MULTI UNIT PARTICULATE SYSTEM FOR CONTROLLED RELEASE OF GLIPIZIDE

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

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IN

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Submitted by

Register Number: 261210017

UNDER THE GUIDANCE OF

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CERTIFICATE

This is to certify that the dissertation work entitled **"MULTI UNIT PARTICULATE SYSTEM FOR CONTROLLED RELEASE OF GLIPIZIDE"** submitted to **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by **Register Number: 261210017** under my Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2013-2014.

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DECLARATION

I here by declare that the thesis entitled **"MULTI UNIT PARTICULATE SYSTEM FOR CONTROLLED RELEASE OF GLIPIZIDE"** has been originally carried out by me under the supervision and guidance of **Dr. M. Bhanu Prasad (**Industrial guide) and **Dr. Grace Rathnam M.Pharm.PhD.,** (Institutional Guide) principal & HOD, Department of Pharmaceutics, C.L.BaidMetha college of Pharmacy,Chennai-97 during the academic year 2013-2014.

Place: Chennai-97
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NOMENCLATURE

%	Percentage
Conc	Concentration
Hr	Hour
Min	Minute
µg/ml	Microgram/milliliter
Sec	Seconds
API	Active pharmaceutical ingredient
g/ml	gram/milliliter

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
IP	Indian Pharmacopoeia
CR	Controlled release
ER	Extended Release
EC	Ethyl Cellulose
GIT	Gastro Intestinal Tract
HPMC	Hydroxy Propyl Methyl Cellulose
ICH	International Conference On Harmonisation
IPA	Iso Propyl Alcohol
MUPS	Multiple Unit Particulate System
PVP	Poly Vinyl Pyrrolidone
PEG	Poly Ethylene Glycol
SR	Sustained Release
UV	Ultra Violet
USP	United State Pharmacopoeia

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(Register Number: 261210017)

CONTENTS


Dedicated to
My
Beloved Parents

1. INTRODUCTION

1.1 Drug Delivery Systems [1]

Drug release systems are the modified dosage forms used to increase the therapeutic efficacy and safety of drugs, thereby reducing both the size and number of doses administered.

1.1.1 Ideal drug delivery system:

- Should deliver drug at a rate dictated by the needs of the body over the period of the treatment.
- Should channel the active entity solely to the site of action.

1.1.2 Types of Drug delivery systems:

Sustained release drug delivery system: Sustained released dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In case of injectable dosage forms, this period may vary from day to months. In case of orally administrator forms, however this period is measured in hours and critically depends on residence time of the dosage form in the gastro intestinal tract.

Advantages:

- For drugs having specific window for absorption increased bioavailability can be attained by localizing the SRDF in that particular region of the GIT.

- Constant blood levels achieve desired effect and this effect is maintained for an intended period of time.

- Better management of disease state is achieved by reduction or elimination of fluctuation in drug blood levels.

- Drug susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR.

- **Controlled release drug delivery system**: Oral controlled drug delivery system is a delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a determined delivery throughout the course of GI transit. These systems deliver the drug at a predetermined rate and /or to a location according to the needs of the body and disease states for a definite period of time.

Advantages:

- Reduce dosage frequency.

- Reduce fluctuation in circulating drug level.

- Increase patient compliance.

- Avoidance of night time dosing.

- More uniform effect.

- Reduction in GI irritation and dose related side effects.

- **Delayed Release Dosage Form:** dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Example: Enteric coated dosage forms.

- **Targeted-release drug products:** A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate-or extended-release characteristics.

- **Repeat Action Dosage Forms:** It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a later time.

- **Prolonged Action Dosage Forms:** It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period of time.

1.2 Pellets[4]:

Pellets can be defined as small, free flowing, spherical or semi-spherical solid units intended for oral administration, which are manufactured by the agglomeration of fine powders or granules of active ingredient & excipients using appropriate processing equipment.

Pellets are usually of diameter range 0.5 mm to 1.5 mm.

1.2.1 Ideal properties of pellets:

- Spherical shape and smooth surface texture.

- Particle size should be of range of 0.5 mm to 1.5 mm

- The quantity of the active ingredient should be maximum so as to maintain the pellet size.

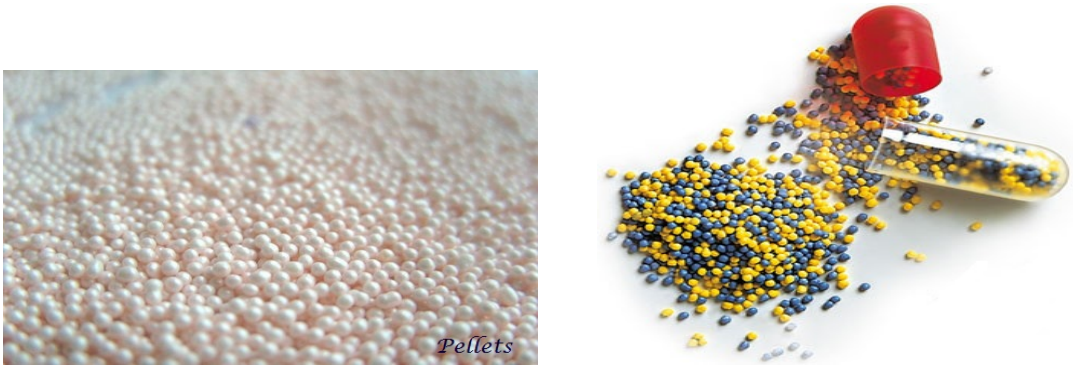


Fig 1. Pellets

1.2.2 Advantages:

- Improved flow properties and ease of packing resulting in uniform and reproducible fill weight of tablets and capsules.
- Improved appearance of products.
- Improved safety and efficacy of active ingredient.
- Decreased handling hazards and easier transport.
- Decreased hygroscopicity.
- High bulk density.
- Little abrasion and decreased friability.
- Uniform size with narrow size distribution.
- High drug loading capacity without producing extensively large particles.
- When formulated as modified release preparations pellets are less susceptible to dose dumping, thus lowering the risk of side effects.
- Pelletization prevents accumulation of drugs in GIT, which in turn prevents GI irritation.

- Pellets disperse freely in GIT fluids due to their small size, producing larger surface area for drug absorption and also reduce peak plasma fluctuations
- Pelletization is used for taste masking of unpalatable drugs.
- Separation of incompatible drugs and/or excipients, such ingredients can be formed into pellets and delivered in a single dose after encapsulation.
- In chemical industries, pelletization an effective method of avoiding powder dust

1.2.3 Disadvantages:

- Pellets are rigid and so cannot be easily compressed into tablets.
- Production of pellets is an expensive process due to requirement of highly specialized equipment and trained personnel.
- The control of production process is difficult (e.g the amount of water added and time is critical for the quality of pellets as over wetting can occur easily).

1.2.4 Significance of pellets:

Pellets may have varied applications in varied industries. It just requires an innovative bend to use it to derive maximum profitability. The smooth surface & the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch.

- Improved appearance of the products. Coating of pellets can be done with different drugs to enable a controlled release rate.
- In case of immediate Release Products larger surface area of pellets enables better distribution.

- Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
- In the chemical industries it is used to avoid powder dusting.
- Pellets ensure improved flow properties, and flexibility in formulation development and manufacture.
- The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats.
- The thickness of the coat on the pellets dictates the rate at which the drug/ contents are released from the coated particles.

1.2.5 Rationale for pelletization:

The use of pellets as a vehicle for drug delivery at a controlled rate has recently received significant attention, pellets disperse freely in gastrointestinal tract, so they invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize potential side effects without appreciably lowering drug bioavailability, pellets also reduce variation in gastric emptying rates and overall transit times, which is common with single unit regimens, is minimized, high local concentration of bioactive agent, which may inherently be irrigative or anaesthetic, can be avoided, when formulated as modified release dosage form, pellets are less susceptible to dose dumping than the reservoir type single unit formulation, better flow properties, narrow particle size distribution, less friable dosage form and uniform packaging.

1.2.6 Theory of pelletization:

It is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. The most thoroughly studied and most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions:

- Nucleation
- Transition
- Ball growth.

However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed:

- Nucleation
- Coalescence
- Layering
- Abrasion transfer.

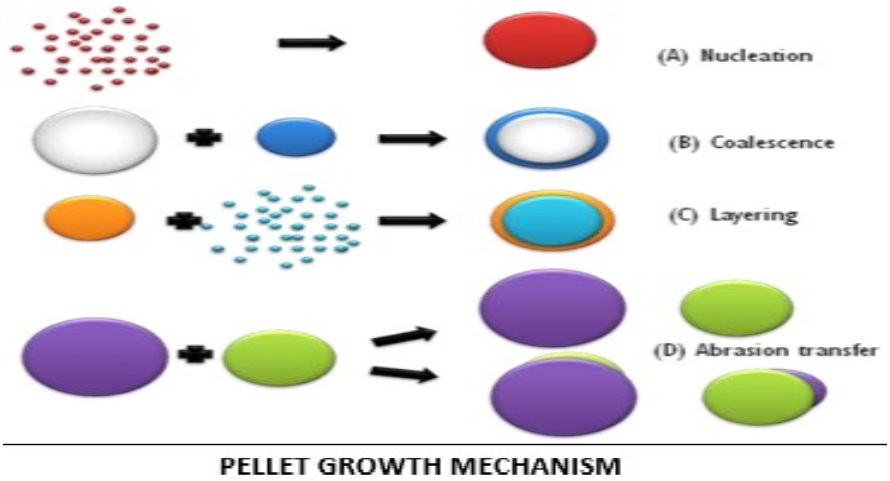


Fig 2. Pellets growth mechanism

1.2.6.1 Nucleation:

Fine powders can readily be formed into agglomerates by the introduction of a liquid phase followed by suitable agitation or tumbling. The liquid and solid phases are brought into close contact; this allows binding forces to develop and bring about agglomeration. Growth of the particles occurs either by collisions

and successful adherence of primary feed particles onto which particles collide and attachés themselves. This result in pellet growth formation.

When two particles come into close contact, the cohesive forces that hold the particles together are:

- Intermolecular attractive forces: these are very short range attractions, van-der Walls dispersive forces make the most significant contribution.

- Electrostatic attractive forces: these are almost always present in particulate systems. They are produced primarily by inter-particle friction. Although these forces are generally less than those experienced in other binding mechanisms, the net effect is to hold or orient particles in a contact region for sufficiently long for other, more dominant mechanism to operate.

- Liquid bridge modes: these are three physical situations in which the amount of liquid present produces cohesive forces between particles. The contributing mechanisms are adsorbed liquid layers, mobile liquid bridges, and viscous or adhesive binders. Oncesufficient liquid is present to produce liquid bridges in an assembly of particles, the cohesive strength of the material increased.

Nucleation is a common stage in all pelletization processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendulum in nature.

1.2.6.2 Transition:

The growth mechanisms affecting the transition region are coalescence and layering.

- **Coalescence** is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface.

- Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step.

- **Layering** is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time.

1.2.6.3 Ball growth:

In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

1.2.7 Mechanism of action:

- Enteric coated capsule dissolves and releases coated pellets.

- The pellets which are resistant to the gastric juice due to the polymer coating, are gradually distributed in the stomach.

- Because of their small size, the pellets pass easily through the pylorus.

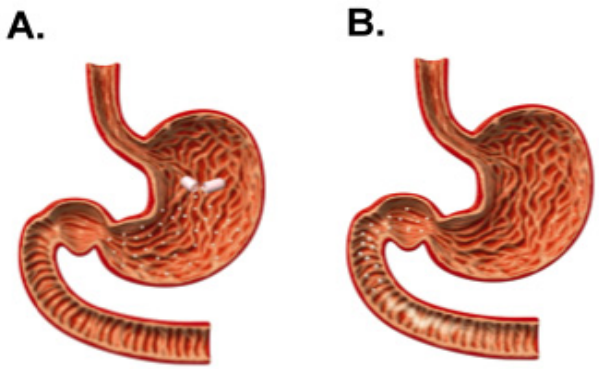


Fig 3. Mechanism of action

The specific milieu of the duodenum with pH levels 6-7, causes the enteric-coating to disintegrate, and the active pharmaceutical ingredient is rapidly absorbed.

1.2.8 Pelletization Techniques:

- Pelletization by extrusion-spheronization
- Drug layering (dry powder layering & solution and suspension layering)
- Cryo-pelletization
- Freeze pelletization
- Globulation
- Compression
- Balling

1.2.8.1 Solution/Suspension layering:

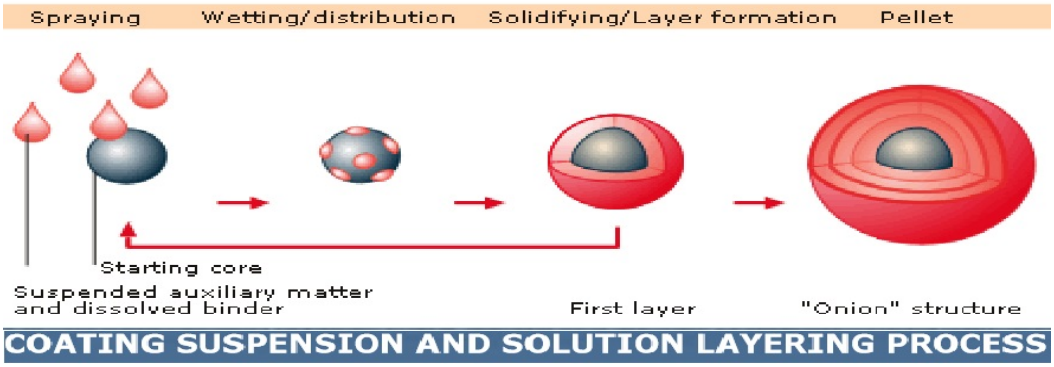


Fig 4. Coating suspension and solution layering process

The Wurster coating process had evolved through elaborate design modifications and tenement into ideal equipment for the manufacture of pellets by solution/ suspension layering. The high drying efficiency inherent in **quid-bed equipment**, coupled with the innovative and efficient design features of the Wurster process, has allowed the machines to hold center stage in pharmaceutical processing technology.

