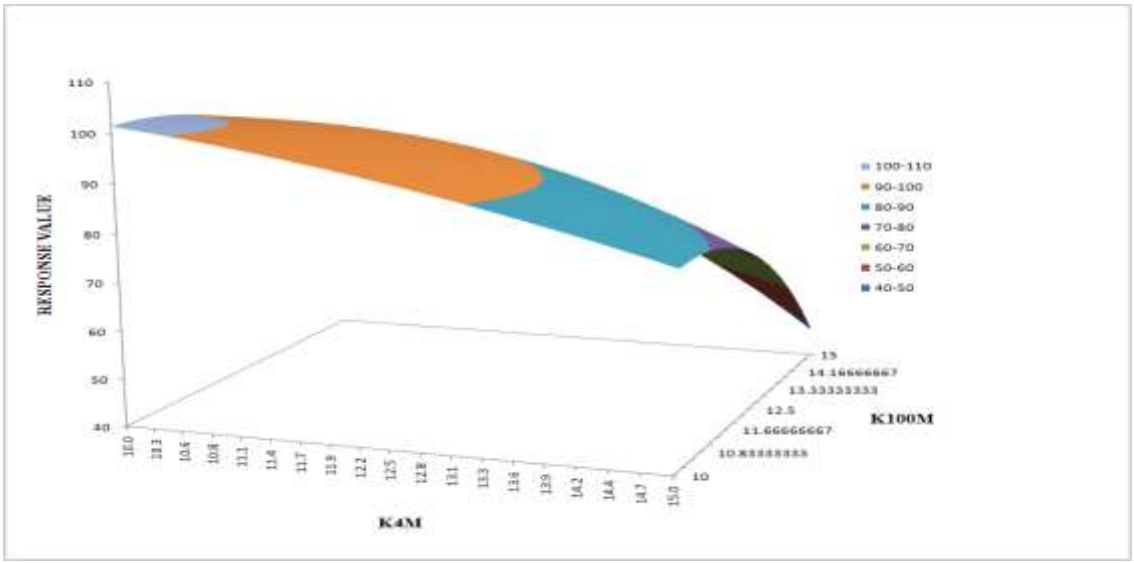

Figure 26: Y-Hat Contour Plot For K4M Vs Guargum For D20(Constant K15M=12.5)

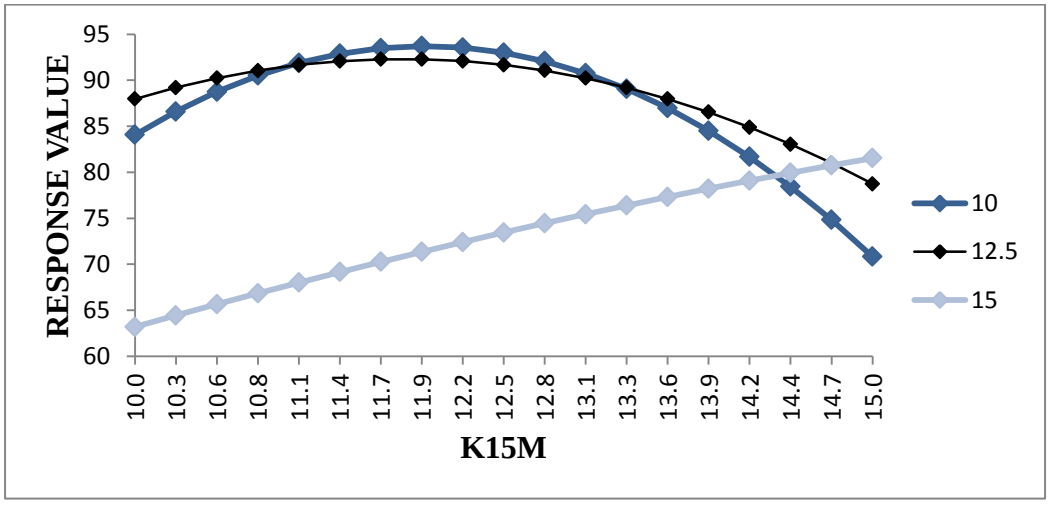

Figure 27: Y-Hat Interaction Plot K15M Vs Guargum For D20(Constant K4M=12.5)

