DESIGN AND DEVELOPMENT OF IMMEDIATE RELEASE AND SUSTAINED RELEASE BI-LAYERED MATRIX TABLETS OF ORAL-HYPOGLYCEMIC DRUGS

Dissertation submitted to

The Tamilnadu Dr. M.G.R Medical University, Chennai

In partial fulfillment for the requirement of the degree of

MASTER OF PHARMACY

(Pharmaceutics)

SEPTEMBER-2012

DEPARTMENT OF PHARMACEUTICS

KMCH COLLEGE OF PHARMACY

KOVAI ESTATE, KALAPATTI ROAD, COIMBATORE-641048

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This is to certify that this dissertation work entitled **"DESIGN AND DEVELOPMENT OF IMMEDIATE RELEASE AND SUSTAINED RELEASE OF BI-LAYERED MATRIX TABLETS OF ORAL-HYPOGLYCEMIC DRUGS"** is a bonafide work carried out by **Reg. No: 26107116** under the guidance of **Mrs. J. Padmapreetha, M.Pharm.,** Assistant Professor, Dept of Pharmaceutics for the partial fulfillment for the Degree of Master of Pharmacy and is forward to The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

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DECLARATION

I do hereby declare that this dissertation entitled **"DESIGN AND DEVELOPMENT OF IMMEDIATE RELEASE AND SUSTAINED RELEASE BI-LAYERED MATRIX TABLETS OF ORAL-HYPOGLYCEMIC DRUGS"** submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** was done by me under the guidance of **Mrs. J. Padmapreetha, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year 2011 – 2012.

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN AND DEVELOPMENT OF IMMEDIATE RELEASE AND SUSTAINED RELEASE BI-LAYERED MATRIX TABLETS OF ORAL-HYPOGLYCEMIC DRUGS"** Submitted by **Reg. No:26107116** to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by the candidate at KMCH College of Pharmacy, Coimbatore, and was evaluated by us during the academic year 2011 – 2012.

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LIST OF ABBREVIATIONS

%	: Percentage
Mg	: Milligrams
pH	: Hydrogen ion concentration
HCl	: Hydrochloric Acid
BCS	: Biopharmaceutical Classification System
FTIR	: Fourier Transform Infra-Red Spectroscopy
C.I.	: Compressibility Index
°C	: Degree Centigrade
API	: Active Pharmaceutical Ingredient
NIDDM	: Non-Insulin Dependent Diabetic Mellitus
HPMC	: Hydroxypropyl Methylcellulose
DCL	: Directly Compressible Lactose
CCS	: Croscarmellose Sodium
CDR	: Cummulative Drug Release
IR Layer	: Immediate Release layer
SR layer	: Sustained Release layer
IR Graph	: Infra-Red Graph.
Ppm	: Parts per million
nm	: Nano meters
RMG	: Rapid Mixer Granulator
US FDA	: United States Food and Drug Administration
USP	: United States Pharmacopoeia
UK	: United Kingdom

% RH	: Percentage Relative Humidity
% RSD	: Percentage Relative Standard Deviation
NFD	: Non-Filling Detecting System
ICH	: International Conference for Harmonization
RPM	: Revolutions per minute
No	: Number

ABSTRACT

The aim of the work is to develop Bi-layered matrix tablets containing a Biguanide (API I) in SR layer and a Thiazolidinedione (API II) in IR layer. The formula is developed by taking In-*vitro* release of both the drugs in to consideration. HPMC K 4M, HPMC K 15M and HPMC K 100M were used as rate retarding polymers and Croscarmellose sodium as superdisintegrant for SR layer and IR layer respectively, in the trials for preparing an optimum formulation of the Bi-Layer tablets. Pre-formulation studies and Compatibility studies were found to be satisfactory. Tablet blend all formulations was evaluated for flow properties, which were found to be optimum. Tablet prepared were evaluated for several parameters like Thickness, Hardness, Weight variation, Friability, Drug content and In-*vitro* release of the drugs. Formulation F-7 was found to be an optimum formula with the release of the API I and API II within specifications. The release rate was found to be following First-order kinetics and mechanism is by combination of diffusion and erosion. Stability studies at conditions 30°C/ 65%RH and 40°C/75%RH are showing that the dosage form is intact after storage for 3 months at both the conditions. It can be concluded that Bi-layered tablets of these drugs are advantageous in having uniform drug content of both the drugs and the sustained release of the API I reduces the dosing frequency thereby improving patient compliance.

1. INTRODUCTION

Definition[1]:

Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated.

The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behaviour of the preparation in the digestive tract, colouring matter authorized by the competent authority and flavouring substances.

Classification of Tablets[2]:

Most commercial tablets are divided into two general classes, by whether they are made by compression or molding. Compressed tablets are prepared by large scale production methods, while molded tablets generally involve in small scale production. Various tablet types are listed below.

- Compressed tablets
- Molded tablets.

Compressed tablets are of again of following types:

- Sugar coated tablets.
- Film-coated tablets.
- Enteric coated tablets

- Multiple compressed tablets
- Controlled release tablets
- Tablets for solution
- Effervescent tablets
- Compressed Suppositories or inserts
- Buccal or sublingual tablets.

Molded tablets are also called as Tablet Triturates can be of two types. These are manufactured in small scale. Two types of Molded tablets are given below.

- Dispensing tablets
- Hypodermic tablets

Advantages of Tablets[3]:

Of all the oral solid dosage forms tablets are most commonly employed, tablet has several advantages:

- ✓ They are unit dosage forms, so they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and least content variability.
- ✓ Their cost is lowest of all dosage forms.
- ✓ They are lightest and most compact of all oral dosage forms.
- ✓ They are in general easiest and cheapest to package and ship of all oral dosage forms.
- ✓ Product identification is potentially the simplest and cheapest requiring no additional processing steps when employing an embossed or monogramming punch face.

- ✓ They lend themselves to certain special release profiles products, such as enteric or delayed release products.
- ✓ They are better suited to large scale production than other unit oral dosage forms.
- ✓ They have best combined properties of chemical, mechanical and microbiological stability of all dosage forms.

Disadvantages of Tablets[3]:

- ✓ Some of the drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- ✓ Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that still provide adequate or full drug availability.
- ✓ Tablets cannot be suggested for the patients with Dysphagia (difficulty in swallowing).

Multiple compressed tablets[1]:

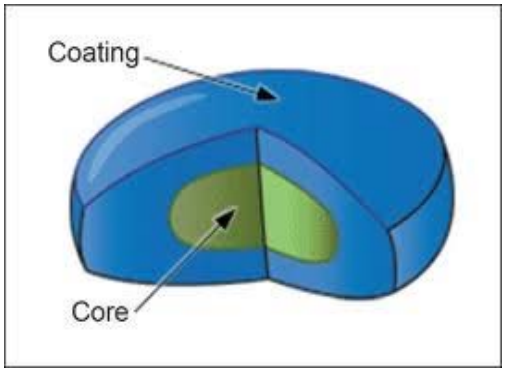
These are compressed tablets made by more than one compression cycle. This process is best used when there is need of separating active ingredients for stability purposes or if mixing is inadequate to guarantee uniform distribution of two or more active ingredients.

They are of two types again

- Layered tablets
- Press coated tablets.

Layered tablets: Layered tablets are formed by compressing the granules on previously compressed blend (First layer). This forms two layers and can be used for making tablets of multilayer. This requires Special Presses, when it comes to large scale manufacturing.

Press coated tablets: Press coated tablets are formed by compressing the granules having already compressed tablets in the core. This forms a dry coat over the core tablets. Special presses are developed for the large scale processes recently.



Core Coating

Layered tablets:

Bi-layered tablet are mostly explored by the pharmaceutical companies not just for the sake of extension of the patents and marketing of the drugs, but also for sake of Bi-modular release of the drugs and to incorporate two drugs in one tablet. There are many formulations of tablets comprising two drug molecules, but there is always possibility of interaction. Bi-layer tabletting is a better option of avoiding the interaction between two different classes of molecules.

Bi-layer tablets are having an advantage of accommodating the layers of two different kinetic profiles of a drug, of which one can be an *immediate release layer* and other a *prolonged release layer* ***(Chan, et al.,)[4].*** There are some works that have two drug molecules in different layers, one drug layer immediately releases and other drug layer is designed to release in delayed or extended time. (***Vaya, et al)[5].***

Preparing the bi-layered tablets is feasible with all desired parameters at small scale. But when transforming the process to a large scale process, the parameters desired are difficult and nearly impossible to obtain. To obtain desired bi-layered tablets, *special presses* are obviously required to avoid the risks like

- ✓ Improper weights of the individual layers.
- ✓ Separation of the layers.
- ✓ Cross-contamination of layers.
- ✓ Hardness problems.

Layered tablet press[6]:

In the earlier times the machines fed controlled volumes of each separate granulation on top of each other and compressed them together at one pressing station. The machines of later stages were engineered to compress each layer separately before deposition of next granulation, with a final compression for the complete tablet.

Wipe-off blades covering the entire face of the die have been installed not to allow the excess blend to circulate around the turret. The excess is directed in to pots at the side of the press and manually returned to the appropriate hopper. Suction pumps were used to remove any blend that escaped the scraper blades.