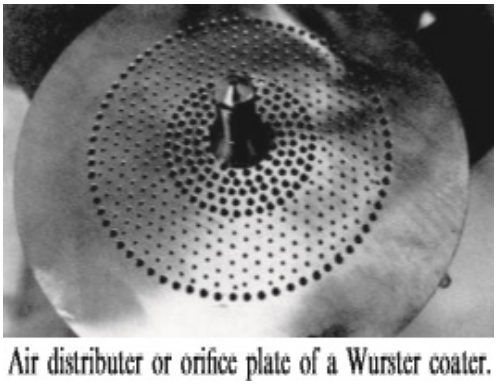

Air distributer or orifice plate of a Wurster coater.

Fig 5. Fluid bed coater

Not only have the manufacture and coating of pellets become routine and efficient, but scaling up of the process, which is key to the viability of any

processing technique, has proved to be predictable and economically feasible. The primary features that distinguish Wurster equipment from other quid-bed equipment are the cylindrical partition located in the product chamber and the configuration of the air distributor plate, also known as the orifice plate. The latter is congaed to allow most of the fluidization or drying air to pass at high velocity around the nozzle and through the partition, carrying with it the particles that are being layered on. Once the particles exit the partition, they enter the expansion chamber, where the velocity of the air is reduced below the entrainment velocity, and the particles fall back to the area surrounding the partition (referred to as the down bed).

The down bed is kept aerated by the small fraction of air that passes through the small holes on the periphery of the orifice plate. The particles in the down bed are transported horizontally through the gap between the air distributor plate and the partition by suction generated by the high air velocity that prevails around the nozzle and immediately below the partition. The volume of air that passes through the down bed outside the partition is just enough to generate modest particle movement. Because the spray direction is concurrent with particle movement, and particle motion is well-organized under optimum conditions, uniform layering of drug substances is consistently achieved. Because the partition height, that is, the gap between the partition and the orifice plate, controls the rate at which the particles enter the spray zone, it is an important variable that needs to be optimized for every batch size. For instance, at a given load size and fluidization air volume, the partition height can be reduced or increased to provide either a well-controlled particle motion that produces the desired pellet movement or a bubbling down bed that leads to disorganized particle movement and inefficient process.

1.2.8.2 Advantages:

- Innovative processes for coating of products.
- Film coating; lipid hot melt coating, Coating of granules, pellets, tablets.
- Specific manipulation of the particle surface characteristics, Protection of the product against moisture, light, air,.

- Specific manipulation of the way in which the particle dissolves the decomposition or the release of active ingredients.
- Process advantages: Uniform, continuous product coating. Aqueous or organic coatings can be applied.
- Coating and drying take place in one machine. In terms of Total Containment, the coating process and the filling and emptying of the machine can be carried out in complete isolation and without product spreading into the environment.

1.2.8.3 Principle:

Principle involved in fluid bed coater is particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating.

1.2.9 Types:

- Top Spray Coating
- Bottom Spray Coating (Wurster Coating)
- Tangential Spray Coating (Rotor Pellet Coating.

- **Top spray coating:**

This process is used for general coatings right up to enteric coating. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform. Coating in the continuous fluid bed is particularly suitable for protective coatings/color coatings where the product through put rates are high.

Fig 6. Top spray

The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into preheating zones, spray zones and drying zones. The dry, coated particles are continuously extracted.

Bottom spray coating (Wurster coating):

This process is particularly suitable for a controlled release of active ingredients. In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed.

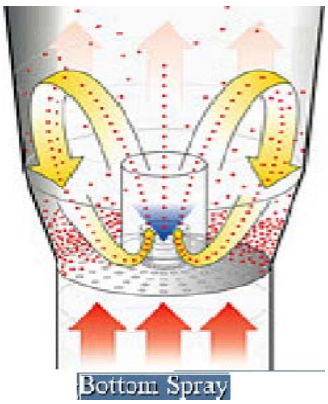


Fig 7. Bottom spray

By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate.

They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated.

Bottom spray coating (Continuous fluid bed):

Particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones whereby spraying can take place from below in the form of a bottom spray. The dry, coated particles are continuously extracted.

Tangential spray coating (Rotor pellet coating):

Ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of the rotor method.

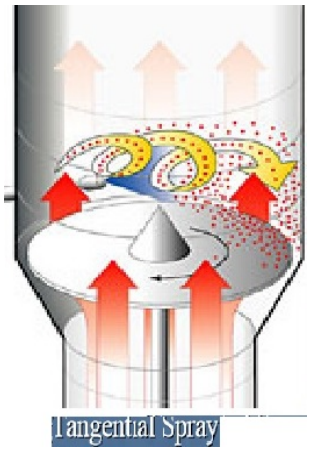


Fig 8. Tangential spray

Limitations:

The disadvantage of the Wurster process is the inaccessibility of the nozzles. If the nozzles are clogged at any time during the layering process, the operation has to be interrupted, and the spray guns must be removed for cleaning. The problem can be alleviated by screening the formulation or by using a spray gun with a bigger nozzle. Another aspect of the process that is challenging when multiple nozzles are used is the potential overlap of adjacent spray zones.

Although the position of the nozzle is fixed, the spray zone over- lap can be minimized using the air cap at the end of the spray gun.

2. LITERATURE REVIEW

1. **NS Dey et al**[11], reviewed that the multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

2. **HP Patel et al[12],** formulated multiple unit particle system (MUPS) of stabilized ramipril and hydrochlorothiazide pellets which produced better dissolution of the system for better bioavailability with improving stability and bioavailability of ramipril. More particularly, the present invention was directed for stabilized ramipril against decomposition into degradation products, namely ramipril-DKP and ramipril-diacid, during formulation and storage conditions. Simple ramipril formulation showed 15.15% related impurities after 3-month accelerated stability study, which was minimized to 2.07%, related impurities in ramipril pellets after 6 month accelerated stability study. By making MUPS of ramipril pellets, hydrochlorothiazide showed better dissolution (100.4% of ramipril and 97.9% of hydrochlorothiazide within 60 min) to produce better bioavailability. So, making MUPS containing ramipril pellets with polymer coating and hydrochlorothiazide and other excipients showed better stability of ramipril along degradation and synergistic effect among hypertension in immediate delivery.

3. **S.Ramu et al [13]** reviewed the potential advantages of multiple unit dosage forms (pellets etc.) over the single unit dosage forms (tablets). Pelletization

is a novel drug delivery system; a technique which converts fine powder particles into pellets. Review deals with the pellet and its various types of pelletization techniques like spheronization and extrusion, pelletization by layering, pelletiztion by solution layering &direct pelletization. The advantages, disadvantages & various applications of above mentioned techniques.spheronization and extrusion pelletization by layering are most widely used techniques. The study also deals with factors and evaluation of pellets.

4. Branka Ivic et al [14] developed diclofenac sodium extended release compressed matrix pellets and optimized using Generalized Regression Neural Network (GRNN). According to Central Composite Design (CCD), ten formulations of diclofenac sodium matrix tablets were prepared. Extended release of diclofenac sodium was acomplished using Carbopol® 71G as matrix substance. The process of direct pelletisation and subsequently compression of the pellets into MUPS tablets was applied in order to investigate a different approach in formulation of matrix systems and to achieve more control of the process factors over the principal response — the release of the drug. The investigated factors were X_1 -the percentage of polymer Carbopol® 71 G and X_2- crushing strength of the MUPS tablet. In vitro dissolution time profiles at 5 different sampling times were chosen as responses. Results of drug release studies indicate that drug release rates vary between different formulations, with a range of 1 hour to 8 hours of dissolution.

5. Phale et al [15]reviewed the use of Multiunit particulate systems (MUPS) in recent years as a controlled drug-delivery method. The current review describes the role and selection of excipients, pellet core, coating materials, and compression with various cushioning agents. MUPS technology enables firms to achieve the desired and therapeutic release with minimal side effects. Thus, MUPS could open a new area of research for scientists with many opportunities for the formulation of controlled- and delayed-release oral dosage forms.

6. Manuel Efentakis et al [16] reviewed the compared the release behavior of single-unit (tablets, capsules) and multiple-unit (minitablets in capsules) controlled-release systems of furosemide. The swelling and erosion behaviors of these systems,

which contained the swellable hydrophilic polymers sodium alginate (high viscosity) and Carbopol 974P, were compared. Swelling and erosion experiments showed a high degree of swelling and limited erosion for the Carbopol preparations, whereas less swelling but greater erosion was observed for the sodium alginate preparations. The sodium alginate preparations were eroded in 6 hours, while Carbopol preparations exhibited limited erosion within this period of time. These results appeared to be attributed to the physicochemical characteristics of the polymers used in this study. Polymer characteristics greatly influenced the release of furosemide (model drug) from the formulations prepared and tested. Sodium alginate had a less pronounced sustained release effect compared with Carbopol (ie, in 8 hours all 3 sodium alginate dosage forms displayed complete release of furosemide, while only 30% of the drug was released from Carbopol dosage forms). Finally, all 3 Carbopol dosage forms (single- and multiple-unit) displayed similar release behavior while sodium alginate dosage forms displayed a different and more distinctive behavior. Mini tablets and tablets showed a greater sustained release effect compared with capsules. Evaluation of the release data indicated that the release mechanism for sodium alginate formulations may be attributed to erosion/dissolution, while for Carbopol it may be attributed mainly to polymer relaxation and diffusion of the drug from the polymer surface.

7. Gaurav Tiwari1 et al [17] prepared glipizide (GPZ) and GPZ-HPC solid dispersion (SD) pellets and characterized for drug release mechanisms from a multi-unit erosion matrix system for controlled release. Solid dispersion with HPC was prepared by co-evaporation method and characterized by Fourier transform infra red spectroscopy (FT-IR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), hot-stage microscopy (HSM), x-ray diffraction (XRD), stability studies. Release rate of glipizide from solid dispersion was measured by the rotating basket method (JP XII). FT-IR study indicated the presence of hydrogen bonding in solid dispersion. SEM confirms the amorphous form in solid dispersion. In DSC melting peak in solid dispersion shifted slightly to lower temperature with respect to drug alone indicated the conversion to amorphous form which was further proved in X-ray diffraction. Hot- stage microscopy SM have demonstrated the ability of

melted HPC to dissolve the crystal of GPZ at increasing temperatures. The release rate of GPZ from solid dispersion granules was markedly larger than that from GPZ powder, and it was larger with a lower HPC molecular weight. The stability study showed that SD systems were not significantly different during six month of accelerating condition storage.

8. Phutane P et al [18] formulated microspheres of glipizide were developed by the emulsion solvent diffusion-evaporation technique by using the modified ethanol,-dichloromethane co-solvent system. The polymer mixture of ethyl cellulose and Eudragit® S100 was used in different ratios (1:0, 1:1, 2:3, 1:4 and 0:1) to formulate batches F1 to F5. The resulting microspheres were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and *in vitro* drug release behavior. The formulated microspheres were discrete, spherical with relatively smooth surface, and with good flow properties. Among different formulations, the fabricated microspheres of batch F3 had shown the optimum percent drug encapsulation of microspheres and the sustained release of the Glipizide for about 12 h. Release pattern of Glipizide from microspheres of batch F3 followed Korsmeyers-Peppas model and zero-order release kinetic model.

9. Shailesh et al [19] reviewed a drug delivery system that can have the entire various active pharmaceutical ingredients in one capsule and can deliver the drug at right time and in proper amount according to body's circadian rhythm. According to recent pharmaceutical applications involving pulsatile delivery the multiparticulate dosage forms are getting much favor over single unit dosage form because of their smaller particle size these systems have capacity for passing through the G.I. tract easily, leading to less inter as well as intra subject variability.

10. N Pandya et al [20] formulated floating multi particulate systems that have been utilized to obtain prolonged and uniform release of drug in the stomach for development of once-daily formulations. A controlled-release system designed to increase residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres by the emulsion solvent diffusion technique, using (i) calcium silicate (CS) as porous carrier; (ii) glipizide,

an oral hypoglycemic agent; and (iii) Eudragit® S as polymer. The effects of various formulations and process variables on the internal and external particle morphology, micromeritic properties, *in vitro* floating behavior, drug loading, and *in vitro* drug release were studied. The microspheres were found to be regular in shape and highly porous. The prepared microspheres exhibited prolonged drug release (~8 h) and remained buoyant for >10 h. The mean particle size increased and the drug release rate decreased at higher polymer concentrations. No significant effect of the stirring rate during preparation on drug release was observed. *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres. Microsphere formulation CS4, containing 200 mg calcium silicate, showed the best floating ability (88% buoyancy) in simulated gastric fluid. The release pattern of glipizide in simulated gastric fluid from all floating microspheres followed the Higuchi matrix model and the Peppas-Korsmeyer model.