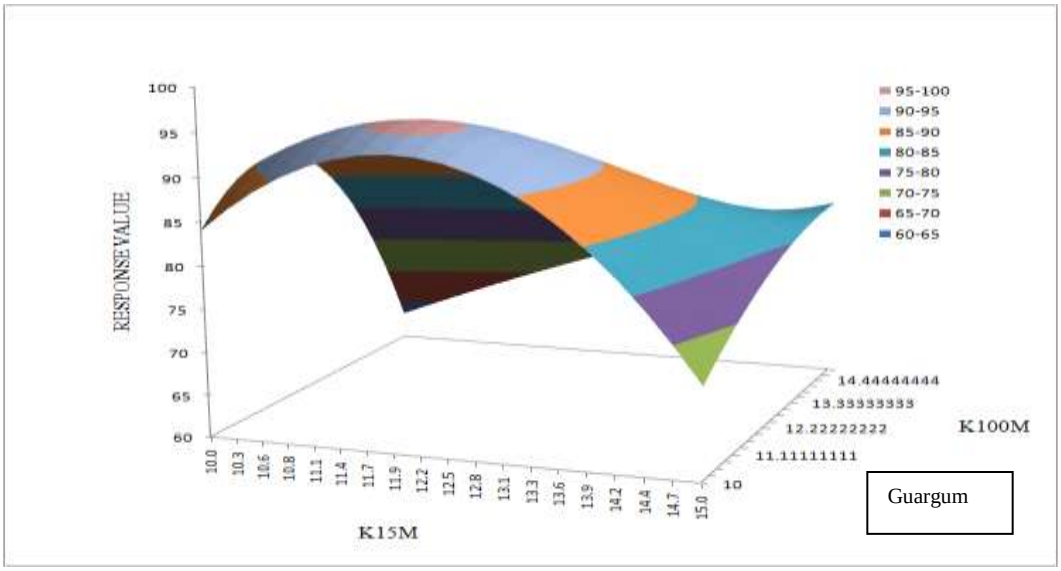

Figure 28: Y-Hat Contour Plot For K15m Vs Guargum For D20(Constant K4M=12.5)

The interaction plot shows a strong interaction between the polymers up to 8 hours of release. However, at 20 hours time point no apparent interaction between the three polymers is observed. The surface response plots were used to find out the range for each of the polymer within which the formulations would always meet the dissolution profile the data which came out of the soft ware indicates the following optimized range of polymer concentration (Table 27).

Table 27: Optimized Range of Polymers of Gliclazide from DOE studies

HPMC GRADE	LOW LEVEL	HIGH LEVEL
K4M	10.8	12.5
K15M	10.8	12.5
Guargum	10.8	12.5

This indicates that for achieving the target product profile for Gliclazide, the three polymers have to be used in a very narrow range of between 32.4% to 37.5% total polymer content..

When we use the Individual polymers the formulation with 45% HPMC- K15M shows the similar dissolution profile as that of TPP but when used in combination some formulations such as MMM, MML, LMM, LML and LLM shows the similar dissolution profile dissolution profile matching with that of TPP. Among those formulations F14-MMM shows perfect dissolution matching with that of 45% K15M. The dissolution profiles of these formulations are shown in Figure: 29, the release rate kinetics for F14-MMM was calculated (Table 28 and Table 29). The Peppas model defines the release rate kinetics and is shown in Figure 29.