The latest refinement is has been the force feeders which retain the individual granulations. But some powder escapes from these also, and same arrangement as described is installed on the presses to prevent one granulation from contaminating the other.

In the operation of older type of machine, the granulation for the first layer is placed in the hopper, and the machine is adjusted until the desired weight is achieved with consistency; then the second hopper is filled with the granulation, and the same procedure is followed until the correct tablet weight is obtained. In this, the single-compression method, the delineation between the layers tends to be little uneven. It is also difficult to adjust the weight during the run.

Of the modern machines, there are two types which differ mainly in the way the layers are separated for weight and hardness checking. In one, the first layer is diverted from the machine. In the other, the first layer is made so hard that the second layer will not bond to it or will bond only weekly; upon ejection of complete tablet, the layers are separated and tested individually.

- A granulation is placed in the in the first hopper that flows in to the feed frame. The machine is started and the volume of granulation in the die is adjusted by the weight adjustment cam.
- The upper and lower punches are brought together by the pre-compression rolls. To form a weak compact. Part of lower cam track is raised hydraulically to eject the first layer, which is swept off the die table by the wipe-off blades affixed to the back edge of the second feeder.
- Samples are weighed and hardness is determined, when conditions are satisfactory, the ejection cam is lowered and the entire process is repeated for the second layer, using feed frame, weight adjusting cam tamping rolls and ejection cam and wipe-off blades.
- The weight of second layer is determined by the difference between the two weights.
- The leading and trailing edges of the feed frames are equipped with wipe-off blades which divert any powders that escape from the feeders in to the collection boxes. The blade of the trailing edge of first feed frame guides the completed tablet down the chute to the collection bin.
- If an adjustment in the weight or thickness of the first or second layer is necessary, then weight of each succeeding layer will probably need correction as weight is related to fill volume

gure 1: Double sided rotary press that can be tooled r Bi-layered compression of tablets; *Oystar by anesty.*

Diabetic Mellitus[7]:

Diabetes mellitus is a heterogeneous group of disorders characterized by abnormalities in carbohydrate, protein, and lipid metabolism. The central disturbance in diabetes mellitus is an abnormality in insulin production or action or both, although other factors can be involved. Hyperglycemia is a common end point for all types of diabetes mellitus and is the parameter that is measured to evaluate and manage the efficacy of diabetes therapy.

Diabetes mellitus has been traditionally classified into Insulin-dependent diabetes mellitus (IDDM), also known as type I (formerly called juvenile-onset diabetes mellitus), and non–insulin-dependent diabetes mellitus (NIDDM), also known as type II.

Type I Diabetes mellitus constitutes about 10% of cases of diabetes mellitus. The pathogenesis of type I diabetes is autoimmune destruction of the cells of the

pancreas. The factor or factors that trigger this autoimmune response are unknown. Predisposing factors appear to include certain major histocompatibility complex haplotypes and auto-antibodies to various islet cell antigens. The progression of the autoimmune response is characterized by lymphocytic infiltration and destruction of the pancreatic cells resulting in insulin deficiency.

Type II Diabetes mellitus, is far more common. In contrast to Type I, Type II is not an autoimmune process and may or may not be insulin dependent; that is, a diabetic state that is most effectively managed by insulin therapy. Frequently, NIDDM is used interchangeably with type II diabetes mellitus. The three major metabolic abnormalities that contribute to hyperglycemia in NIDDM are defective glucose-induced insulin secretion, increased hepatic glucose output, and inability of insulin to stimulate glucose uptake in peripheral target tissues.

There are several complications that arise due to Diabetes such as Diabetic Keto-acidosis, Macro-vascular diseases, Micro-angiopathy, dysfunction of vascular endothelium. There is a risk of formation of oxygen derived free radicals. Chronic renal failure is another complication where Diabetes becomes a reason.

Management of Diabetes Mellitus:

WHO provides guidelines for the management of Diabetes Mellitus. It was suggested that the major components[8] of treatment of Diabetes are

- Diet with exercise
- Oral-Hypoglycemic drugs.
- Insulin.

Type 2 diabetes is a syndrome characterized by insulin deficiency, insulin resistance and increased hepatic glucose output. Medications used to treat Type 2 Diabetes are designed to correct one or more of these metabolic abnormalities[7]. Currently, there are five distinct classes of hypoglycemic agents available, each class displaying unique pharmacologic properties. There are five important classes of Oral Hypoglycemic drugs namely,

- Sulfonylureas
- Biguanides
- Meglitinides
- Thiazolidinediones
- Alpha-Glucosidase inhibitors.

Sulfonylureas	**Biguanides**	**Meglitinides**	**Thiazolidinediones**	**α-Glucosidase inhibitors**
First generation: Tolbutamide, Acetohexamide, Chlorpropamide	Metformin	Repaglinide, Nateglinide	Pioglitazone, Rosiglitazone	Acarbose, Voglibose, Miglitol
Second generation: Glimipride, Glyburide, Gliclazide				

TABLE 1 Showing various classes of Oral-Hypoglycemic drugs.

Combination of Oral-Hypoglycemic Drugs[9]:

If adequate control is not obtained with the use of a single agent, combination therapy is an option. Several of the available oral agents have been studied in combination and have been shown to further improve glucose control when compared to monotherapy. As with monotherapy, the choice of a second agent should be based on individual characteristics. Reasonable combinations of agents include the following,

- Sulfonylurea+ Biguanide or Thiazolidinedione or Alpha Glucosidase inhibitors.
- Biguanide+ Meglitinide
- Biguanide + Thiazolididnedione
- Biguanide + Alpha- glucosidase inhibitors.

Triple combination is therapy is done with:

- Sulfonylurea + Biguanide + Thiazolidinedione.
- Sulfonylurea + Biguanide + Alpha-Glucosidase inhibitors.

Biguanides[7] does not affect insulin secretion but requires the presence of insulin to be effective. The exact mechanism of Biguanide's action is not clear, but it does decrease hepatic glucose production and increase peripheral glucose uptake. When used as monotherapy, Biguanides rarely causes hypoglycemia.

Thiazolidinediones[7] (sometimes termed glitazones) are a novel class of drugs that were initially identified for their insulin-sensitizing properties. They all act to decrease insulin resistance and enhance insulin action in target tissues. Thiazolidinediones activate the nuclear peroxisome proliferator–activated receptor (PPAR), a nuclear orphan receptor that is predominantly expressed in adipose tissue and to a lesser extent in muscle, liver, and other tissues.

Biguanides act by inhibiting the hepatic glucose output and to a lesser extent by enhancing the Insulin sensitivity in hepatic and some peripheral tissues. The glucose level in the body is found to be reduced up to 50 to 70 mg/dL. ***Thiazolidinediones*** act by increasing the sensitivity in the Adipose tissues and muscles and to a lesser extent by reducing the hepatic output of glucose.

These are found to be reducing the hepatic glucose by 25 to 50 mg/dL. So it can be implied that combination of these two classes can have Synergistic effect over glucose regulation.

SUSTAINED RELEASE FORMULATIONS:

During a course of therapy, patient is advised to take medicines more than once a day. This can be because of fast elimination of the drug from the body. To maintain the drug concentration within the therapeutic range, there would be a need of administration of drug for more than once a day. Patients with multiple drug regimens and with several dosing intervals are usually non-compliant with the therapy. There is also a fluctuation observed in case of multiple dosing of a drug. The therapeutic effect cannot be achieved.

The solution for this is achieved by the Sustained release formulations where the release of drug is manipulated in such a way that the concentration of drug will be in the therapeutic window for longer durations than the conventional drug delivery systems.

There are several advantages that make sustained drug delivery a choice of drug delivery systems:

- The therapeutic effect of drug can be enhanced at lower concentrations.
- The adverse effects can be minimized.
- Frequency of dosing can be minimized.
- Improvement of patient compliance.

The release of drug form a system can be controlled either[13]

❖ ***By forming a Membrane around***[10] the Dosage form that sustains the release of drug by forming a layer that retards the release form the core. Polymers are employed, in forming the membrane around the dosage form. Polymeric membrane can be a Micro-porous, Non-porous or a semi-permeable membrane. A polymer like Ethylene-vinyl acetate copolymer is found to be used in many formulations as polymer membrane to control the release in several products.

The equation[13] that explains several variables that influence release from this kind of system:

$$\frac{Q}{t} = \frac{K_{m/r} K_{a/m} D_d D_m}{K_{m/r} D_m h_d + K_{a/m} D_d h_m} C_R$$

Where Km/r and Ka/m are, respectively, the partition co-efficients for the interfacial partitioning of drug molecules from the reservoir to the membrane and from the membrane to the aqueous diffusion layer; Dm, and Dd are, respectively, the diffusion coefficients in the rate-controlling membrane with a thickness of h_m, and in the aqueous diffusion layer with a thickness of h_d.

❖ Another technique of controlling the rate of drug from the dosage is by forming a ***matrix around the drug molecules*** *with Lipophilic or Hydrophilic polymers*. This can be achieved by dispersion of the drug particles blend in the semisolid polymer and then cross-linking of the polymer chains. By Kneading the polymer with the drug particles well that forms a matrix on contact with the water (Hydroxy Propyl Methyl Celluloses). Melt extrusion is also used in fabricating the polymer matrix systems.