11. Pahwa et al [21] prepared the gastroretentive floating multiple-unit drug delivery system for glipizide as a model drug for prolongation of gastric residence time. Floating microspheres were prepared by ionotropic gelation method using polymeric material such as chitosan. D-optimal design was utilized to investigate the joint influence of two variables: drug to polymer ratio (X1) and concentration of effervescent agent (X2) on the drug entrapment efficiency, percentage buoyancy, and cumulative percentage drug release. Particle size and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy respectively. Formulated microspheres exhibited prolonged drug release and remained buoyant for more than 12 h.

12. Nagarjuna Naik R et al [22] formulated and evaluated enteric coated multi particulate systems for Esomeprazole magnesium dihydrate to reduce the gastrointestinal tract side effects. The delayed release multiple units were prepared by using fluid-bed Wurster technology. These multiple units were prepared by seal coating, drug coating and enteric coating and were evaluated for assay, acid resistence, drug release, dissolution. This stud concluded that Esomeprazole magnesium dihydrate could be prepared by using combination of polymers and reduced the GI tract side effects.

13. **Anuranjita Kundu et al** [23] formulated norfloxacin as a suitable micro particulate system of Norfloxacin for controlled release delivery system by varying the alginate concentrations, calcium chloride concentrations and curing time. Norfloxacin microbeads were prepared by ionotropic gelation technique. Prepared microbeads were evaluated for granulometric studies, micrometric, scanning electron microscopy, drug entrapment efficiency, swelling studies and in-vitro dissolution studies. The prepared beads were free flowing and white in color. The drug loaded beads showed 37.26% to 91.73% drug entrapment, which was found to increase with increase in alginate concentration. In vitro drug release study of these microbeads indicated controlled release for Norfloxacin 96.19 – 97.83% release after 12 hours. From this study it could be concluded that the free flowing microbeads of Norfloxacin could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.

14. **K Senthil Kumaran et al** [25] formulated mosapride-controlled release beads with the help of the ionotropic gelation method, using sodium alginate containing $KHCO_3$ as the gas-forming agent. The physical characterization of the mosapride beads was examined by SEM. The results showed that the shape and texture of the beads were uniform before and after dissolution. The percentage of mosapride drug entrapment efficiency ranged from 97.4 ± 0.08 to 99.1 ± 0.04. The percentage of mosapride content from the beads was determined by high-performance liquid chromatography (HPLC) and ranged from 97.9 ± 0.08 to 99.6 ± 0.01.The *in-vitro* percentage release of mosapride from the beads at the end of 14 hours ranged from 90.0 ± 0.2 to 99.5 ± 0.12. The formulated beads in formulations 1 and 3 were sealed in vials and kept for 90 days at 40°C / 75% RH. After 90 days of exposure the percentage drug content was found to be 99.2 ± 0.04. The floating beads designed for the gastroretentive dosage form could be suitable for controlled drug delivery.

15. **Tanmoy Ghosh et al** [24] studied different subcoats containing calcium chloride, citric acid or Eudragit E, respectively for immediate release theophylline pellets which were subsequently coated with shellac. Drug release from the resulting pellet formulations was measured. The mechanism of interaction between the

modifying subcoat ingredients and the shellac coating was investigated using FT-IR spectroscopy. All formulations with modifying subcoat prolonged drug release. Whereas the effect of calcium chloride was a result of ionic interactions with shellac, the effect of citric acid was a reduction of the degree of dissociation of shellac. The influence of Eudragit(®) E was explained by the solubility characteristics of this basic polymer. The application of modifying subcoats was an easy and effective means to achieve sustained release from shellac-coated dosage forms. The choice of a suitable substance and the adjustment of its concentration allow tailor made sustained release profiles.

16. Sachin B Somwanshi et al [29] reviewed the multiparticulate drug delivery systems suitable for achieving sustained or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. One of the approaches toward this goal was to develop the floating multiparticulates so as to increase the gastric retention time. Such systems have more advantages over the single-unit dosage forms. The development of floating multiparticulates involved different solvent evaporation techniques to create the hollow inner core. In this review, the current status of floating multiparticulate drug delivery systems including hollow microspheres (micro balloons), low density floating micro pellets and floating micro beads (acrylic resin based), microcapsules etc, their evaluation parameter, advantages, application, limitation and future potential for oral sustained release drug delivery were discussed.

17. M. Thriveni et al [26] formulate and evaluated tizanidine hydrochloride sustained release pellets. Tizanidine hydrochloride is an immadazole α2-adrenergic agonist used in the management of increase in muscle tone associated with spasticity. It has short biological half-life of 2-2.5 h and is rapidly eliminated from the body. Sustained release dosage form of Tizanidine hydrochloride was developed for reduction in total amount of dose administration, to improve patient compliance, and increase efficiency in the treatment. The pellets were prepared by pan coating and fluidized bed coating technique (Wurster type) using hydroxy propyl methyl cellulose E5 (HPMC E5), Ethyl cellulose N-50, Eudragit L-100 as polymers and

isopropyl alcohol, methylene dichloride as solvents. The pellets were filled in capsules and evaluated for weight variation, content uniformity, moisture content, lock length, disintegration and *in-vitro* dissolution tests and the results were found to be within the limits. A comparative study of dissolution profile of different batches with marketed product was performed. The dissolution data was fitted with various kinetic models, and the optimized formulation followed zero order kinetics by non-Fickian case-II diffusion process. Stability studies were conducted for 3 months according to ICH guidelines and found to have good results.

18. Keerthi Kancharla et al [27] prepared and evaluated multiparticulate floating drug delivery system of aceclofenac. The microspheres were prepared by emulsification solvent evaporation technique using Eudragit RS 100 as a release rate controlling polymer in the ratios 1:1, 1:2 and 1:3. The prepared microspheres were evaluated for drug-polymer compatibility, micromeritic properties, drug entrapment efficiency, in-vitro buoyancy and drug release studies. The mean particle size increased with increase in the polymer concentration, when compared to pure drug and it was lying between 14.71-25.93 µm. The micromeritic properties were found to be improved when compared to pure drug .Scanning electron microscopy confirmed the hollow structure with smooth external surface. The drug and polymer were found to be compatible as seen in IR studies. The entrapment efficiency considerably decreased with increase in the polymer concentration ranging from 78-36 % respectively. The microspheres floated up to 12 h over the surface of the gastric buffer medium and the buoyancy percentage was found to be in the range of 85-94%. In-vitro drug release studies showed that the prepared microspheres exhibited prolonged drug release for more than 12 hours. The mechanism of drug release was found to be a combination of both Peppas and zero order release kinetics. The developed floating microspheres of aceclofenac may be used for prolonged drug release for at least 12 h for maximizing the therapeutic efficacy along with patient compliance.

19. Neeta et al [28] prepared gastroretentive floating multiple-unit drug delivery system for glipizide as a model drug for prolongation of gastric residence time. Floating microspheres were prepared by ionotropic gelation method using

polymeric material such as chitosan. D-optimal design was utilized to investigate the joint influence of two variables: drug to polymer ratio (X1) and concentration of effervescent agent (X2) on the drug entrapment efficiency, percentage buoyancy, and cumulative percentage drug release. Particle size and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy respectively. Formulated microspheres exhibited prolonged drug release and remained buoyant for more than 12 h.

20. Manas Tripathi et al [30] Formulated and evaluated the gastro-retentive floating microballoons of glipizide using hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and Eudragit RS100 (RS 100) by emulsion solvent evaporation technique. The floating microballoons were evaluated using micromeritic properties,buoyancy, in vitro drug release, scanning electron microscopy and stability studies. The densities of floating microspheres (0.475-0.975 g/cm3) were found to be less than the density of gastric fluid (1.004 g/cm3), therefore showed an extended floating time of more than 12 h over the gastric fluid. The entrapment efficiency of prepared floating microspheres was satisfactory (41.32-76.19%). The scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface which imparted floating properties to the prepared floating microballoons. Among all formulations, F4 (Drug:HPMC:RS 100::1:4:3) was found to be the best as it exhibited highest drug release (99.12%) in 12 h followed by diffusion mechanism and was stable for three months at ambient conditions.

3. AIM AND OBJECTIVES

3.1 Aim:

Glipizide is one of the most widely used oral hypoglycemic agents in the control of diabetes mellitus. It belongs to the class sulphonyl urea and is available as an immediate release tablet and controlled release tablet for once a day dosing. The innovator controlled release product of glipizide is glucotrol XL which is based on the osmotic drug delivery system is difficult to formulate and expensive to scale up since it involves investment in putting up a laser drill for drilling the hole required for the fluid to permeate into the system.

The current work is aimed at formulating a drug delivery system which will deliver the drug over 24 hours at the same rate of delivery as that of glucotrol XL but using the micro porous membrane drug delivery system and the multi unit particulate platform (MUPS).

3.2 Objectives:

(1) To standardize a procedure for loading drug on to non peril pellets.

(2) To determine the optimum level of ethyl cellulose needed to coat the pellets in order to get nearly zero order drug release from the pellets.

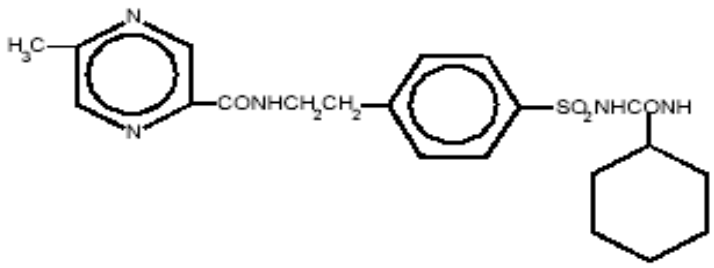
(3) To study the role of two different types of pore formers in modulating drug release to match to the target product profile. This study was conducted using full factorial design of experiments.

4. DRUG PROFILE

Drug : Glipizide[8]

Description : It is white odorless powder.

Molecular structure:



Molecular formula : $C_{21}H_{27}N_5O_4S$

Molecular weight : 445.535

Solubility: Practically insoluble in water, sparingly soluble in acetone and soluble in ethylene chloride (Dichloromethane), chloroform and diethyl form amide.

P^{ka} Value: P^{ka} (strongest acidic) = 4.32

P^{kb} (strongest basic)=0.059

Category: Oral blood-glucose-lowering drug of the sulfonylurea class Anti-diabetic agent.

Dose : 5-20 mg in once or twice daily.

Half Life : 2-5 hours.

4.1 Mechanism of action[2] :

Sulfonylurea's likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis of insulin.

4.2 Pharmacokinetics[3]:

Absorption: Gastrointestinal absorption is uniform, rapid, and essentially complete.

Distribution (protein binding): 98-99%, primarily to albumin.

Metabolism: Hepatic. The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite which accounts for less than 2% of a dose, an acetylaminoethylbenzene derivatives is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound.

Elimination: 70 to 80% through urine.

4.3 Doses[8]:

Dose: 5-20 mg in once or twice daily.

Administer glipizide in fixed combination with metformin once daily with a meal.

Individualize initial dosage of glipizide; usually 5–10 mg daily. The other oral antidiabetic agent may be discontinued abruptly..

For more severe hyperglycemia (i.e., fasting plasma glucose concentrations of 280–320 mg/dl), 2.5 mg of glipizide and 500 mg of metformin hydrochloride twice daily.

EXCIPIENT PROFILES

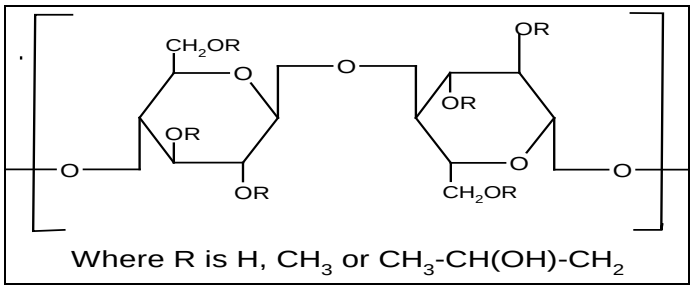
4.4 Hydroxyl propyl methyl cellulose[7] :

Non-proprietary names	:	JP	:	Hydroxyl propyl methylcellulose
		BP	:	Hypromellose
		Ph Euro	:	Methyl hydroxyl propyl cellulosum
		USP	:	Hypromellose

Chemical Name : Cellulose, 2-hydroxypropyl methyl ether.

Synonyms : Methyl Hydroxyl Propyl Cellulose, Propylene Glycol ether of methylcellulose, Mythical, Met lose, E464, Pharmacia, Culminal MHPC.