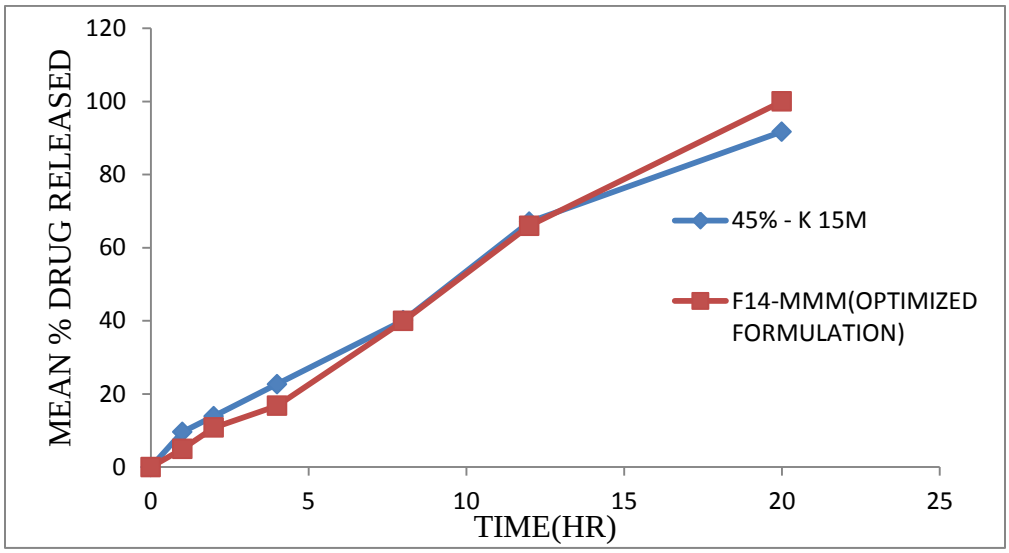

Figure 29: Dissolution Profiles Of Optimized Formulation And 45% HPMC-K15M of Gliclazide

Table 28: Release Rate Kinetics For F14-MMM (Optimized formulation)

Cumulative(%) Release Q	Time (T)	Root (T)	Log(%) Release	Log(T)	Log(%)Remaining	Release Rate(Cumulative %Release/T)	1/Cum%Release	Peppas Log Q/100	%Drug Remaining	Q0 1/3	Qt 1/3	Q0 1/3-Qt 1/3
0	0	0			2.000				100	4.642	4.642	0.000
4.93	1	1.000	0.693	0.000	1.978	4.930	0.2028	-1.307	95.07	4.642	4.564	0.078
10.81	2	1.414	1.034	0.301	1.950	5.405	0.0925	-0.966	89.19	4.642	4.468	0.174
16.74	4	2.000	1.224	0.602	1.920	4.185	0.0597	-0.776	83.26	4.642	4.367	0.275
39.96	8	2.828	1.602	0.903	1.778	4.995	0.0250	-0.398	60.04	4.642	3.916	0.726
65.98	12	3.464	1.819	1.079	1.532	5.498	0.0152	-0.181	34.02	4.642	3.240	1.401
86.74	16	4.000	1.938	1.204	1.123	5.421	0.0115	-0.062	13.26		2.367	
99	20	4.472	1.962	1.301	0.000	4.950	0.0101	-0.004	1		1.000	

Table 29: Release Rate Kinetic Model For F14-MMM

	RELEASE KINEITCS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**	**Hixson Crowell**
	1	**2**	**3**	**4**	**5**
	R(CvT)	**R(CvRoot(T))**	**Log T vs Log C**	**TIME vs LOG % REMAINING**	**TIME Vs (Q1/3-Qt1/3)**
Slope	5.195	23.961	1.019	-0.016	0.114
Correlation	0.9968	0.9619	0.9968	-0.9070	0.9849
R 2	0.9935	0.9253	0.9936	0.8227	0.9701