The equation that explains several variables that influence release from this kind of system:

$$\frac{dQ}{dt} = \frac{K_{a/r} D_a}{h_a(t)} C_p(h_a)$$

In which the time-dependent thickness [$h_a(t)$] of the diffusional path for drug molecules to diffuse through, which is increasing with time, is compensated by the proportional increase in the drug-loading level [$C_p(h_a)$],and a constant drug release profile is thus obtained.

❖ A technique includes the ***combination of both the Membrane permeation system and Matrix systems.*** The core would be a matrix comprising of Polymer matrix and the membrane is employed for further regulation of drug release.

The equation that explains several variables that influence release from this kind of system:

$$\frac{dQ}{dt} = \frac{AC_pD_p}{\left[D_pK_m(1/P_m + 1/P_d\right]^2 + 4AC_pD_pt^{1/2}}$$

where A is the initial amount of drug solid impregnated in a unit volume of polymer matrix with solubility C_p and diffusivity D_p; Km is the partition coefficient for the interfacial partitioning of drug molecules from polymer matrix toward polymer coating membrane; P_m is the permeability coefficient of the polymer coating membrane with thickness h_m; and P_d is the permeability coefficient of the hydrodynamic diffusion layer with thickness h_d

❖ ***Micro-reservoir systems*** are another way regulating the release of the drug from the dosage forms. This includes fabrication of several micro-reservoirs, by dispersing solid drug particles in a water miscible polymer and again dispersing this matrix in another polymer that forms several micro-reservoirs which is bio-compatible in nature.

The equation that explains several variables that influence release from this kind of system:

$$\frac{dQ}{dt} = \frac{D_p D_d m K_p}{D_p h_d + D_d h_p m K_p} \times \left[n S_p - \frac{D_l S_l (1-n)}{h_t} \left(\frac{1}{K_l} + \frac{1}{K_m} \right) \right]$$

Where m = a/b and n is the ratio of drug concentration at the inner edge of the interfacial barrier over the drug solubility in the polymer matrix,[1,6] in which a is the ratio of drug concentration in the bulk of elution solution over drug solubility in the same medium and b is the ratio of drug concentration at the outer edge of the polymer coating membrane over drug solubility in the same polymer and S_l and S_p are the solubility of the drug in the liquid compartments and in the polymer matrix, respectively.

A drug molecule that is having high solubility, small elimination half-life, which is usually administered for more than once a day is suitable for formulating in to a sustained release formulation.

Conclusion:

Keeping everything in a nutshell, it can be noted that Bi-layered tablets can be an ideal carrier for drugs that are usually prescribed in Combinational therapy. Thiazolidinedone and Biguanides are suitable candidates for Bi-layered tabletting. As Biguanides usually have shorter half life and are administered for more than three times a day, Biguanide is selected as drug candidate for sustained release layer. Thiazolidinediones are having higher half-lives and so selected as drug candidate for immediate release layer in the Bi-layered tablets

2. OBJECTIVE AND PLAN OF WORK

AIM:

The aim of the work is to design and develop Bi-layered matrix tablets comprising of a Thiazolidinedione derivative in the immediate release layer and a Biguanide in the Sustained release layer and to carry out the In *vitro* release study of the drugs.

The objectives which were destined to achieve during the work are:

- Bi-layered tablets with good physical strength.
- Tablets with correct content of active pharmaceutical ingredients without variation.
- To obtain optimal sustained release of the drug in the First layer and optimal release from the Immediate release layer.

PLAN OF WORK:

- Literature survey
- Pre-formulation studies:
  API characterization and
  Drug-Excipients compatibility studies.
- Optimization of the formula that results all the desired physical characteristics.
- Pre-Formulation analysis like
  1. Angle of repose
  2. Bulk density
  3. Tapped density
  4. Compressibility index
  5. Hausner's ratio
- Post- Compression analysis of tablets to know the parameters like Hardness, Uniformity of weight, Dimensions, %Friability, and amount of drugs in the units.
- In *vitro* dissolution study and
- Analysis of data to know the kinetic pattern of the drug.
- Stability studies to be done on the optimized formula at two conditions 45°C/75% RH and 30°C/65%RH.

3. LITERATURE REVIEW

- ***Naeem et al*** [11]developed and characterized bi-layered tablets of Tramadol HCl and Acetaminophen micro particles in which they have used Ethylcellulose as drug release retarding polymer. The micro particles were prepared separately and were compressed as Bi-layered tablets. The release of drug was observed for 8 hours and 12 hours where the formulations followed Higuchi's pattern of controlled release. Although a conventional solid dosage combination of TmH and AAP has been approved by the United States Food and Drug Administration (FDA) for use, patients still have to take the conventional tablets 3 - 4times a day. To improve patient's compliance, a controlled-released combination was developed and characterized in this study for its physical and chemical stability as well as for release characteristics.
- ***Laxmi Goswami et al [12].*** Formulated and evaluated Bi-layered floating tablets of two anti-diabetic drugs to increase the gastric residence time of a drug in one layer and to release another drug immediately from second layer. They have carried out the work by using HPMC, Carbapol, Polyvinylpyrrolidone as chief ingredients. The formulated tablets were subjected for In *vitro* studies which were carried out in USP Type II apparatus. The tablets were found to be buoyant for 12-20 hrs.
- ***Durga Prasad Pattanayak et. al.[13]*** formulated bilayered tablets comprising Metformin and Glimipride, where they have optimized the blends of both the layers separately. They have used HPMC and Polyethylene oxide for sustaining the drug release for about 24 hours. Form the stability profile they have concluded that HPMC based formulations are found to be giving better

release profile than that of PEO. Those formulations also exhibited Zero-order release ki*netics.*

- ***Bhala chirag et al*** [14]**.** Formulated and evaluated bilayered tablets of two model Anti-Diabetic drugs by using HPMC K 4M for sustained release layer and Croscaramellose Sodium for Immediate release layer. the work suggests that the increase concentration of the polymer brought about the sustained release effect of drug in the Sustained release layer. They have used wet granulation for sake of sustained release layer and direct mixing for immediate release layer. The sustained release followed Higuchi's kinetic pattern. Thay have concluded that Bi-layered tablets can be a good alternative for conventional tablets of the model Anti-Diabetic drugs.
- ***Dhaval Patel et.al.***[15] formulated and evaluated Bi-layered floating tablets for Gastric retention of Ciprofloxacin HCl. Both the layers were prepared by direct compression. HPMC K 15M and Carbapol 934P were used for sustained release of drug. Sodium bicarbonate was used for producing the floating effect. Sodium starch glycolate was used for immediate release layer. They have concluded that Carbapol 934 P and HPMC K 15M gave a desired kinetic profile for the Immediate release layer and Sodium bicarbonate produced optimum Lag time for obtaining the release profile for 12h.
- ***Pankaj et al***[16]**.** designed and developed a Bi-layered tablets formulation of Simvastatin. HPMC (104) was used for the sake of Suatined release layer and Croscaramellose sodium and Sodium starch glycolate for the immediate release layer. They have concluded that Bi-layered tablets are good application for sustaining the drug release and also releasing the drug immediately from a single dosage form.

- ***Preeti Karwa et al***[17] designed and evaluated the release of the Bi-layered tablets of Zolpidem Tartarate. HPMC K 100M was used for retarding the release in the sustained release layer and Croscaramellose sodium for the sake of immediate release in the immediate release layer. HPMC K 100M was found to be retarding the release of the drug for 6 hours. The release profile was found to be fitting Korsmeyer-Peppas kinetic model and Quasi-Fickian diffusion.
- ***Mohana Raghava Srivalli et al***[18]**.** designed novel Bi-layered gastric muco-adhesive systems for localized and unidirectional release of Lamotrigine. Carbapol 974 p and Polyox were used for Muco-adhesion and HPMC K 15M was used for control release of the drug. The formulations were evaluated for the ex*vivo* mocoadhesion and also for In *vitro* release of the drug. The formulations were found to be giving optimal muco-adhesion and also controlled release. It was also concluded that uni-directional release of the drug is possible.
- ***Sharad Darandale et. al***[19] designed and characterized a Gastroretentive dosage form consisting of Furosemide. The dosage consists of two layers in which one layer is controlled release formulation (CR layer) and an IR layer. These are muco-adhesive films that are placed in capsule, adhere to mucosa after swelling. Controlled release of the drug was brought by the Hydroxypropyl β-cyclodextrins in both layers and Carbapol 971P in CR layer. Optimum release, Bio-adhesion and mechanical properties were also the result of incorporation of these polymers.
- ***Kiran musle et al***[20] designed and formulated Bi-layered tablets of Paracetamol and Diclofenac sodium, where the former drug in immediate

release layer and latter in to sustained release layer. HPMC K 4M was used as release rate retard agent. It is stated that for combiaton therapy Bi-layered tablets are better alternatives for multiple drug dosage form intake.