Structural Formula:



Physical and chemical properties:

Molecular weight : 10,000 – 15, 00,000

Color : White to creamy-white

Nature : Fibrous or granular powder

Odor : Odorless

Taste	:	Tasteless
Density	:	0.3-1.3 g/ml
Specific gravity	:	1.26
Solubility	:	Soluble in cold water, practically insoluble Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane.
Viscosity	:	HPMC 5cps, HPMC-K4M-3,000-5600mPas, K15M: 12,000-21,000 maps, K100M: 80,000-1, 20,000 maps.
Melting point	:	Browns at 190-200°C, chars at 225-230°C, Glass transition temperature is 170-180°C.
Functional category	:	Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.
Stability & storage	:	Stored in an air-tight container in a cool and dry place. It is stable although it is slightly hygroscopic.

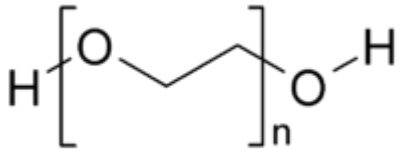
4.5.1 Applications:

- In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.

- HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products. In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and

particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

4.5.3 Polyethylene Glycol[5]:



Molecular formula : C18 H38 O10.

Molar mass : 380-420 gm/mol.

Density : 1.128g/cm^3

Melting point : 4-8 0^oc

Viscosity : 90 cst at 25^0c, 7.3 cst at 99 ^{0}c

PEG-4000 is low molecular weight grade of PEG. It is clean, colorless. viscous liquid, due in part to its low toxicity. PEG-4000 is widely used in variety of pharmaceutical formulation . more recently, it has been used to make" E-liquid" for electronic cigarettes (personnel vaporizers).

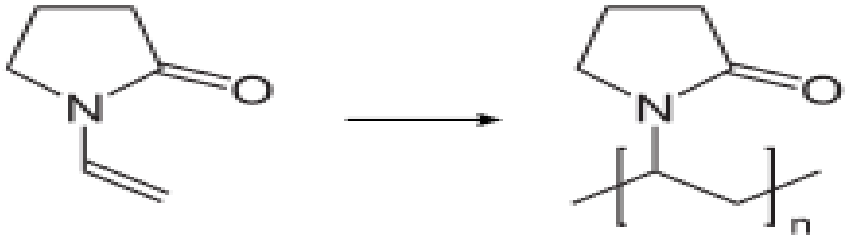
Chemical Properties:

PEG-4000 strongly hydrophilic. The partition-coefficient of PEG-4000 between hexane and water is 0.000015(log=-4.8),indicating that when PEG-4000 is mixed with water and hexane there are only 15 parts of PEG-400 in the hexane layer per 1 million parts of PEG-400 in the water layer.

PEG-400 is soluble in water, acetone, alcohols, benzene, glycerin, glycol and aromatic carbons and is slightly soluble in aliphatic hydrocarbons**.**

4.5.4 Polyvinyl pyrrolidone[6]:

Polyvinyl pyrrolidone (PVP), also commonly called Polyvidone or Povidone, is a water-soluble polymer made from the monomer *N*-vinylpyrrolidone:



Properties:

PVP is soluble in water and other polar solvents. When dry it is a light flaky hygroscopic powder, readily absorbing up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

4.5.5 Uses:

It is used as a binder in many pharmaceutical tablets. It simply passes through the body when taken orally.

PVP added to iodine forms a complex called providence-iodine that possesses disinfectant properties. This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs.

4. PLAN OF WORK

- Literature survey
- Analytical method development.
- Pre formulation studies
    - Drug and excipient profile.
- Base coated Drug loading to pellets (FBC).
- Assay of drug coated pellets.
- Functional coating (FBC).
- Evaluation of final coated pellets
    - Dissolution studies using pH-7.2 phosphate buffer.
    - DOE
- Stability studies
- Results and discussion

6. MATERIALS AND METHODS

6.1 Table No 1: List of materials /excipients /chemicals

Chemical	Manufacturer/supplier
Glipizide	Emcoind , Hyderabad
Isopropyl alcohol	Merck India
HPMC 5cps	Dow Chemicals
Dichloromethane	Luzenac, U.S
Ethylcellulose	Evonik Industries
Polyvinylpyrrolidone	Evonik Industries
PEG-400	Merck India

6.2 Table No 2: List of equipments

Name of equipment	Make
Fluid Bed Processor	Gansons
Mechanical Stirrer	Remi Motors
Uv-Visible Spectrophotometer	Shimadzu
Friability Tester	Electro Lab
Dissolution Tester	Electro Lab
Digital Balance	Mettler Toledo
Weighing Balance 5 Kg	Mettler Toledo
Weighing Balance 10 Kg	Mettler Toledo
Mechanicalsieve Stirrer	Remi Motors
pH Meter	Elico Ltd
Stability Chamber	Thermo Lab
Tap Density Tester	Electro Lab

6.3 Formulation development[10]:

Glipizide controlled release pellets :

In this work, the method used for preparing Glipizide layered release pellets was solution/suspension- layering technique.

The three main steps followed in solution/suspension layering technique to prepare controlled release pellets of Glipizide were,

i. Drug loading.

ii. Seal coating.

iii. Functional coating.

6.3.1 Drug loading:

2 g of glipizide was taken in a beaker and 35 ml of isopropyl alcohol and 15 ml dichloromethane was added. The contents were mixed thoroughly by using mechanical stirrer. Then the drug solution was sprayed onto non-pareil sugar seeds (25 g) by using fluidized bed-dryer technique.

6.3.2 Seal coating:

5 g of HPMC was taken in beaker and 35 ml of isopropyl alcohol and 15 ml dichloromethane was added. The contents were mixed thoroughly by using mechanical stirrer. During stirring 0.5 ml of PEG-400 was added drop by drop to the solution. Then the seal coated solution was sprayed onto sugar seeds drug loaded pellets using fluidized bed-dryer technique.

6.3.3 Functional coating:

The functional coating was done using ethyl cellulose and using two pore formers namely, PEG 4000 and PVP.

Functional coating plays most important role in controlling drug release.

The first type of functional coating is as given below.

1. Composition of functional coating on are given in Table No. 3. Ethyl cellulose and PEG-400 was taken in beaker and dichloromethane was added. The contents were mixed thoroughly by using mechanical stirrer. Then the coating solution was sprayed onto seal coated pellets by using fluidized bed-dryer technique.

The second type of functional coating with PEG 4000 as pore former is as given below.

2. Composition of functional coating is given in Table No. 4. Ethyl cellulose and PEG-4000 were taken in beaker and dichloromethane was added. The contents were mixed thoroughly by using mechanical stirrer and during stirring PEG-400 were added drop by drop to the solution. Then the coating solution was sprayed onto seal coated pellets by using fluidized bed-dryer technique.

The third type of functional coating with PVP as pore former is as given below.

3. Composition of functional coating is given in Table No. 5. Ethyl cellulose and PVP were taken in beaker and dichloromethane was added. The contents were mixed thoroughly by using mechanical stirrer and during stirring PEG-400 were added drop by drop to the solution. Then the coating solution was sprayed onto seal coated pellets by using fluidized bed-dryer technique.

Table No 3: Composition of glipizide pellets using ethyl cellulose:

Ingredients	F1
Non-pariel sugar seeds (g)	25
Glipizide (g)	2
HPMC 5cps (g)	5
Isopropyl alcohol (ml)	70
Dichloromethane (ml)	130
PEG-400 (ml)	1
Ethyl cellulose (g)	10

Table No 4: Composition of glipizide pellets using PEG – 4000 as pore former:

Ingredients	F2	F3	F4	F5	F6	F7	F8	F9	F10
	LL	LM	LH	ML	MM	MH	HL	HM	HH
Non-pariel sugar seeds (g)	25	25	25	25	25	25	25	25	25
Glipizide (g)	2	2	2	2	2	2	2	2	2
HPMC 5cps (g)	5	5	5	5	5	5	5	5	5
Isopropyl alcohol (ml)	70	70	70	70	70	70	70	70	70
Dichloromethane (ml)	130	130	130	130	130	130	130	130	130
PEG-400 (ml)	1	1	1	1	1	1	1	1	1
PEG-4000 (g)	5	5	5	10	10	10	15	15	15
Ethyl cellulose (g)	15	20	25	15	20	25	15	20	25

Table No 5: Composition of glipizide pellets using PVP as pore former:

Ingredients	F11	F12	F13	F14	F15	F16	F17	F18	F19
	LL	LM	LH	ML	MM	MH	HL	HM	HH
Non-pariel sugar seeds (g)	25	25	25	25	25	25	25	25	25
Glipizide (g)	2	2	2	2	2	2	2	2	2
HPMC 5cps (g)	5	5	5	5	5	5	5	5	5
Isopropyl alcohol (ml)	70	70	70	70	70	70	70	70	70
Dichloromethane (ml)	130	130	130	130	130	130	130	130	130
PEG-400 (ml)	1	1	1	1	1	1	1	1	1
PVP (g)	5	5	5	10	10	10	15	15	15
Ethyl cellulose (g)	15	20	25	15	20	25	15	20	25

6.4 Analytical methods:

6.4.1 Preparation of glipizide standard stock solution in phosphate buffer solution

PH 7.2:

A standard stock solution of glipizide was prepared by dissolving accurately weighed 100 mg of glipizide with 10 ml of methanol and the volume was made up to 100 ml in volumetric flask with phosphate buffer , pH 7.2 to obtain a stock solution of 1000 µg /ml.

6.4.2 Determination of analytical wavelength:

From the standard stock solution, 1ml was pipette out into 100 ml volumetric flask. The volume was made up to 100 ml with phosphate buffer, pH 7.2 and the resulting solution containing 10 µg /ml was scanned between 200 and 400 nm using Schimadzu UV-1601 UV-Visible Spectrophotometer. The λ_{max} was found to be 226 nm.

6.4.3 Calibration curve of glipizide in Ph 7.2 Buffer:

Accurately weighed quantity of glipizide (100 mg) was dissolved in little quantity of pH 7.2 phosphate buffer solution and volume was made up to 100 ml. From this, 5 ml of solution was pipette out into a volumetric flask and volume was made up to 50 ml. Appropriate aliquots were taken (0.2, 0.5, 1, 1.5, 2 ml) into different volumetric flasks and volume was made up to 10 ml with pH 7.2 buffer so as to get drug concentrations of 2, 5, 10, 15, to 20 µg/ml. The absorbance of these drug solutions were estimated at 226 nm in Schimadzu UV-1601 UV-Visible Spectrophotometer. This procedure was performed in triplicate to validate the calibration curve.

6.5 Evaluation of glipizide pellets:

6.5.1 Assay of glipizide [31]:

100 mg of drug loaded pellets were taken in 100 ml volumetric flask. To this required quantity of methanol was added and placed in sonicater to dissolve the pellets. Then volume was make up to 100 ml using pH 7.2 phosphate buffer. The solution was filtered, from this 1ml was pipetted out and the volume was made upto10 ml using pH 7.2 phosphate buffer. The absorbance was measured at 226 nm.

6.5.2 Dissolution of glipizide pellets in 7.2 phosphate buffer [31]:

Apparatus : USP-I basket apparatus.

RPM : 100

Temperature : 37 ± 0.5^0 C

Wave length : 226 nm

Procedure:

900 ml of the dissolution medium was placed in the dissolution apparatus and temperature was equilibrated to 37 ± 0.5^0C . The sample equivalent to

5 mg of glipizide pellets was placed in the basket of the dissolution apparatus and rotated at 100 rpm. At regular time intervals 5 ml of the dissolution medium was withdrawn, and replaced with the buffer. The absorbance was measured at 226 nm in Schimadzu UV-1601 UV-Visible Spectrophotometer. In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted with various kinetic equations like zero order (% release vs. t), first order (log % release vs. t) and Higuchi model (M_t/M_∞ vs. $t^{1/2}$). In order to define a model which would represent a better fit for the formulation, drug release data was further analyzed by Peppas equation, $M_t/M_\infty=kt^n$, where M_t is the amount of drug released at time t and M_∞ is the amount released at time ∞, thus the M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. R^2 values were calculated for the linear curves obtained by regression analysis of the above plots.

Fig 9. SP-I basket EI apparatus

6.6 Stability studies[31]:

The stability studies on formulation scale up batch were carried out according to ICH guidelines. The design and execution of the stability study followed the principles outlined in the ICH parent guidelines. The purpose of the study was to establish, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar conditions. The glipizide pellets were filled in capsules and were stored in clean, dry, moisture

proof bottles. They were stored in air tight containers and placed in the humidity chamber at $40^{o}C \pm 2^{o}C/75\% \pm 5\%$ RH. The accelerated studies were carried out for three months and the testing frequency was at 0, 1, 2 and 3 months. The recommended storage condition for Climatic Zone IV was followed which was $40^{o}C \pm 2^{o}C/75\% \pm 5\%$ RH. The attributes tested were assay and dissolution study.

The following were considered as significant change

- A 5% change in assay from initial value
- Failure to meet acceptance criteria for appearance, physical attributes and functionality test.

7. RESULTS AND DISCUSSION

7.1 Calibration curve of glipizide:

The values for the absorbance at different concentration are shown in Table No 6 and Fig.10. The calibration curve constructed for samples covered a range of concentrations from 2 to 20 µg/ml and was found to be linear with a linear regression coefficient value of 0.998.