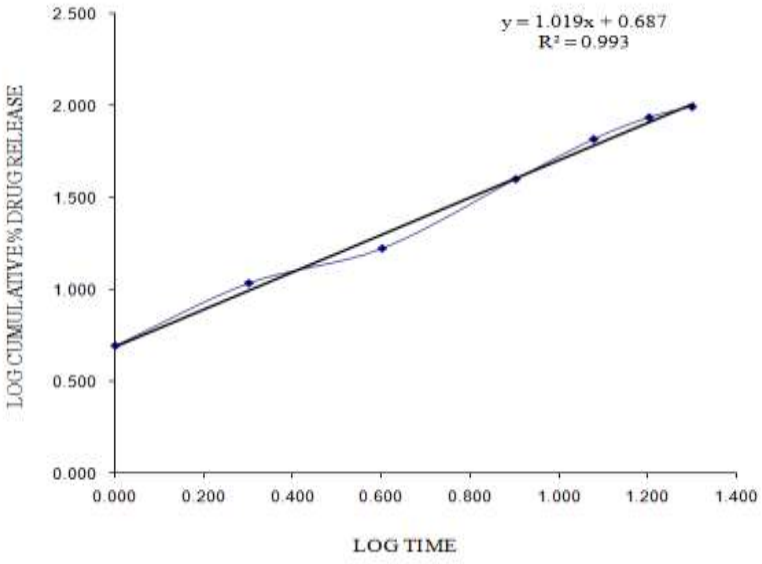

Figure 30: Peppas Model Plot

The DOE Method Thus Provides A Very Simple Experimental Tool To Optimize The Polymer Range For A Targeted Release Rate Of 5 To 6 % Hour. Combination Of Polymers Of Different Viscosity Grade Helps In Keeping The Total Polymer Requirement Within Narrow Use Levels.

Formulation and evaluation parameters of controlled release Gliclazide tablets by MADG process

Physical Properties of Gliclazide controlled released Tablets

The tablets of all formulations were subjected to various evaluation tests such as uniformity of the weight, hardness, friability the results of the tests are in Table 30

Table 30: Pre-compression studies of Gliclazide in MADG process

Formulation Code	Angle of repose	Bulk density	Tapped density	Compressibility index	Hausners ratio
F1	31° 95	0.491	0.523	6.11	1.06517312
F2	35° 80	0.513	0.642	20.09	1.25146199
F3	36° 89	0.462	0.521	11.32	1.12770563
F4	35° 89	0.431	0.531	18.83	1.23201856
F5	31° 89	0.482	0.541	10.90	1.12240664
F6	30° 89	0.461	0.532	13.34	1.15401302
F7	35° 89	0.454	0.521	12.85	1.14757709
F8	32° 24	0.432	0.544	20.58	1.25925926

Table 31: Post-compression studies of Gliclazide in MADG process

Formulation Code	Av. Wt (mg)	Thickness (mm)	Hardness Kg/cm^2	Friability (% w/w)	Assay (%)
F1	299	3.124	7.62	0.162	98.79
F2	296	3.085	7.31	0.191	99.93
F3	300	3.11	7.68	0.025	99.51
F4	298	3.092	7.65	0.271	98.66
F5	299	3.12	7.36	0.321	99.89
F6	301	3.13	7.38	0.072	97.53
F7	300	3.11	7.65	0.304	99.57
F8	299	3.126	7.62	0.022	98.92

All the tablets of different formulations complied with the official requirements of uniformity of weight. All the tablets of different formulations complied with the official requirements of uniformity of hardness. The hardness of the tablets ranged from 50N to 60 N of three runs R1, R2&R3.

All tablets had acceptable friability and no tablet was cracked, split or broken in all formulations from F1 to F8. The method and sequence of addition of Gliclazide, HPMC K15M and fluid uptake has no significant impact on the hardness of the tablets both at high and low compression forces. So that hardness was found to be independent in all cases. Drug content (Assay) was found to be uniform among different batches of the tablets and are in within the limits. **Dissolution profile of Gliclazide controlled released Tablets :**