- ***Rajendran et al*[21].** formulated and evaluated Bi-layered tablets of Anti-diabetic drugs in which one drug is incorporated in sustained release layer for prolonged effect by using HPMC K 100M and HPMC K 100M as rate retardants of release of the drug. Second layer is an immediate release layer with Croscaramellose sodium and Sodium starch glycolate as Superdisintegrants. The formulations comprising HPMC K 100M and HPMC K 15M in combination were fopund to be giving optimum release profile for drug in sustained release layer. The release of the drug is observed up to 8 hours. The release profile fits in to Higuchi's kinetic model for drug release.
- ***Mohammed Mofizur Rahman et al*[22]** formulated and evaluated matrix tablets of Ranolazine with Eudragit L 55 100 and with different viscosity grades of HPMC polymers (Methocel E50 and Methocel K 15M CR). The dissolution study was done 2h in simulated gastric fluid and for 6h in pH 6.8 phosphate buffer. It was stated that by increasing the concentration of polymers, there was a decrease in the rate of release of the drug. Further it was found that the release from formulations containing Eudragit L 55 100 and high viscosity grades of HPMC is slower than that of the low viscosity grades of HPMC (Methocel E50).
- ***Maggi et al*[23]** studies compared the capabilities of PEO with two different grades of HPMC polymers in case rate controlling of drug release. They have employed these polymers in different polymers where only the concentrations

are varying by having other parameters constant. They concluded that HPMC polymers retarded the release of drug better that of PEO polymers.

- ***Mohamed Halith et al***[24] formulated Bi-layered tablets of Amlodipine Besilate and Metoprolol Succinate by having the former in the SR layer and the latter in IR layer. HPMC was used as release retardant and Sodium Starch Glycolate as superdisintegrant. The release of drug in the SR layer was studies for 20 hrs. It was found to be following Zero-order kinetics.
- ***Patel Naveen et. al.***[25] designed and formulated Floating matrix tablets of Metoprolol Tartrate in a view of increasing its gastric residence time. HPMC K 100M was used as release retarding agent. It was concluded that the formulations with higher percentages of HPMC K 100M decreased the release rate of the drug than the formulations with HPMC K100M in lower percentages.
- ***Beatriz Luna et. al .***[26] have suggested in their article that combination of a Biguanide and Thiazolidinedione derivatives for a synergestic action in control of elevated Glucose levels. It was suggested that this combinational therapy is advised when there are no predicted results from single Oral Anti-Diabetic agent.
- ***Patel Mehul***[27] reviewed challenges in formulation of Bi-layered tablets. It was suggested that Bi-layered tablets are purpose-built Bi-layered tablet presses are of good choice to preclude several problems during manufacturing process like Layer separation, insufficient hardness, and inaccurate weight control of individual layers and cross contamination. It was concluded that whenever high-quality bi-layer tablets need to be produced at high speed, the use of an ‘air compensator’ in combination with displacement control appears

to be the best solution. The sensitivity of the displacement-based control system increases as pre-compression force decreases, resulting in a higher accuracy.

- ***Kumara Swamy et. al.***[28] formulated and evaluated the Oro-dispersible tablets of Theophylline using various superdisintegrants. Oro-dispersible tablets were prepared with superdisintegrants Crosscaramellose sodium, Crosspovidone, Sodium starch glycolate with concentarations 2%, 3% and 5%. Formulations with 5% superdisintegrants have shown good disintegrant effects. Formulations with Croscaramellose Sodium and Crosspovidone have shown good dissolution profiles and less disintegration time.

MATERIALS USED FOR STUDY

MATERIAL	SOURCE
API I	Wanbury limited
API II	Biocon limited
Hydroxypropyl Methycellulose K 100M	DOW chemicals / Colorcon Asia
Hydroxypropyl Methycellulose 15CPS	Taian Ruitai Cellulose Co., Ltd
Croscaramellose sodium	DMV Fonterra Ltd.
Sodium Carboxy Methyl Cellulose	Pioma Chemicals
Di-Basic Calcium Phosphate	Sudeep pharma
Povidone	BASF Ltd.
Low-substituted Hydroxy Propyl Cellulose	Aqualon Ltd
Lactose	DMV Fonterra Ltd.
Colloidal Silicon Dioxide	Wacker Silicones
Talc	Luzenac Ltd.
Indigo Caramine Lake	Roha dye chem..
Magnesium stearate	Amishi drugs and chemicals

EQUIPMENTS USED FOR THE STUDY

INSTRUMENTS	MAKE
Top loading balance	Sartorius
Rapid Mixer Granulator	Allen-Bradley
Octagonal Blender	PAM Machineries
Rapid Dryer	Retsch T-200
8-station Bi-layer Tablet Press	Rimek
Mechanical Stirrer	Remi Motor
Tap density testing apparatus	Electrolab
Hardness tester	Schleuniger 8M Tablet tester
Friability testing apparatus	Electrolab
Disintegration time testing apparatus	Electrolab
Moisture Balance	Sartorius
Analytical Balance	Sartorius
Dissolution apparatus	Lab India Disso 2000
High Performance Liquid Chromatography	SHIMADZU LC 2010 C HT
FTIR	IR PRESTIGE 21

API I[29, 30, 31]

Category : Oral Anti-Hyperglycemic drug.

Description : White crystalline powder.

BCS classification : Class III drug.

Physico-chemical properties

Solubility : Freely soluble in water, slightly soluble in ethanol, Insoluble in Acetone, Chloroform

pKa : 12.4

Mechanism of action: Decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for the drug's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Its administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake

Pharmacokinetics

Absorption : Absorbed over 6 hours, bioavailability is 50 to 60% under fasting conditions. Administration along with food decreases and delays absorption.

Volume of Distribution : 654 L for 850 mg administered as a single dose. The volume of distribution following IV administration is 63-276 L, likely due to less binding in the GI tract and/or different methods used to determine volume of distribution. Peak action occurs 3 hours after oral administration.

Excretion : Approximately 90% of the drug is eliminated in 24 hours in those with healthy renal function. Renal clearance of the drug is approximately 3.5 times that of creatinine clearance, indicating the tubular secretion is the primary mode of elimination.

Half-life : 6.2 hours. Duration of action is 8-12 hours.

Dosage : The maximum recommended daily dose in adults is 2000 mg.

Indications : For use as an adjunct to diet and exercise in adult patients (18 years and older) with NIDDM. May also be used for the management of metabolic and reproductive abnormalities associated with polycystic ovary syndrome (PCOS).

Side effects : Diarrhoea, Nausea, Gas, Weakness and indigestion are some of the side effects.

API-II[29, 30, 31]

Category : Oral Anti-Hyperglycemic drugs.

BCS Classification : Class IV drug

Description : White crystalline powder.

Dosage : 15mg and 30mg upto 45mg

Solubility : Practically insoluble in water, ether. Soluble in Di-methyl formamide,

very slightly soluble in Acetonitrile.

Mechanism of action: This acts as an agonist at peroxisome proliferator activated receptors (PPAR) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors increases the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In this way, it both enhances tissue sensitivity to insulin and reduces hepatic gluconeogenesis. Thus, insulin resistance associated with type 2 diabetes mellitus is improved without an increase in insulin secretion by pancreatic β cells.

Pharmacokinetics

Absorption : Following oral administration, in the fasting state, it is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours.

Volume of distribution: 0.63 ± 0.41 L/kg.

Metabolism : This undergoes Hepatic metabolism.

Excretion : This is found to be eliminated unchanged by the Biliary excretion. The renal excretion is said to be negligible.

Half-Life : 3-7 hours.

Indications : Treatment of Type II diabetes mellitus.

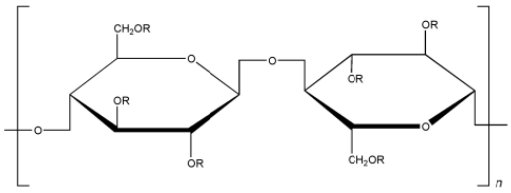
Side effects : Sore throat, weight gain, muscle pain, tooth problems are likely to occur.

6. EXCIPIENT PROFILES[32]

HYPROMELLOSE

Synonyms: Hydroxypropyl methylcellulose, HPMC, Methocel, methylcellulose propylene glycol ether.

Molecular Structure:



Where R is H, CH_3, or CH_3CH (OH) CH2

Category: Rate-controlling polymer for sustained release, stabilizing agent, viscosity-increasing agent.

Description: Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Solubility: Soluble in cold water; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and Dichloro-methane, and mixtures of water and alcohol.

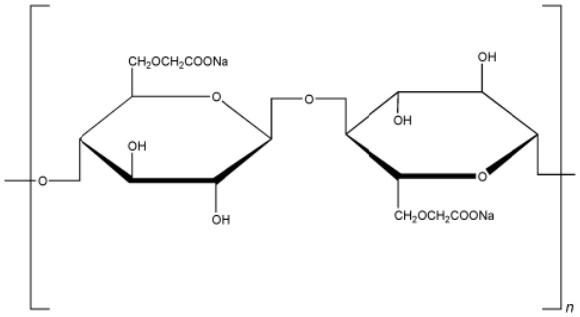
Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Storage: Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

SODIUM CARBOXY METHYLCELLULOSE

Synonyms: Akucell; Aquasorb; Blanose; cellulose gum; CMC sodium; SCMC; sodium carboxymethylcellulose.

Molecular Structure:



Functional Category: Tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

Description: Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular powder.

Solubility: Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear colloidal solutions. The aqueous solubility varies with the degree of substitution.

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose sodium may be irritant to the eyes. Eye protection is recommended.

Storage: The bulk material should be stored in a well-closed container in a cool, dry place.