Table No 6: Calibration curve of glipizide

Concentration (µg/ml)	Absorbance
0	0
2	0.102
5	0.256
10	0.512
15	0.768
20	0.978

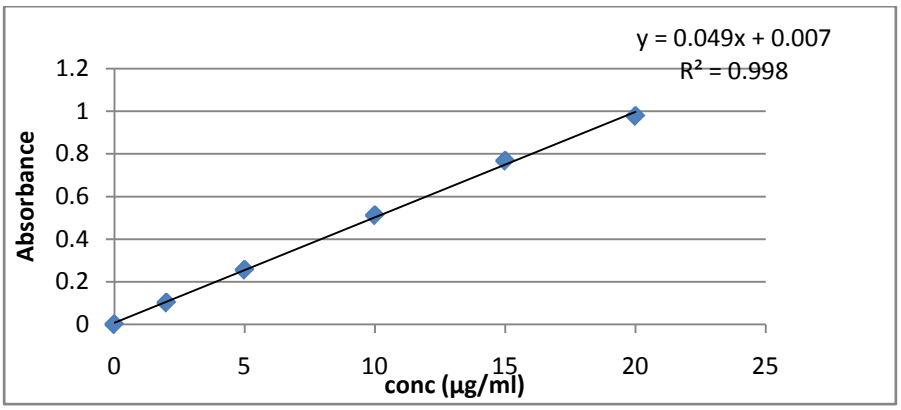


Fig 10. Calibration curve of glipizide

7.2 Assay:

The drug content determined was found to be as shown in Table No 7-9.

Table No 7: Assay of formulation F1

Formulation	% drug content
F1	93.2

Table No 8: Assay of formulation F2-F10

Formulation	% drug content
F2	96.3
F3	94.2
F4	94.6
F5	98.2
F6	94.0
F7	96.1
F8	92.7
F9	96.8
F10	95.7

Table No 9: Assay of formulation F11-F19

Formulation	% drug content
F11	94.3
F12	98.2
F13	96.3
F14	96.7
F15	98.2
F16	97.5
F17	96.9
F18	98.1
F19	99.1

7.3 Dissolution parameters of glipizide pellets :

The results of the dissolution profile of the prepared pellets are shown in Table No 10-13. and represented graphically in Fig.11-13.

The minimum weight gain required for ethyl cellulose coating onto drug loaded pellets required to seal the pellets was 30 % w/w. Hence all experiments with pore former were conducted at 30% weight gain.

In case of formulation F1, different thickness of coating was applied. As the percentage of coating increased the rate of dissolution decreased.

When PEG 4000 was used as pore former, formulation with medium/lower that is medium level of ethyl cellulose (20%), low level of PEG (5%) (formulation F5) alone was able to give dissolution profile matching to the target product profiles.

When PVP was used as pore former only medium/low and high/medium (formulation F14) were matching to the target product profile.

Both PEG 4000 and PVP can be effectively used as pore formers.

Table No 10: Dissolution profile of glipizide pellets using ethyl cellulose

Time (in hrs)	Ethyl cellulose (%weight gain)							
	F1							
	5%	10%	15%	20%	25%	30%	35%	40%
O	0	0	0	0	0	0	0	0
2	25.48±5.3	10.09±4.2	7.08±2.1	8.78±1.0	2.98±2.55	0	0	0
4	56.09±2.3	44.28±3.6	16.88±5.2	22.76±5.8	4.07±0.1	3.68±1.5	0	0
8	88.09±3.6	65.78±4.1	37.89±2.8	30.09±5.6	10.76±0.8	9.76±1.2	2.45±1.5	0
12	90.26±2.6	82.27±5.3	46.67±6.3	35.77±7.2	12.85±5.2	10.54±2.4	5.76±4.2	1.54±1.2
16	92.17±2.6	90.08±3.3	60.98±0.9	42.56±1.5	22.65±2.6	20.44±3.6	8.97±4.5	3.07±0.6
24	98.09±2.1	92.09±4.2	74.78±3.2	55.88±2.5	30.28±2.5	30.77±3.2	10.09±1.5	5.48±5.3

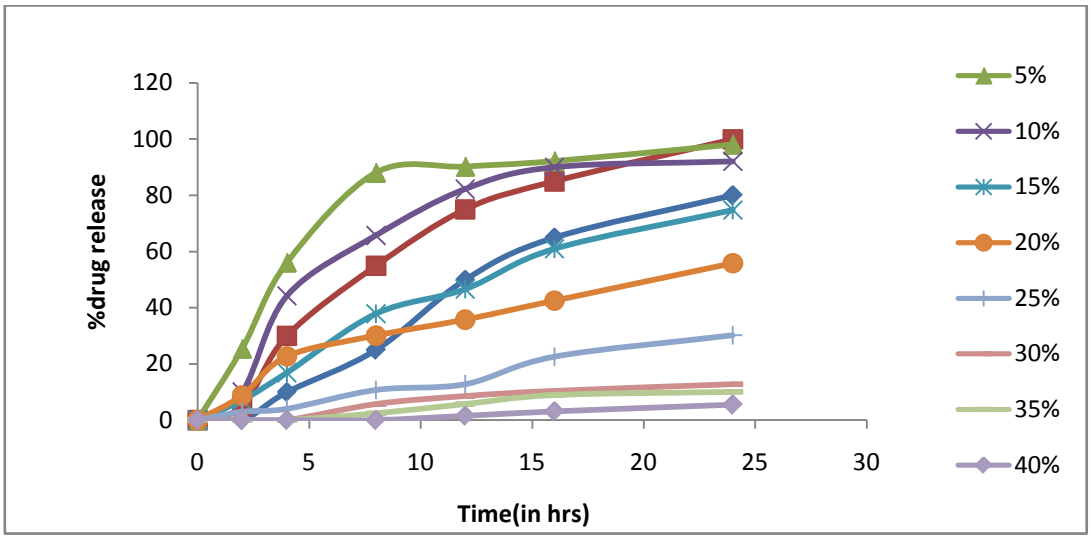


Fig 11. Dissolution profile of glipizide pellets using ethyl cellulose

Table No 11: Concentration of polymers used coating

POLYMER	CONCENTRATION (%)		
	L	M	H
PEG	5	10	15
PVP	5	10	15
Ethyl cellulose	15	20	25

Table No 12: Dissolution profile of Glipizide pellets using polyethylene glycol-4000

Time (in hrs)	TPP		F2	F3	F4	F5	F6	F7	F8	F9	F10
	Low	High	LL	LM	LH	ML	MM	MH	HL	HM	HH
0	0	0	0	0	0	0	0	0	0	0	0
2	0	5	7.54±1.3	12.45±2.3	27.09±3.3	4.23±4.1	5.87±1.5	14.32±3.2	0	0.37±1.2	3.29±0.9
4	10	30	28.87±2.1	38.45±3.2	54.98±5.2	17.89±6.3	20.61±1.2	29.45±0.6	1.29±2.1	7.58±3.2	12.76±1.2
8	25	55	30.79±2.3	62.67±3.2	67.78±1.8	28.44±5.2	37.45±3.2	43.08±4.2	5.35±2.6	13.49±3.6	25.48±2.1
12	50	75	55.32±2.1	75.34±2.1	80.97±3.2	53.87±1.2	62.07±3.4	78.12±0.9	14.48±2.3	26.55±2.3	44.07±0.8
16	65	85	75.29±1.2	84.35±5.2	85.67±3.1	72.64±5.1	68.34±1.2	80.16±1.21	34.08±5.1	42.78±6.1	67.57±2.1
24	80	100	84.28±2.6	87.28±1.4	87.54±2.5	83.24±0.9	85.28±5.6	87.54±2.6	55.87±4.3	66.08±5.0	78.09±0.9

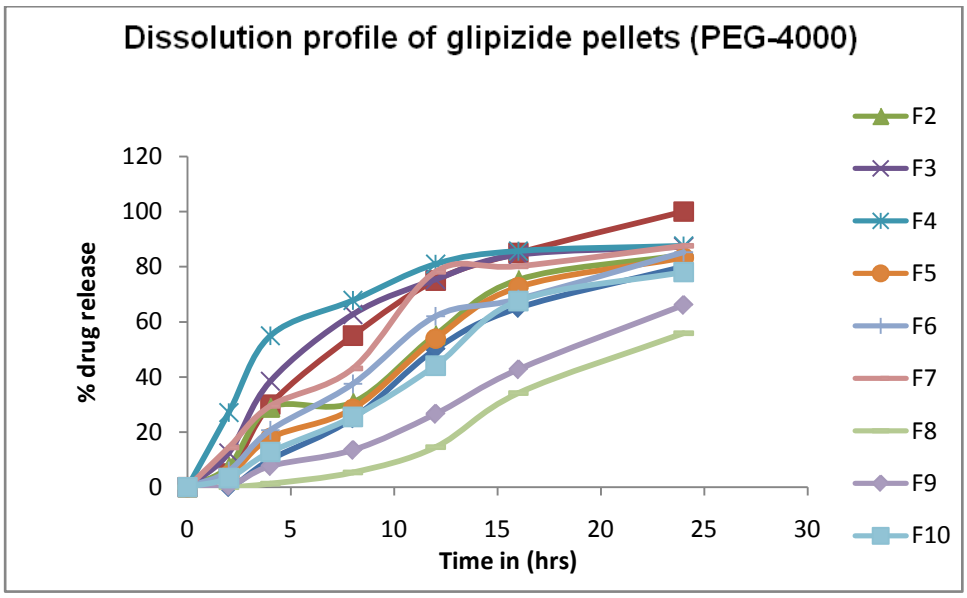


Fig 12. Dissolution profile of Glipizide pellets using polyethyleneglycol-4000

Table No 13: Dissolution profile of glipizide pellets using PVP

Time (in hrs)	TPP		F11	F12	F13	F14	F15	F16	F17	F18	F19
	Low	High	LL	LM	LH	ML	MM	MH	HL	HM	HH
O	0	0	0	0	0	0	0	0	0	0	0
2	0	5	10.35±1.2	20.23±1.4	37±2.4	3.23±2.3	9.87±3.4	24.32±4.5	2.32±2.4	3.54±3.5	9.29±3.8
4	10	30	41.87±1.4	58.45±2.4	74.98±3.6	27.89±3.4	25.61±3.8	39.45±4.4	5.29±2.8	12.58±3.6	22.76±3.5
8	25	55	44.79±1.8	72.67±2.5	87.78±3.5	38.44±3.5	47.45±3.6	48.76±3.5	10.35±4.5	23.49±4.6	65.48±2.5
12	50	75	65.32±1	85.34±2.7	90.97±3.6	63.87±2.6	80.26±2.6	88.12±2.4	28.44±2.6	66.48±3.5	72.56±3.8
16	65	85	85.29±1.1	94.35±4.2	95.67±4.5	82.64±3.5	88.23±2.4	98.50±2.9	42.48±3.8	82.64±2.6	86.57±1.6
24	80	100	100±1.5	97.28±3.5	96.54±3.4	90.24±1.4	93.09±4.4	99.26±3.0	75.08±4.6	96.78±3.7	90.45±1.9

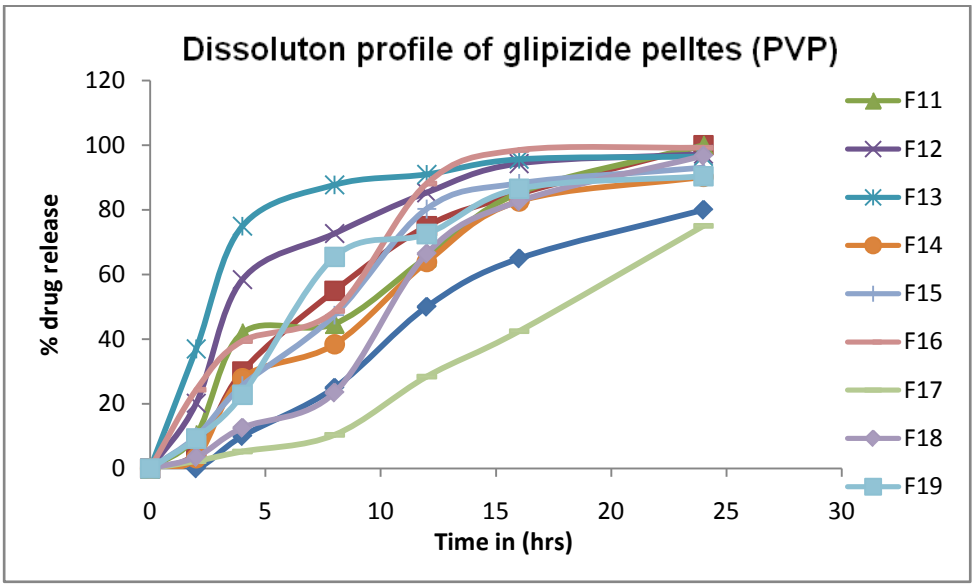


Fig 13. Dissolution profile of Glipizide pellets using polyvinylpyrrolidone

7.4 Release kinetics:

Different kinetic models (zero-order, first-order, Higuchi's, Korsmeyer's and Hixson Crowell) were applied to interpret the release profile (the order and mechanism of glipizide release) from the pellets as shown in Table No 14-16 and Fig.14-16. To study the mechanism of drug release from the pellets, the release data were fitted to zero-order, first-order, and Higuchi equation. However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer Peppas equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems.

$$\text{Log } (Mt/Mf) = \text{Log } k + n \text{ Log } t \text{ --15---------- (1)}$$

where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release.