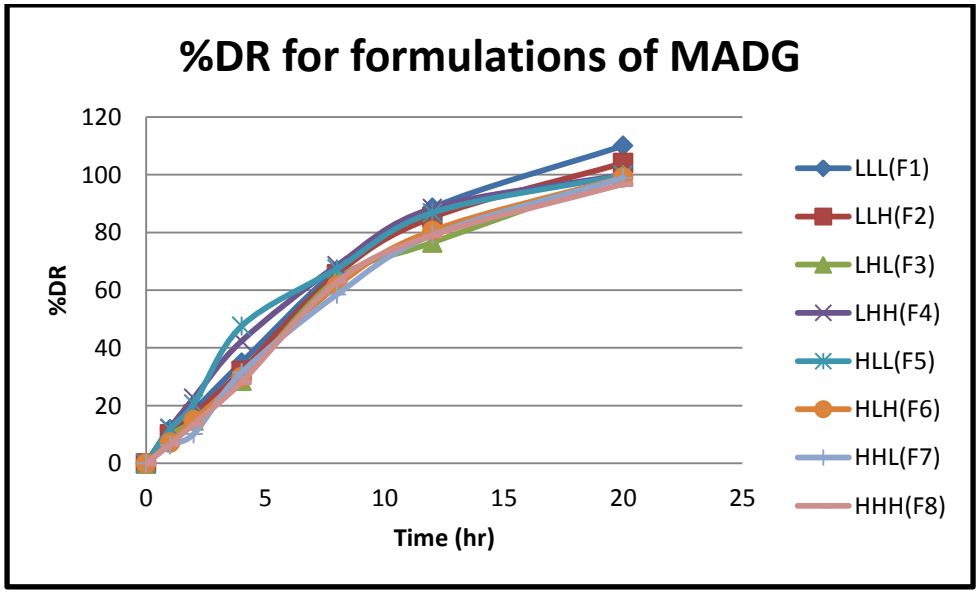

Figure 31: Dissolution Profile of Gliclazide 60mg tablets by MADG process (n=3)

The physical properties of all batches in the DOE run are significantly similar indicating that the level of the API, Polymer mixture and fluid uptake in the agglomeration stage does not significantly affect the physical properties of the tablet.

The dissolution is within the target profiles for all formulations product profile. Level of fluid uptake and level of drug in agglomeration stage do not show a significant effect.

CONCLUSSION:

- The current work focuses on the Comparision and evaluation of three granulation processes of antidiabetic drug by using the DOE. The drug was selected as Gliclazide which is insoluble in water.
- The development was initiated with standard calibration curve using UV spectro photometric methods as it is required to routine analysis of the drugs. The UV spectro photometric method developed in P^H 7.4 phosphate buffer at 226nm for Gliclazide. The method shows the linearity with R^2 value 0.999.
- **Polymer effect:** It was evaluated in three different polymers in different concentration for two drugs and concentration effect on drug was studied.
- The tablets were prepared and Evaluation done on the basis of comparison of pre and post compression data and dissolution profile in official media for respective drugs in different formulations.
- The individual polymers effect were analysed and combination of polymers were used for better results.
- 3^3 design was carried out for three different polymers i.e., combination of polymers.
- The tablets were formulated by using wet granulation and dry granulation methods.
- Pre and Post compression studies were evaluated and also in vitro dissolution effects were analysed in official media of drug.
- For the disso results DOE studies were conducted and effect of combination of polymers were analysed. Finally optimized level of combined polymer effect was known which is used in the MADG process as a Polymer Mix.
- In MADG (Moisture Activated Dry Granulation) API, Polymer Mix, fluid uptakes are the main ingredients.
- MADG contains three steps

  1. Agglomeration step, 2. Fluid uptake stage, 3. Moisture distribution stage
- The concentration of API, Polymer Mix and fluid uptake were varied at two levels, low and high in the agglomeration stage of the MADG process and a full factorial 2^3 DOE was run.
- 2^3 formulation Pre, post compression studies were carried and invitro dissolution carried out in official media for respective drugs.
- Gliclazide is an anti diabetic drug which is very small in dose. Gliclazide 60mg was developed by using three different processes.

- In Wet granulation the 27 formulations were following the limits of physical properties and dissolution profile but it is time taking process.
- In Dry granulation method the pre compression studies were observed and those are beyond the limit so tablets were not compressed.
- In MADG process API, Polymermix (which is obtained fron DOE results of the wet granulation process 11%),fluid uptake are the main ingreadients.
- When the pre-compression studies of wet and MADG in table 24 & 33 compared the MADG process showing excellent flow properties when compared with wet granulation formulations.
- In MADG process the dissolution results of all formulations were showing same release profile, it was not affected by the fluid added.
- In MADG the results were within the limit and MADG is a simple, economical, clean, lean and robust process that creates granulation with very good physical properties and finished products with satisfactory quality attributes.
- MADG process is easy, time saving and single pot process which gives the final product which is equivalent to the conventional wet granulation product.
- The MADG process gives tablets which have excellent flow properties, hardness, and dissolution profile.
- The Design space is defined by the DOE.

There by I conclude from my work that MADG is the best suitable process for drugs which are highly difficult to compress and the drugs which are in low dose. By using MADG process one can eliminate the drying step which is highly time taking and money consuming process in industries. By using MADG we can sustained the drug profile with respective to the targated profile.

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