DIBASIC-CALCIUM PHOSPHATE

Synonyms: A-TAB; calcium monohydrogen phosphate; calcium orthophosphate; *Di-CafosAN*; Dicalcium orthophosphate; E341; Emcompress Anhydrous; Fujicalin; phosphoric acid calcium salt (1 : 1); secondary calcium phosphate.

Structural Formula: $CaHPO_4$

Category: Tablet and capsule diluent**.**

Description: Anhydrous dibasic calcium phosphate is a white, odorless, tasteless powder or Crystalline solid. It occurs as triclinic crystals.

Solubility: Practically insoluble in ether, ethanol, and water; soluble in dilute acids.

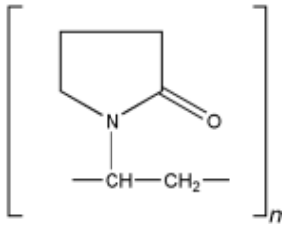
Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. The fine-milled grades can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

Storage Conditions: The bulk material should be stored in a well-closed container in a dry place.

POVIDONE

Synonyms: Kollidon; Plasdone;; Polyvidone; Polyvinylpyrrolidone; PVP.

Structural Formula:



Functional Category: Disintegrant; dissolution aid; suspending agent; tablet binder.

Description: Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Storage Conditions: Povidone may be stored under ordinary conditions. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

COLLOIDAL SILICON DIOXIDE

Synonyms: Aerosil; Cab-O-Sil; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed.

Structural Formula: SiO_2

Functional Category: Adsorbent; anticaking agent; emulsion stabilizer; glidant; Suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Description: Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersionwith water.

Handling Precautions: Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. In the absence of suitable containment facilities, a dust mask should be worn when handling small quantities of material. For larger quantities, a dust respirator is recommended. Inhalation of colloidal silicon dioxide dust may cause irritation to the respiratory tract but it is not associated with fibrosis of the lungs (silicosis), which can occur upon exposure to crystalline silica.

Storage Conditions: Colloidal silicon dioxide powder should be stored in a well-closed container.

TALC

Synonyms: Altalc; Hydrous magnesium calcium silicate; Hydrous magnesium silicate; Magnesium hydrogen metasilicate; Magsil Osmanthus; Powdered talc; Purified French chalk; Purtalc; Soapstone; Steatite.

Structural Formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional Category: Anticaking agent; glidant; tablet and capsule lubricant.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. In the UK, the occupational exposure limit for talc is 1 mg/m^3 of respirable dust long-term (8-hour TWA). Eye protection, gloves, and a respirator are recommended.

Storage Conditions: Talc should be stored in a well-closed container in a cool, dry place.

MAGNESIUM STEARATE

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Structural Formula: $[CH_3 (CH_2)_{16}COO]_{2Mg}$

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functional Category: Tablet and capsule lubricant

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

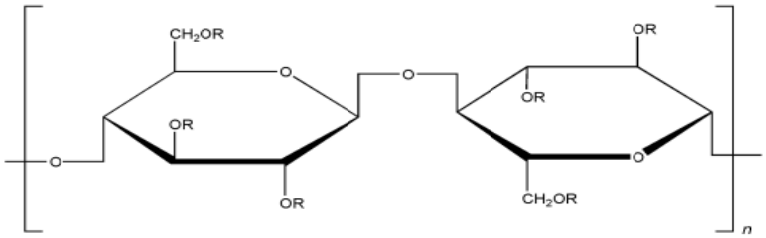
Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

Storage Conditions: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

HYDROXYPROPYL CELLULOSE, Low-substituted

Synonyms: Hyprolose, low-substituted; *L-HPC*.

Structural Formula:



R is H or $[CH_2CH(CH_3)O]_mH$

Functional Category: Tablet and capsule disintegrant; tablet binder.

Description: Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor, and it is tasteless.

Solubility: *Practically insoluble in ethanol (95%) and in ether. Dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution. Insoluble,but swells in water.*

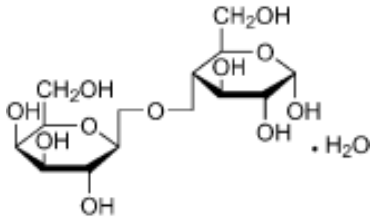
Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be avoided to minimize the risk of explosions.

Storage Conditions: Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well-closed container.

LACTOSE

Synonyms: Pharmatose DCL 15 CapsuLac, GranuLac, Tablettose, Lactose Monohydrate PrismaLac

Structural Formula:



α-Lactose monohydrate

Functional Category: Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

Description: Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

Solubility: Practically insoluble in ethanol, chloroform, ether. Slightly soluble in water

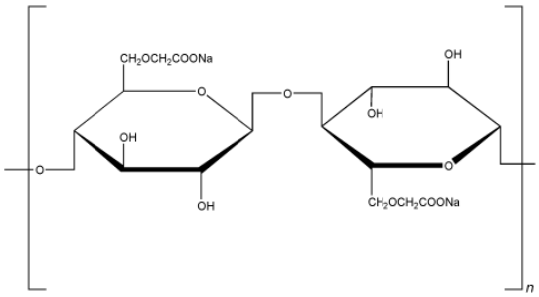
Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

Storage Conditions: Lactose should be stored in a well-closed container in a cool, dry place.

CROSCARMELLOSE SODIUM

Synonyms: Ac-Di-Sol; Crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Structural Formula:



Functional Category: Tablet and capsule disintegrant.

Description: Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

Solubility: Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

Storage Conditions: Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

EVALUATION OF ACTIVE PHARMACEUTICAL INGREDIENTS[33, 34]:

The active pharmaceutical ingredients to be used were analysed to know several physico-chemical properties during pre-formulation stage. They are;

1) Solubility.
2) Bulk density.
3) Tapped density.
4) Carr's index.
5) Hausner's ratio.
6) Loss on drying.
7) Assay

Solubility:

Solubility of the substance is determined by adding 1 gram each of the APIs to different quantities of solvent, as the solubility of solute depends on the type of solvent used. Several solvents were used (Water, Methanol, Chloroform, Acetone, Ethyl acetate). The solubility of API is reported by using the specifications of IP i.e. in the following manner.

Descriptive terms	Parts of solvents for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

Table 2 Description of solubility

Bulk density:

Bulk density is mass of the powder per Bulk volume of the drug. Bulk density is determined by filling the graduated measuring cylinder with 50 grams of APIs and noting down the volume occupied by them. It is calculated by using the formula;

$$\text{Bulk density} = \frac{\textbf{Mass of the powder}}{\textbf{Bulk volume of powder}}$$

Tapped density:

Tapped density is the ratio between a given mass and the volume of the powder after tapping for some fixed number of taps. Electrolab tapped density tester is used for determining the tapped density of the powder for 750 taps. Tapped density is found from the formula:

$$\textbf{Tapped density} = \frac{\textbf{Mass of the powder}}{\textbf{Tapped volume of the powder}}$$

Carr's index:

The flow property of the APIs is can be inferred from the value of Compressibility index or Carr's index. This can be measured from the Bulk density and Tapped density.

$$\textbf{CI} = \frac{\textbf{(Tapped density – Bulk density)}}{\textbf{Tapped density}} \times \textbf{100}$$

When the values of CI are less than 15% the powder possesses good flow properties and when it is more than25% it indicates poor flow.

Hausner's ratio:

It is ratio of Tapped density and the Bulk density. It is a measure of the frictional resistance of the drug. The ideal range of Hausner's ratio is 1.0-1.18.

Hausner's ratio = Tapped density / Bulk density

Loss on drying:

This gives the moisture content of the powder. It is determined by testing the APIs at a temperature of 105°c for 5 minutes in Sartorius Moisture testing apparatus. The ideal moisture content must be 0.5% for both the APIs.

Assay:

For API I:

60 mg of API is weighed accurately and dissolved in 4ml of anhydrous formic acid. This is added with acetic anhydride. 0.1M Perchloric acid is used for titration. The end point is determined potentiometrically. Calculate the content of API I

The content of drug should be in the range 98.5 – 101.0 percent.

For API II:

For API II, the assay is done using Liquid Chromatography. The conditions for study were given below

Column: 25 cm × 4.6 cm stainless steel column packed with Octadecylsilane-porous silica -(5µ)

Mobile phase: 50 volumes of 0.01M Potassium dihydrogen phosphate and 50 volumes of Acetonitrile

Column temperature: 25°C

Flow rate: 1 ml/min.

Inject volume: 20µl.

Wavelength: 225 nm.

The standard and sample were injected and the amount of drug can be calculated from area of the peak obtained. The content should be in the range of 98.0 – 102.0 percent.

Standard preparation:

A 0.03% w/v solution of API II *RS* in methanol. Dilute 1 ml of reference solution to 100 ml with methanol.

Sample preparation:

Dissolve 30 mg of the substance under examination in 100 ml of methanol.

Drug-Excipient Compatibility study[35]:

The successful formulation of a stable and effective dosage form depends on the careful selection of the excipients that are added to facilitate administration, promote the consistent release and Bioavailability of the drug and protect it from degradation. The excipients are selected by conducting compatibility studies with the APIs.

Procedure:

The APIs were mixed with some of the excipients that can be used for formulation in the ratio given in the Table. These are placed in stability chambers at conditions 25°C/60% RH and 40°C/75% RH for 30 days. The samples that were placed in 40°C/75%RH chambers were analysed with Infra-Red spectroscopy after 30 days. For IR studies Shimatzu FTIR (IR Prestige 21) was used.