(1) Zero, Higuchi , first order kinetics indicates the order of release of drug i.e. the release is dependent on time (first)/square root of time (Higuchi)/independent of time (Zero).

(2) Peppas model indicating the mechanism of drug release i.e, release of drug from the formulation is by diffusion, erosion, swelling and may by the combination of diffusion and swelling.

(3) Hixson Crowell model indicates that the release of drug is by dissolution.

(4) The values obtained for 24 hrs are indicated by the regression co-efficient values of the respective kinetic models and the graphs are also plotted in the individual charts.

(5) Greater the regression coefficient greater the linearity towards the kinetic model.

Criterion of selecting the most appropriate model was based on the best goodness of fit. The values of the kinetic rate constant (k) and correlation coefficient (R^2) as calculated from equations are presented in Table No 14-16.

Generally speaking, the ± majority of formulations did not seem to follow a zero order profile of drug release based on the lower R^2 values obtained compared to the other kinetic models examined. On the other hand, the R^2 values obtained from examining the first order and the Hixson-Crowell models were found to be very close to each for the formulations investigated. Nevertheless the R^2 values for Hixson-Crowell model were slightly higher than the other models, showing a better conformance to this model. The release of drug was predominantly by dissolution.

Table No 14: Kinetic evaluation of drug release data of medium/lower concentration of PEG-4000 as pore former

	RELEASE KINETICS				
	ZERO	HIGUCHI	PEPPAS	FIRST ORDER	HIXSON CROWELL
Slope	3.792	19.053	1.1876	0.0095	0.0942
R^2	0.9272	0.9137	0.9547	0.9846	0.9866

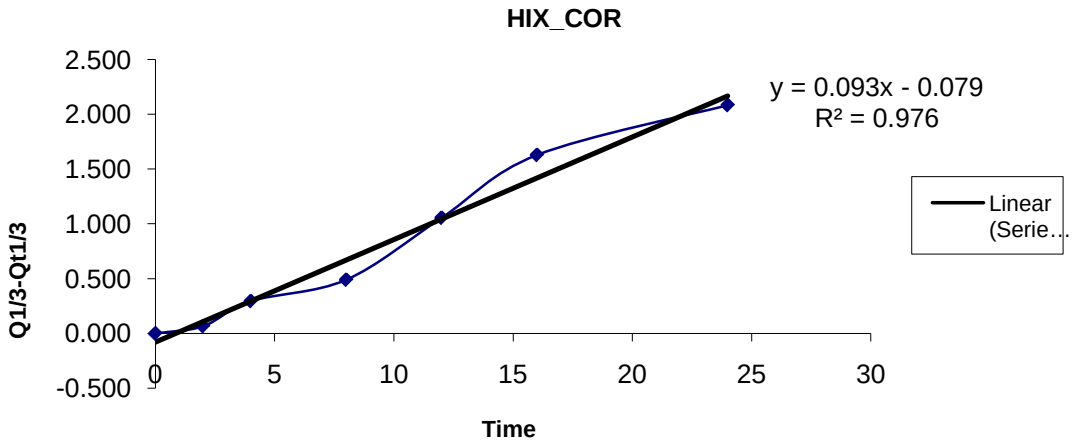


Fig 14. Drug release data of medium/lower concentration of PEG-4000

Table No 15: Kinetic evaluation of drug release data of medium/lower concentration of PVP as pore former

	RELEASE KINETICS				
	ZERO	HIGUCHI	PEPPAS	FIRST	HIXSON CROWELL
Slope	4.094	21.080	1.257	0.010	0.113
R^2	0.9269	0.9291	0.9582	0.9838	0.9882

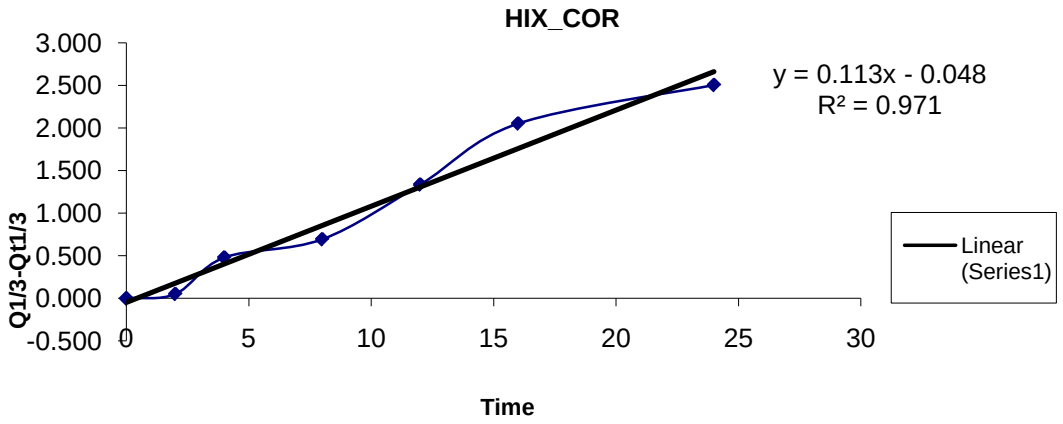


Fig 15. Drug release data of medium/lower concentration of PVP

Table No 16: Kinetic evaluation of drug release data of higher/medium concentration of PVP as pore former

	RELEASE KINETICS				
	ZERO	HIGUCHI	PEPPAS	FIRST	HIXSON CROWELL
Slope	4.559	22.515	1.383	0.013	0.140
R^2	0.9396	0.8663	0.9687	0.9837	0.9961

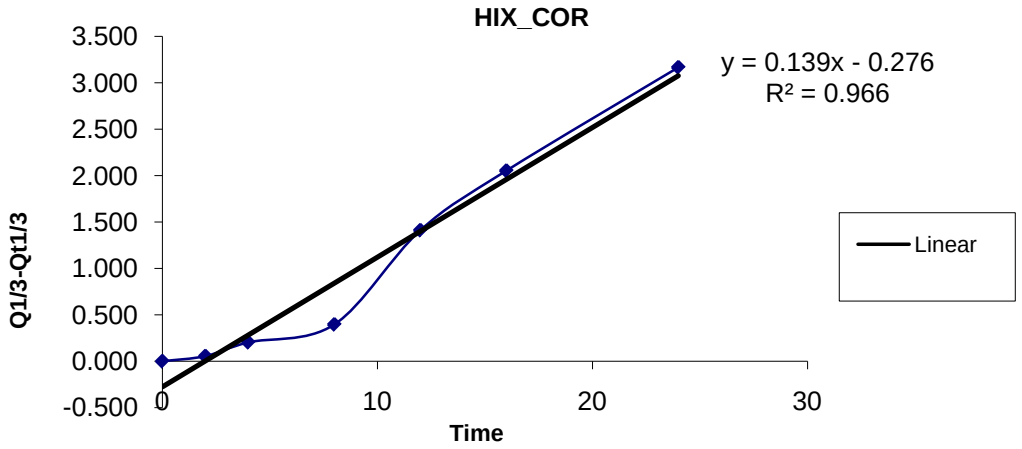


Fig 16. Drug release data of higher/medium concentration of PVP

7.5 Design of experiment:

The conduct of an experiment and the subsequent interpretation of its experimental outcome are the twin essential features of the general scientific methodology. This can be accomplished only if the experiments are carried out in a systematic way and the inferences are drawn accordingly. The theme of the DOE optimization methodology provides thought-through and thorough information on diverse DOE aspects organized in a seven-step sequence

The optimization study begins with Step I, where an endeavor is made to ascertain the initial drug delivery objective(s) in an explicit manner. Various main response parameters, which closely and pragmatically epitomize the objective(s), are chosen for the purpose. In Step II, the experimenter has several potential independent product and/or process variables to choose from. By executing a set of suitable screening techniques and designs, the formulator selects the vital few influential factors among the possible “so many” input variables. Before going to the more detailed study, experimental studies are undertaken to define the broad range of factor levels as well. During Step III, an apposite experimental design is worked out on the basis of the study objective(s), and the number and the *type* of factors, factor levels, and responses being explored. Working details on variegated vistas of the experimental designs, customarily required to implement the DOE optimization of drug delivery, have been elucidated in the subsequent section. Afterward, the response surface methodology (RSM) is characteristically employed to relate a response variable to the levels of input variables, and a design matrix is generated to guide the drug delivery scientist to choose optimal formulations. In Step IV, the drug delivery formulations are experimentally prepared according to the approved experimental design, and the chosen responses are evaluated. Later in Step V, a suitable mathematical model for the objective(s) under exploration is proposed, the experimental data thus obtained are analyzed accordingly, and the statistical significance of the proposed model discerned. Optimal formulation compositions are searched within the experimental domain, employing graphical or numerical techniques. This entire exercise is invariably executed with the help of pertinent

computer software. Step VI is the penultimate phase of the optimization exercise, involving the validation of the response prognostic ability of the model put forward.

The drug delivery performance of some studies, taken as the checkpoints, is assessed vis-à-vis that is predicted using RSM, and the results are critically compared. Finally, during Step VII, which is carried out in the industrial milieu, the process is scaled up and set forth ultimately for the production cycle.

The dissolution values at 2 hrs, 8 hrs and 24 hrs were fed into the DOE pro-excel software surface plots and interaction plots are shown in Fig.17-28 and Table No 17-24.

Table No 17: Design of experiment for 2 hrs

Formulation	Polymers		% drug release
	Ethyl cellulose	PEG-4000	
F2	15	5	7.54
F3	15	10	12.45
F4	15	15	27.09
F5	20	5	4.23
F6	20	10	5.87
F7	20	15	14.32
F8	25	5	0
F9	25	10	0.37
F10	25	15	3.29

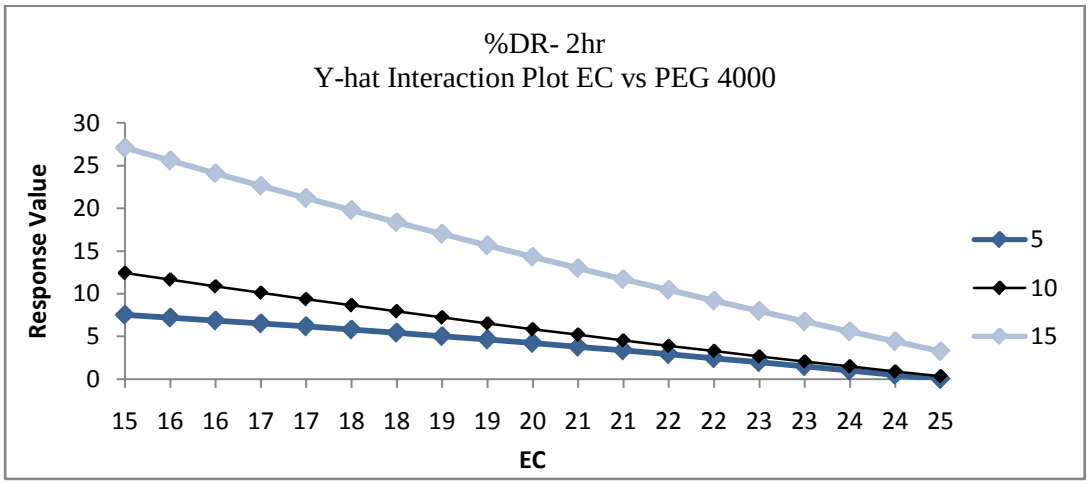


Fig 17. Interaction plot of 2 hrs

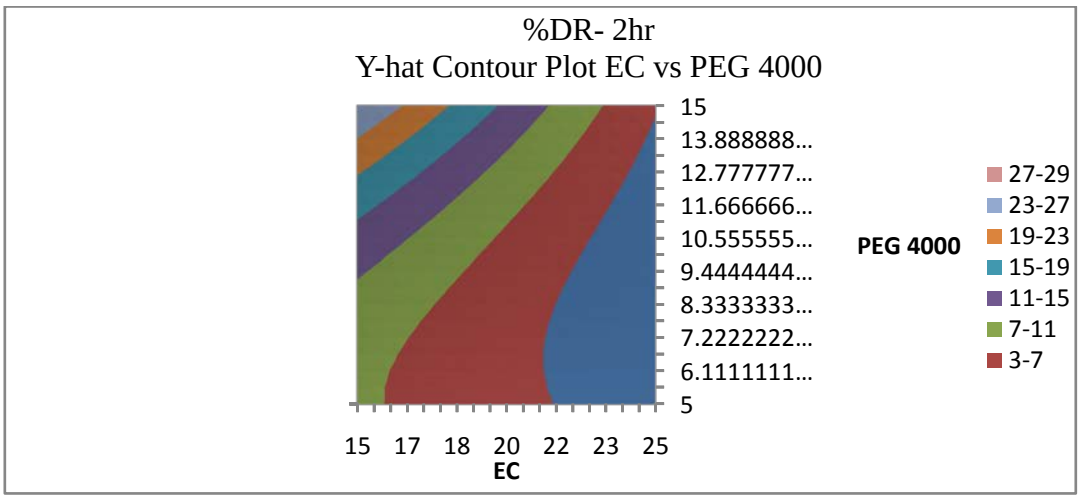


Fig 18. Surface plot of 2 hrs

Table No 18: Design of experiment for 8 hrs

Formulation	Polymers		% drug release
	Ethyl cellulose	PEG-4000	
F2	15	5	30.79
F3	15	10	62.67
F4	15	15	67.78
F5	20	5	28.44
F6	20	10	37.45
F7	20	15	43.08
F8	25	5	5.35
F9	25	10	13.49
F10	25	15	25.48

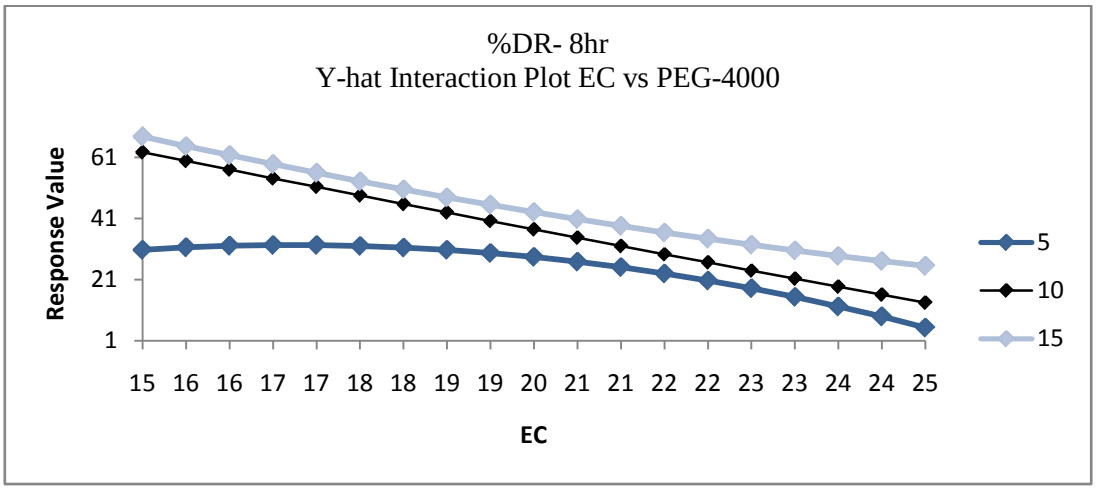


Fig 19. Interaction plot of 8 hrs

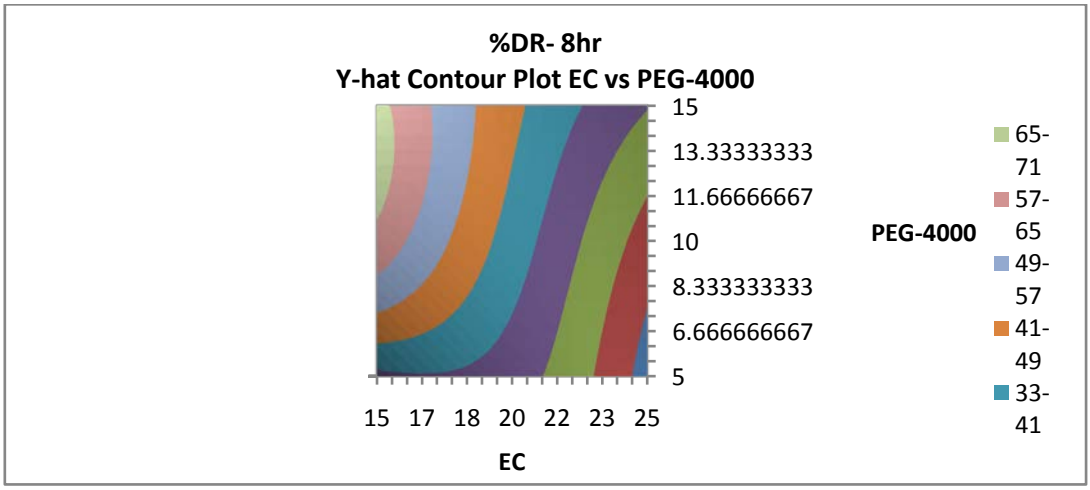


Fig 20. Surface plot of 8 hrs

Table No 19: Design of experiment for 24 hrs

Formulation	Polymers		% drug release
	Ethylcellulose	PEG-4000	
F2	15	5	84.28
F3	15	10	87.28
F4	15	15	87.54
F5	20	5	83.24
F6	20	10	85.28
F7	20	15	87.54
F8	25	5	55.87
F9	25	10	66.08
F10	25	15	78.09

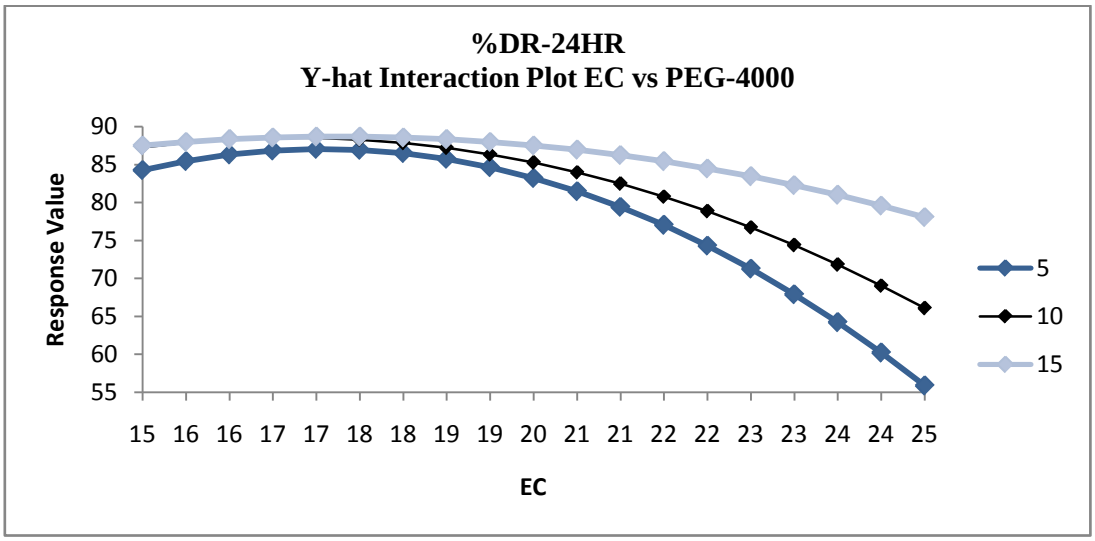


Fig 21. Interaction plot of 24 hrs

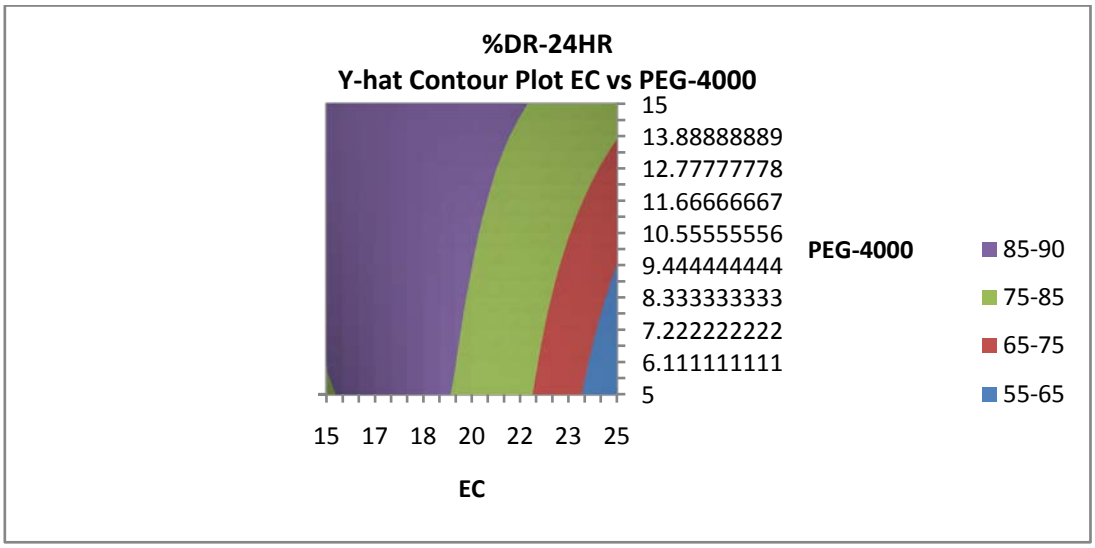


Fig 22. Surface plot of 24 hrs

Table No 20: Design space for glipizide controlled release pellets coated with ethyl cellulose using PEG- 4000 as pore former [9]

INGREDIENTS	LOW	MEDIUM	HIGH
Ethyl cellulose	19	20	21
Polyethylene glycol	13.8	14.2	14.5

Table No 21: Design of experiment for 2 hrs

Formulation	Polymers		% drug release
	Ethyl cellulose	Polyvinyl pyrrolidone	
F11	15	5	10.35
F12	15	10	20.23
F13	15	15	37
F14	20	5	3.23
F15	20	10	9.87
F16	20	15	24.32
F17	25	5	2.32
F18	25	10	3.54
F19	25	15	9.29

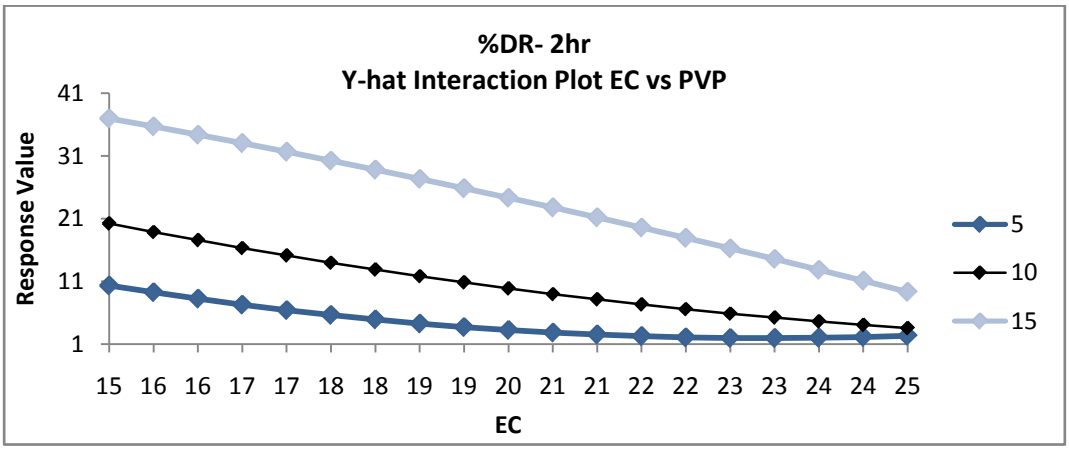


Fig 23. Interaction plot of 2 hrs

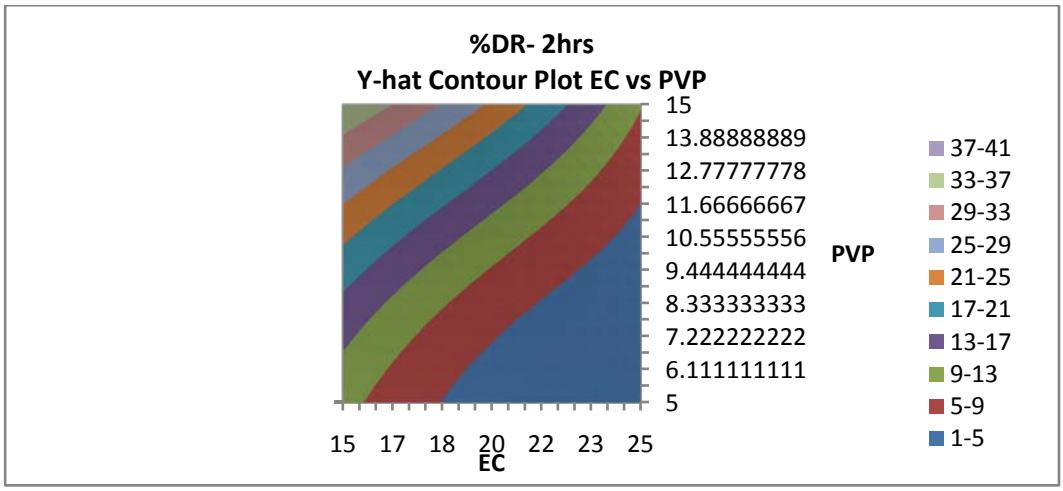


Fig 24. Surface plot of 2 hrs

Table No 22: Design of experiment for 8 hrs

Formulation	Polymers		% drug release
	Ethyl cellulose	PVP	
F11	15	5	44.79
F12	15	10	72.67
F13	15	15	87.78
F14	20	5	38.44
F15	20	10	47.45
F16	20	15	48.76
F17	25	5	10.35
F18	25	10	23.49
F19	25	15	65.48