The IR spectroscopy graphs obtained were compared with standard graphs. Any possible interactions can be detected from changes in graphs of IR studies. The excipient that is causing a change will not be used in the formulation.

Containers:

- Containers and closures for the compatibility study are 10 ml flint glass vials (USP Type I), Bromo butyl rubber stoppers and tears off clear lacquer aluminium seals.
- Remove vials from packaging and sort out the vials with defects like cracks, broken edges, air bubbles and reject them form using.
- Clean the vials by rising initially with potable water followed by rinsing with purified water.

- Dry the washed vials in hot air oven (70°C for 1hour). Physically sort the washed and dried vials for any kind of defects like broken edges, cracks or air bubbles, white or black fibres/particles, foreign matter, etc and reject those vials.

Sample preparation:

Binary mixture of drug and excipients as per the ratio mentioned in Table 3 were prepared and placed with accurate amount of drug and excipient in a polybag and mixed. Then these samples were placed in separate flint glass vials. Then these samples were charged in stability chamber of conditions 40°C/75%RH and 25°C/60%RH.

After 15days and 30 days, samples were also seen for changes in the colour and odour (samples placed in both the conditions).

Particulars		Ratio	Description	Parameters				
				Initial	25°C/60%RH		40°C/75%RH	
					15 days	30 days	15 days	30 days
API I	Dry	-	White crystalline powder and mass	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
	Aqueous							
	Non-aqueous							
API II	Dry	-	White crystalline powder and mass	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
	Aqueous							
	Non-aqueous							
API I + API II		2:1	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + HPMC K 4M		1:1	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + HPMC K 15M		1:1	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + HPMC K 100M		1:1	white powder mixture	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + HPMC 15 CPS		1:0.25	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + S-CMC		1:0.50	white powder mixture	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + Lactose monohydrate		1:1	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + Dibasic Calcium phosphate		1:0.50	white powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + Povidone		1:0.25	White powder mixture	Physical observation	Physical observation	Physical obseLactoser vation	Physical observation	Physical observation
API I + Colloidal silicon dioxide		1:0.25	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + Talc		1:0.25	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API I + Magnesium stearate		1:0.25	White powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API II + L.S. HPC (LH- 11)		1:1	Off white powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation

(.....continued)

Particulars	Ratio	Description	Parameters				
			Initial	25°C/60%RH		45°C/75%RH	
				15 days	30 days	15 days	30 days
API II + CCS	1:1	Off white powder Mixture	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API II + Indigo caramine lake	1:0.50	Sky blue coloured powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API II + Talc	1:0.5	White coloured powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation
API II + Magnesium Stearate	1:0.5	White coloured powder	Physical observation	Physical observation	Physical observation	Physical observation	Physical observation

Table 3 Parameters to be checked for Compatibility studies of Drug and excipients.

FORMULATION TRIALS

To develop an optimum formula for the Bi-layered tablets, several trials were done. The general procedure for preparation of both the layers in all the trials is given below.

Procedure for LAYER I:

1. **Dispensing:** Materials required are dispensed in separate poly bags and are kept ready for sifting.
2. **Sifting:** Materials are sifted to obtain uniform sized particles and improve the mixing. API-I, Polymer (HPMC K 4M or HPMC K 15M or HPMC) S-CMC, HPMC 15CPS, Di-calcium phosphate, Colloidal Silicon Dioxide are sifted through 40# mesh. Magnesium Stearate and Talc were sifted through 60# mesh.
3. **Binder solution:** binder solution is prepared by mixing Povidone in sufficient quantity of hot water.
4. **Dry mixing:** materials are loaded in RMG and are mixed for about 10 minutes at slow speed.
5. **Granulation:** Binder solution is added for three minutes at slow speed. After the addition of the binder, it is mixed for about three minutes.
6. **Wet milling:** the wet mass is milled in a Multi-mill using a 2 mm screen and the mass is subjected for drying.
7. **Drying:** Blend of above step is loaded in a rapid dryer at a temperature of 50^0 C with airflow of 50. Drying continued until the Loss on Drying reaches a range of 1.5% to 2%.
8. **Sifting:** The blend of above step is subjected to milling with final screen of 1.5 mm and th blend is subjected for Pre-lubrication.
9. **Pre-lubrication:** Colloidal Silicon Dioxide and HPMC K 100M** sifted and kept aside in the Sifting step is added to the blend and blended in an Octagonal blender for 5 minutes.

10. **Lubrication:** Talc and Magnesium stearate sifted in 60 # Screen were added to the blend and mixed for 2 minutes.

[**]Only in Trials 6 & 7.

Procedure for LAYER II:

1. **Dispensing:** Materials required are dispensed in separate poly bags and are kept ready for sifting.
2. **Sifting:** Materials are sifted to obtain uniform sized particles and improve the mixing. API-II, LS-HPC, Lacotse DCL 15, Croscarmellose Sodium are sifted through 40# sieve. Indigo Caramine Lake is sifted through 100 # sieve. Magnesium stearate and Talc were sifted through 60# mesh.
3. **Dry Mixing:** API II is mixed with Lactose DCL 15 of second step *geometrically* for uniform mixing and then with other materials. The mixing is done for about 30 minutes in an Octagonal Blender.
4. **Lubrication:** Lubrication is done using the Talc and Magnesium Stearate sifted with 60# sieve before for 2 minutes.

Blend obtained is compressed along with blend of Layer I.

COMPRESSION: Compression is carried out in Bi-layered tablet press. The punches selected were 20.5x 9.5 mm punches. Physical parameters like Hardness, Thickness, Length and Width are controlled as per required and noted**.**

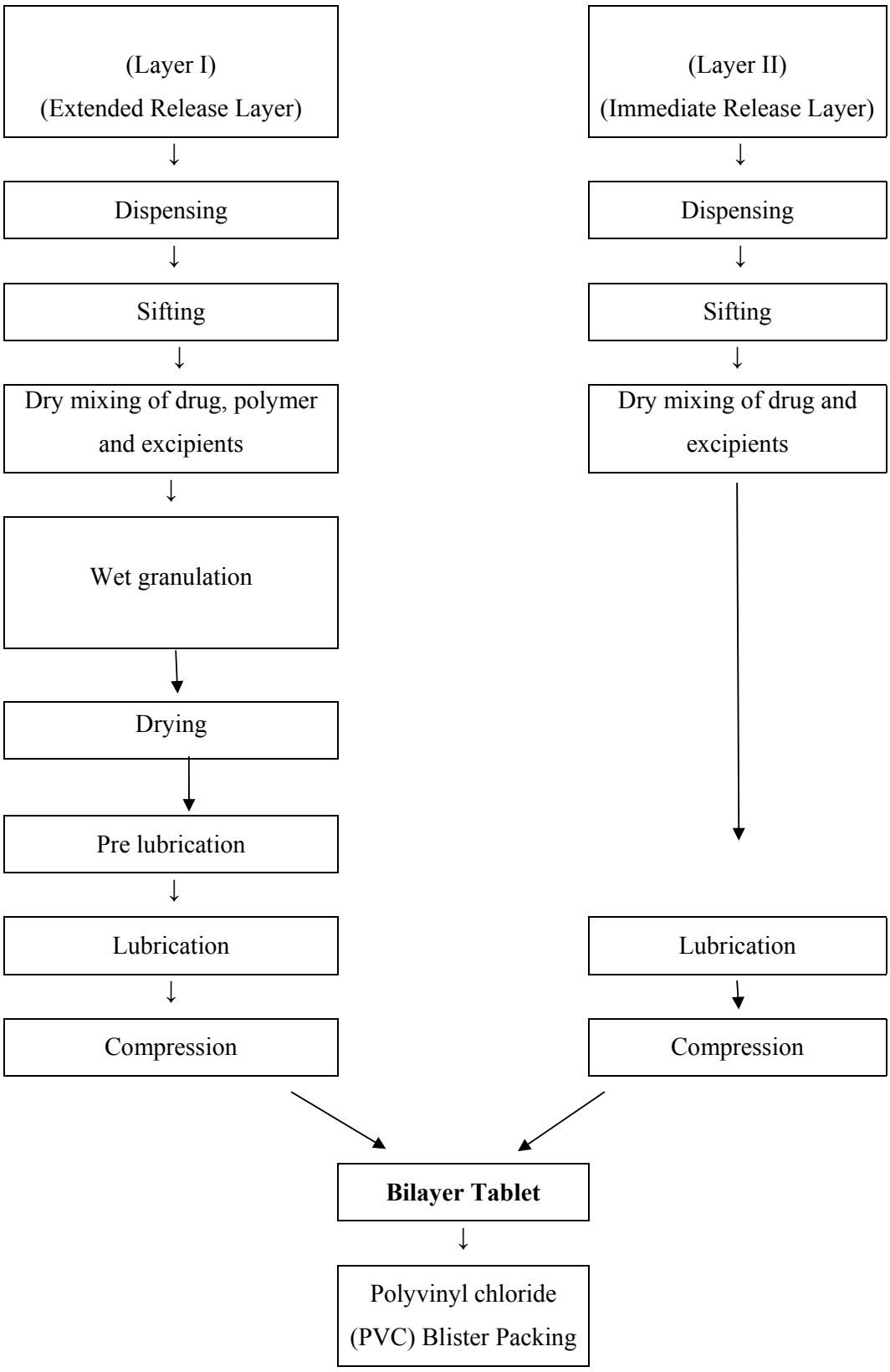


Table 4 Process Flow Chart

TRIAL-1 (F1)