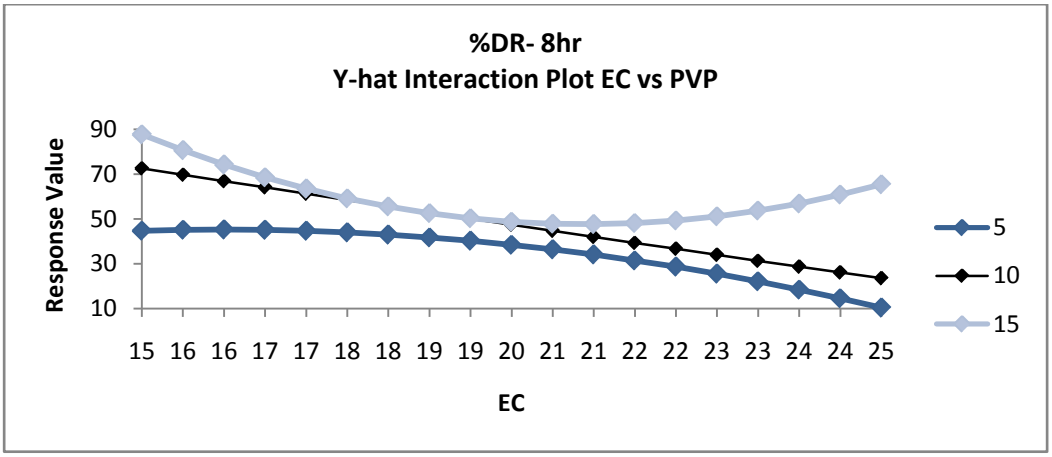


Fig 25. Interaction plot of 8 hrs

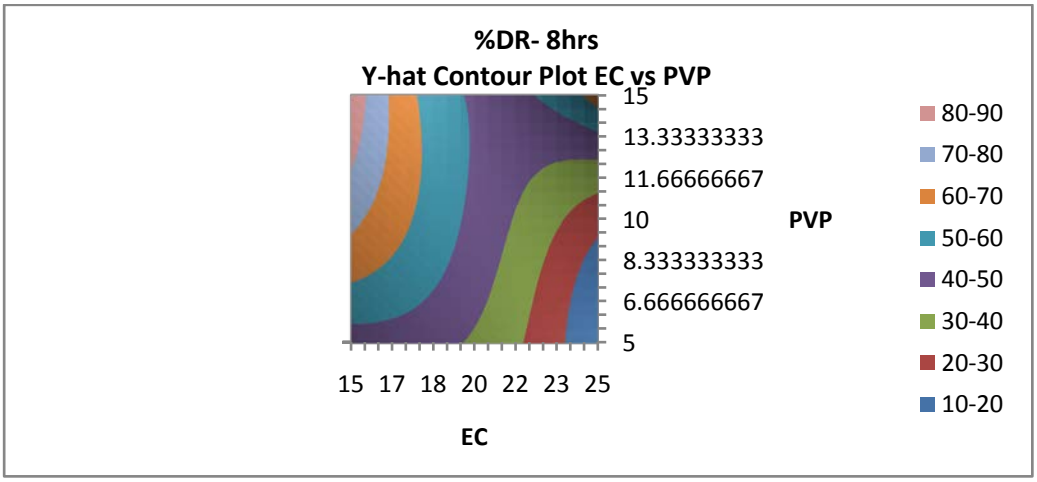


Fig 26. Surface plot of 8 hrs

Table No 23: Design of experiment for 24 hrs

Formulation	Polymers		% drug release
	Ethyl cellulose	PVP	
F11	15	5	100
F12	15	10	97.28
F13	15	15	96.54
F14	20	5	90.24
F15	20	10	93.09
F16	20	15	99.26
F17	25	5	75.08
F18	25	10	96.78
F19	25	15	90.45

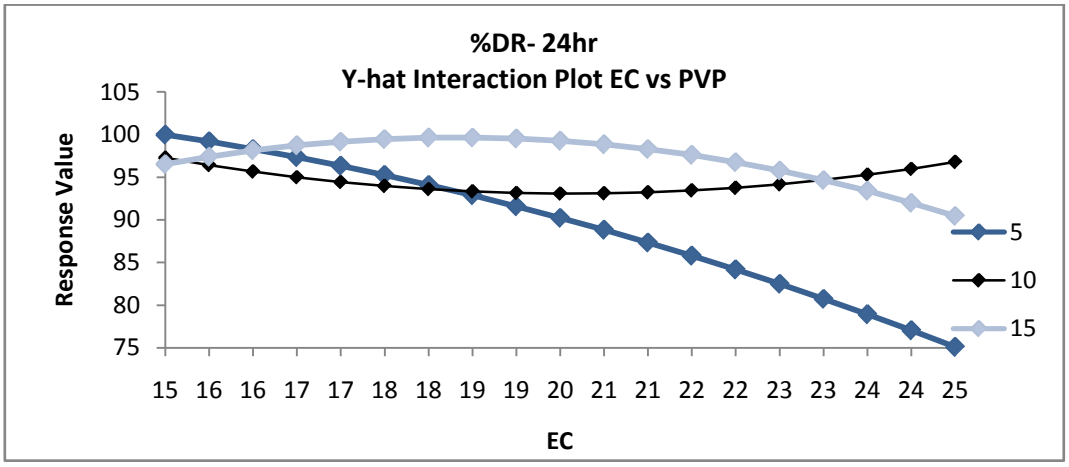


Fig 27. Interaction plot of 24 hrs

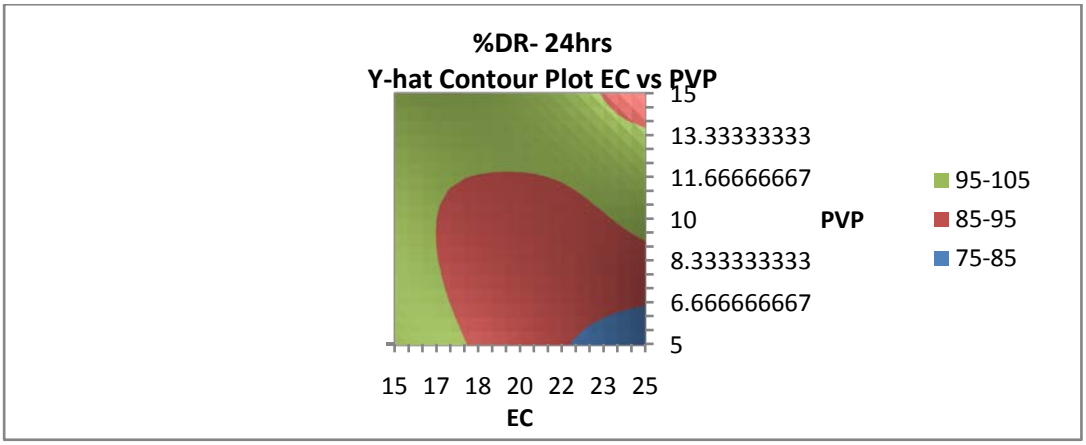


Fig 28. Surface plot of 24 hrs

Table No 24: Design space for glipizide controlled release pellets coated with ethyl cellulose using polyvinyl pyrrolidone as pore former [9]

INGREDIENTS	LOW	MEDIUM	HIGH
Ethyl cellulose	18	21	22
Polyvinyl pyrrolidone	6.6	9	11.67

7.6 Stability testing:

The following were considered as significant change

The stability studies were carried out according to ICH guidelines. The design and execution of the stability study followed the principles outlined in the ICH parent guidelines. The purpose of the study was to establish, based on testing a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar conditions. They were stored in air tight containers and placed in the humidity chamber at $40^{o}C \pm 2^{o}C/75\% \pm 5\%$ RH. The accelerated studies were carried out for three months and the testing frequency was at 0, 1, 2 and 3 months. The recommended storage condition for Climatic Zone IV was followed which was $40^{o}C \pm 2^{o}C/75\% \pm 5\%$ RH. The attributes tested were assay and dissolution profile. The real time study was done at $25°C \pm 2^{o}C$ /65% ± 5% RH.

- A 5% change in assay from initial value

- Failure to meet acceptance criteria for assay and dissolution profile. The guidance and recommendations detailed in the ICH guidelines to propose a retest or shelf life was followed. The scale up batch was fabricated by using the fluid bed processor as described previously, filled into size '2' hard gelatin capsules shells and subjected to evaluation for assay and dissolution profile testing. Capsules were filled in 90 cc white HDPE containers at 30 s count per container and loaded on to accelerated and real time stability study. The samples were withdrawn at 1, 2 and 3 months from the accelerated stability chamber and at 3 months from the real time stability chamber and subjected to evaluation. The batches selected for the stability

testing contained 100% of the label claim. The stability information presented includes results from physical, chemical and release profile tests. The attributes tested were assay and dissolution profile. Each attribute was assessed separately. The results are shown in Table No 25 and 26.

Table No 25: Formula for the scale up and reproducibility batch

S.No	Ingredient	Specification	Quantity
1	Non-pariel sugar seeds (g)	USP	61.5
2	Dichloromethane (ml)	USP	300
3	IPA (ml)	USP	700
4	Glipizide (g)	USP	15
5	HPMC 5cps (g)	USP	5
6	PEG – 400 (ml)	USP	1.0
7	ETHYL CELLULOSE (g)	USP	20
8	PVP K30 (g)	USP	7.5
9	Hard gelatin capsules shells size '2'		1

Table No 26:

S.NO			TIME (IN MONTHS)				
			At 40°C/ 75% RH				25°C/65% RH
			0	1 month	2 months	3 months	3 months
Assay (% drug content) (95% to 105%)			100.09	99.97	98.74	97.49	98.93
TARGET PRODUCT PROFILE							
	TIME (H)	Mean % drug released					
	0	0	0	0	0	0	0
	2	0-5	3.54	3.87	4.02	4.09	4.17
	4	10-30	12.58	10.74	19.41	19.27	10.13
	8	25-55	32.49	28.78	33.45	35.78	30.87
	16	65-85	72.64	79.76	75.17	81.21	77.33
	24	80-100	96.78	98.76	97.06	99.17	98.54

The F optimized formula was scaled up to 1000 Capsules.

- The pellets were filled in “2“size.
- Capsules were filled in HDPE containers and the cap was induction sealed.
- The containers were incubated at 25°C/ 65% RH and 40 ºC /75% RH.
- The samples were withdrawn at 1M, 2M and 3M time intervals for 40°C/ 75% RH and 3M for 25°C/ 65% RH and analyzed for % drug content.
- The data is compiled and compared with the initial values for % drug content and dissolution profile and found that the results are within the acceptable limits.

Assay:

The assay of the pellets selected and filled in capsules was determined individually at time intervals of 0, 1, 2 and 3 months. The assay was found to be 97.49 % at the end of 3 months. The dissolution profile matched the TPP till the end of 3 months. In case of real time study the assay at the end of 3 months was found to be 98.93 % and the dissolution profile matched the TPP till the end of 3 months.

8. SUMMARY AND CONCLUSION

Glipizide controlled release formulation is one of the most widely prescribed oral hypoglycemic agent. The innovator for product Glucotrol XL is based on the osmotic drug delivery platform and has a very peculiar dissolution profile. There is a two hours lag time in which less than 5% of the drug is targeted to be release followed by a zero order drug release at a rate of 3 to 7 % per hour. Ordinary matrix diffusion systems are very difficult to formulate for such type of specialized release rate requirements since these systems are based mainly on diffusion across swollen matrix.

The MUPS technology provides a unique platform to modulate the drug release to match the target release profile since it is possible to coat the pellets in a controlled manner with an polymer and a pore former.

In the current work, Glipizide controlled release product was developed using the MUPS platform, and ethyl cellulose as the membrane. The role of two water soluble polymers in modulating the drug release was evaluated using full factorial design of experiments.

The process followed for fabricating the dosage form was by first loading the drug on to pellets by using the fluid bed processor attached with bottom spray assembly. These pellets were then coated with either of the following:

(1) Ethyl cellulose: Weight gain 5% to 30%. This study was conducted to establish the level of coating required to completely seal the drug release. At 30% weight gain, the drug release was low over 24 hours.

(2) All further coatings were conducted up to 30% weight gain of the polymer.

(3) Full factorial 3^2 design of experiments was conducted by varying the levels of EC and PEG 4000 as pore former. The dissolution profile was conducted for all 9 batches and the values at 2, 8 and 24 hours were fed into DOE Pro XL software. The design space achieved was as given in below Table No 27.

Table No 27: Design space of PEG-4000

INGREDIENTS	LOW	MEDIUM	HIGH
Ethyl cellulose	19	20	21
Polyethyleneglycol4000	13.8	14.2	14.5

(4) Full factorial 3^2 design of experiments was conducted by varying the levels of EC and PVP as pore former. The dissolution profile was conducted for all 9 batches and the values at 2, 8 and 24 hours were fed into DOE Pro XL software. The design space achieved was as given in below Table No 28.

Table No 28: Design space of PVP

INGREDIENTS	LOW	MEDIUM	HIGH
Ethyl cellulose	18	21	22
Polyvinylpyrrolidone	6.6	9	11.67

(5) Based on the DOE experiments, it was established that PVP is a better pore former for Glipizide controlled release pellets as compared to PEG 4000. This may be due the fact that PVP acts as a solubilizer for the practically insoluble Glipizide.

(6) A reproducibility batch of 100 gram pellets was taken in which the drug loaded pellets were coated with 20% EC and 7.5% PVP .

(7) The pellets were filled in size ‘2’ hard gelatin capsules shells and subjected to accelerated stability studies for 3 months.

(8) The reproducibility and stability experiments indicate that it is possible to develop a controlled release product of Glipizide using the micro porous film platform and the MUPS platform with the product matching to the target product profile and having excellent reproducibility and stability.

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