AIM: To take a feasibility trial of Bi-layered tablets comprising SR layer and IR layer of API-I and API-II using HPMC K4M as polymer for sustaining release of API-I.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Oral Anti hyperglycemic	856.00
2	HPMC K4M	Release retarding polymer	170.00
3	Sodium Carboxy methyl cellulose	Channelling agent	35.00
4	Di-calcium phosphate	Diluent	19.50
5	Polyvinlypyrrolidone (Povidone)	Binder	7.50
6	Purified water	Granulating solvent	q.s.
	Extra granular material		
7	Colloidal silicon dioxide	Glidant	8.00
8	Talc	Glidant	4.00
9	Magnesium Stearate	Lubricant	4.00
	Total		1100

Table 5 Formula for (F-1) Layer I

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Oral Anti-hyperglycemic	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	62.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.5000
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		100

Table 6 Formula for F-1 Layer II

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TRIAL-2 (F2)

AIM: To take a trial batch of Bi-layered tablets as Trial 1, but by replacing the HPMC K4M with HPMC K15M to retard the release in Layer I and increasing the amount of Binder and Diluent in Layer II.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Oral Anti hyperglycemic	856.00
2	HPMC K15M	Release retarding polymer	170.00
3	Sodium Carboxy methyl cellulose	Swelling agent, channelling agent	35
4	Di-calcium phosphate	Diluent	11.00
5	Polyvinlypyrrolidone (Povidone)	Binder	8.00
6	Purified water	Granulating solvent	q.s.
	Extra granular material		
7	Colloidal silicon dioxide	Glidant	8.00
8	Talc	Glidant	4.00
9	Magnesium stearate	Lubricant	8.00
	Total		1100

Table 7 Formula for F-2 Layer I

- HPMC K4M is replaced with HPMC K15M.
- Increase the amount of binder to improve hardness.
- The amount of Lubricant is doubled to avoid the sticking observed in compression during Trial 1.

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Anti- oral hyperglycemic drug	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	162.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.5000
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		200

Table 8 Formula for F-2 Layer II

TRIAL-3 (F3)

AIM: To take a trial batch of Bi-layered tablets as Trial 2, but by replacing the HPMC K15M with HPMC K100M at lower amount to retard the release in Layer I and increasing the amount of Binder.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Oral Anti hyperglycemic	856.00
2	HPMC K100M	Release retarding polymer	100.00
3	Sodium Carboxy methyl cellulose	Channelling agent	35.00
4	Di-calcium phosphate	Diluent	80.00
5	Polyvinlypyrrolidone (Povidone)	Binder	9.00
6	Purified water	Granulating solvent	q.s.
	Extra granular material		
7	Colloidal silicon dioxide	Glidant	8.00
8	Talc	Glidant	4.00
9	Magnesium stearate	Lubricant	8.00
	Total		1100

Table 9 Formula for F-3 Layer I

- HPMC K15M is replaced with HPMC K100M.
- The amount increase of binder to improve hardness.

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Oral Anti-hyperglycemic drug	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	162.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.5000
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		200

Table 10 Formula for F-1 Layer II

TRIAL-4 (F4)

AIM: To take a trial batch of Bi-layered tablets as Trial 3, but by addition of HPMC 15 CPS to retard the release in Layer I and increasing the amount of Binder.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Oral Anti hyperglycemic	856.00
2	HPMC K100M	Release retarding polymer	100.00
3	HPMC 15 CPS	Synergises the polymer effect	15.00
3	Sodium Carboxy methyl cellulose	Channelling agent	35.00
4	Di-calcium phosphate	Diluent	64.00
5	Polyvinlypyrrolidone (Povidone)	Binder	10.00
6	Purified water	Granulating solvent	q.s.
	Extra granular material		
7	Colloidal silicon dioxide	Glidant	8.00
8	Talc	Glidant	4.00
9	Magnesium stearate	Lubricant	8.00
	Total		1100

Table 11 Formula for F-4 Layer I

- HPMC 15CPS is added along with HPMC K100M to improve sustained release of API I.
- Increase the amount of binder to improve hardness.

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Oral Anti-hyperglycemic drug	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	162.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.5000
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		200

Table 12 Formula for F-4 Layer I

TRIAL-5 (F5)

AIM: To take a trial batch of Bi-layered tablets similar to Trial 4, but by increasing the amount of HPMC K 100M to retard the release of API I in Layer I.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Oral Anti hyperglycemic	856.00
2	HPMC K100M	Release retarding polymer	125.00
3	HPMC 15 CPS	Synergises the polymer effect	15.00
3	Sodium Carboxy methyl cellulose	Channelling agent	35.00
4	Di-calcium phosphate	Diluent	39.00
5	Polyvinlypyrrolidone (Povidone)	Binder	10.00
6	Purified water	Granulating solvent	q.s.
	Extra granular material		
7	Colloidal silicon dioxide	Glidant	8.00
8	Talc	Glidant	4.00
9	Magnesium Stearate	Lubricant	8.00
	Total		1100

Table 13 Formula for F-5 Layer II

- Amount of HPMC K100M was increased to improve sustained release of API I.

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Oral Anti-hyperglycemic drug	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	162.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.5000
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		200

Table 14 Formula for F-5 Layer II

TRIAL-6 (F6)

AIM: To take a trial batch of Bi-layered tablets similar to Trial 5, but by addition of Polymer Extra-granularly to improve the sustained release of API I in Layer I.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Anti hyperglycaemic	856.00
2	HPMC K100M	Release retarding polymer	125.00
3	HPMC 15 CPS	Synergises the polymer effect	15.00
4	Sodium Carboxy methyl cellulose	Channelling agent	35.00
5	Di-calcium phosphate	Diluent	14.00
6	Polyvinlypyrrolidone (Povidone)	Binder	10.00
7	Purified water	Granulating solvent	q.s.
	Extra granular material		
8	HPMC K 100M	Polymer for retarding the release	25.00
9	Colloidal silicon dioxide	Glidant	8.00
10	Talc	Glidant	4.00
11	Magnesium stearate	Lubricant	8.00
	Total		1100.00

Table 15 Formula for F-6 Layer I

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Oral Anti-hyperglycemic drug	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	162.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.5000
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		200

Table 16 Formula for F-6 Layer II

TRIAL-7 (F7)

AIM: To take a trial batch of Bi-layered tablets as Trial 6, to check the reproducibility of Trail-6.

LAYER - I

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
	Intra granular material		
1	API I	Anti hyperglycaemic	856.00
2	HPMC K100M	Release retarding polymer	125.00
3	HPMC 15 CPS	Synergises the polymer effect	15.00
4	Sodium Carboxy methyl cellulose	Channelling agent	35.00
5	Di-calcium phosphate	Diluent	14.00
6	Polyvinlypyrrolidone (Povidone)	Binder	10.00
7	Purified water	Granulating solvent	q.s.
	Extra granular material		
8	HPMC K 100M	Polymer for retarding the release	25.00
9	Colloidal silicon dioxide	Glidant	8.00
10	Talc	Glidant	4.00
11	Magnesium stearate	Lubricant	8.00
	Total		1100.00

Table 17 Formula for F-7 Layer I

LAYER-II

S.No.	INGREDIENTS	USE	Quantity per tablet (mg)
1	API II	Oral Anti-hyperglycemic drug	7.560
2	Low Substituted Hydroxy Propyl Cellulose (LH-11)	Dry Binder	12.000
3	Lactose DCL 15	Diluent	162.940
4	Croscarmellose sodium	Disintegrant	12.000
5	Indigo Caramine Lake	Colouring agent	1.500
6	Talc	Glidant	2.000
7	Magnesium Stearate	Lubricant	2.000
	Total		200

Table 18 Formula for F-7 Layer II

LAYER-I							
Ingredients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**
API I	856.00	856.00	856.00	856.00	856.00	856.00	856.00
HPMC K 4M	170.00	-	-	-	-	-	-
HPMC K 15M	-	170.00	-	-	-	-	-
HPMC K 100M	-	-	100.00	100.00	125.00	125.00	125.00
HPMC 15 CPS	-	-	-	15.00	15.00	15.00	15.00
Sodium CMC	35.00	35.00	35.00	35.00	35.00	35.00	35.00
Dibasic Calcium Phosphate	19.50	11.00	80.00	65.00	39.00	14.00	14.00
Povidone	7.50	8.00	9.00	9.00	10.00	10.00	10.00
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
HPMC K 100M	-	-	-	-	-	25.00	25.00
Colloidal Silicon Dioxide	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Talc	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Magnesium Stearate	4.00	8.00	8.00	8.00	8.00	8.00	8.00
Total	1100.00	1100.00	1100.00	1100.00	1100.00	1100	1100
LAYER-II							
API II	7.560	7.560	7.560	7.560	7.560	7.560	7.560
L.S.HPC (LH-11)	12.000	12.000	12.000	12.000	12.000	12.000	12.000
Lactose DCL 15	62.940	162.940	162.940	162.940	162.940	162.940	162.940
Croscarmellose Sodium	12.000	12.000	12.000	12.000	12.000	12.000	12.000
Indigo Caramine Lake	1.500	1.500	1.500	1.500	1.500	1.500	1.500
Talc	2.000	2.000	2.000	2.000	2.000	2.000	2.000
Magnesium Stearate	2.000	2.000	2.000	2.000	2.000	2.000	2.000
Total	100.00	200.00	200.00	200.00	200.00	200.00	200.00

Table 19 Compilation of Formulas of all Trials

TABLET BLEND ANALYSIS[33]:

Blend of formulations is subjected for analysis to find out the Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose. To determinate the occupancy of the blend in any equipment Blend analysis is important. The flow properties can be known from these parameters.

Angle of Repose

The angle of repose of each powder blend was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated by using the following equation,

$$\tan \theta = \frac{h}{r}$$

Where,

h = height of cone

r = radius of powder cone.

Table 20 Fate of flow property by change in angle of repose

Angle of repose (degrees)	Type of flow
<20	Excellent
20-30	Good
30-34	Passable8
>40	Very poor

Bulk Density

Bulk density of the granules was determined by pouring gently 5 gm of sample through a glass funnel into a 10 ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated by the following formula,

$$\text{Bulk Density} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}}$$

Tapped Density

About 5 gm of granule was poured gently through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after 50 taps were recorded and tapped density was calculated by the following formula,

$$\text{Tapped Density} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}}$$

Carr's Index

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index, which is determined by the following equation**,**

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

Hausner's ratio is related to inter-particle friction and as such used to predict powder flow properties.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 21 FLOW PROPERTIES

Compressibility index	Flow character	Hausner's ratio
5-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.45
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
More than 40	Very very poor	More than 1.60

EVALUATION OF TABLETS[34]:

Tablets are evaluated to check their mechanical strength that influences their Physico-chemical characters like dissolution, absorption etc. Several parameters like:

- Hardness.
- Thickness.
- Length and width.
- Uniformity of weights.
- Friability.
- Assay

HARDNESS TEST:

Hardness of tablets is known from the pressure applied on it to form a crack along its axis. It is tested by using Dr. Schleuniger 8M tablet tester. The hardness of tablet is reported in Kg/cm^2. Hardness of tablet influences the release of the drug from the tablet as a hard tablet takes a long time to disintegrate. Five tablets were tested during every trial.

Thickness and diameter:

The thickness and diameter of tablets was carried out using *Mitutoyo* Vernier calliper. Five tablets were used for the above test from each batch results were expressed in milli-meter.

Weight variation test:

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was calculated. The uniformity of weight was determined according to I.P. specification. As per U.S.P not more than two of individual weight should deviate from average weight by more than 5% and none deviate more than twice that percentage.

Friability test:

It was done in friability test apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre-weighed samples of 20 tablets were placed in the friability tester, which is then operated for 100 revolutions. The tablets were then dusted and reweighed. Conventional compressed tablets that loss than less than 1.0% of their weight are generally considered acceptable.

$$\% \text{ Friability} = \{1-(Wt/W)\} \times 100$$

Where % F = Friability in percentage

W = Initial weight of table

Wt = Weight of tablets after revolution.

Assay[34]:

The amount of API I & II in the dosage form units were determined using High Performance Liquid Chromatography.

Particulars	API I	API II
Column	C_{18} 250 mm × 4.6 mm 10µ (Waters Bondapack is suitable)	C_{18} 250 mm × 4.6 mm 5µ (Hypersil BDS C_{18} is suitable)
Flow rate	1.0 ml/min.	1.0 ml/min.
Detector	UV/PDA detector	UV/PDA detector
Wavelength	218nm	270 nm
Injection volume	20µl	20µl
Column temperature	30°C	25°C
Run time	15 minutes	15 minutes
Elution	Isocratic	Isocratic
Buffer	1g of sodium heptanes sulphonte and 1g of Sodium chloride in 1800 ml of water and this is adjusted to pH 3.85 with dilute Orthophosphoric acid.	1.36 gms of Potassium dihydrogen phosphate in 1000ml of water
Mobile phase	900:100 ratio of buffer and aceonitrile	500 : 500 ratio of buffer and acetonitrile
Diluent	Methanol	Mix water and acetonitrile in the ratio 350:650 respectively.
Standard	50 mg of working standard in to 50 ml flask , add 35 ml of diluent, dilute up to 50 ml and mix well.5 ml of this is taken and this is added to 50 ml volumetric flask and this is diluted to 50 ml with diluents. The concentration would be 100 ppm.	41.5 mg of working standard is added to 50 ml volumetric flask and 20 ml of diluents is added and dilute it with 50 ml of diluents. 5 ml is taken and is diluted to 50 ml with dilunt. The concentration would be 75 ppm.
Sample	20 tablets were crushed and weighed equivalent to 1000mg of API I and added in to 500 ml volumetric flask and this is added with 350 ml of diluents, shaken well and is diluted up to 500 ml with the diluent. 5 ml is taken from this and this is diluted to 100 ml with the diluent. The concentration would be 100ppm.	20 tablets were crushed and tablet powder equivalent to 7.5 mg of API II was added to a 100 ml volumetric flask and this mixed up with 70 ml of diluent. This is sonicated for about 20 minutes and this made up to 100 ml with the diluent. The concentration would be 75 ppm.

Table 22 Chromatographic conditions for Assay

Procedure for both the APIs: Equilibrate the column with the mobile phase until a baseline is obtained. Inject the sample and standard solutions. Record the chromatogram and measure the peak area response of both standard and sample preparations of the APIs.

Calculation for percentage of API I and API II:

$$\% \text{ of API I} = \frac{AT_I}{AS_I} \times \frac{WS_I}{50} \times \frac{5}{50} \times \frac{500}{WT_I} \times \frac{100}{5} \times \frac{AW_I}{LC_I} \times \frac{P_I}{100} \times 100$$

$$\% \text{ of API II} = \frac{AT_I}{AS_I} \times \frac{WS_I}{100} \times \frac{5}{50} \times \frac{100}{WT_{II}} \times \frac{AW_{II}}{LC_{II}} \times \frac{P_{II}}{100} \times \frac{356.54}{392.95} \times 100$$

- AT_I and AT_{II} are the areas of the peaks obtained for the test solution of APIs in the chromatogram.
- WS_I and WS_{II} are the weight of working standards of the APIs taken in Milligrams.
- LC_I and LC_{II} are the labelled amount of APIs in Milligrams per tablet.
- P_I and P_{II} are the potencies of the APIs as on basis.

In *vitro* DISSOLUTION STUDY[34]

Dissolution studies become very important in characterization of the dosage forms particularly in case of sustained release dosage forms. They are also used to control the quality of dosage forms during the manufacturing process.

In the In *vitro* dissolution study of the present study following parameters were employed to study the release characteristics of both the drugs from Immediate release (API II) and Sustained release layers (API I).

Dissolution parameters	API I	API II
Medium	pH 6.8 phosphate buffer	0.1N Hydrochloric acid
Apparatus	USP apparatus Type II	USP Apparatus Type II
Volume	900 ml	900 ml
Agitation	100 rpm	100 rpm
Measuring time	10 hours	45minutes
Temperature	37°C±0.5°C	37°C ± 0.5°C
Volume withdrawn	10 ml	10 ml

Table 23 Dissolution conditions for API I and API II

The samples of study were analysed using High Performance Liquid chromatography. Chromatographic conditions used for both the APIs were given in the following tabular column.

Particulars	API I	API II
Column	C_{18} 250 mm × 4.6 mm 5µ (Waters Symmetry C18 is suitable)	C_{18} 250 mm × 4.6 mm 5µ (Hypersil BDS C_{18} is suitable)
Flow rate	1.0 ml/min.	1.0 ml/min.
Detector	UV/PDA detector	UV/PDA detector
Wavelength	218 nm	270 nm
Injection volume	20µl	20µl
Column temperature	25°C	25°C
Run time	10 minutes	15 minutes
Elution	Isocratic	Isocratic
Mobile phase	500 :500 v/v of buffer and aceonitrile	500 : 500 v/v of buffer and acetonitrile
Diluent	Dissolution medium	Dissolution medium

Table 24 Chromatographic conditions for Dissolution study of API I & API II

Standard preparation for API I:

Weigh accurately 55 mg of API I working standard and transfer to 100 ml volumetric flask and this diluted with 70 ml of diluent, sonicate to dissolve with intermittent shaking and make the volume up to 100 ml. Further dilute 10 ml of this solution in 100 ml volumetric flask with the diluent. The concentration of the API I working standard would be 55 ppm.

Sample preparation for API I:

Set the dissolution apparatus as per above conditions. Place one tablet in each dissolution bowl. Rotate the paddle for 1^{st}, 3^{rd} and 10^{th} hours with the RPM as mentioned above. Perform dissolution and withdraw sample aliquot at specified interval. Collect the filtrate after discarding first few ml of the filtrate. Dilute 3ml of filtrate to 50 ml with diluents at each time point and use the solution as sample preparation. The concentration would be 55 ppm.

System suitability:

The standard is injected in to the system and the system suitability parameters are checked. The %RSD of five replicate injections of API I should not be more than 2.0. Number of USP theoretical plates should not be less than 1500. In the chromatograms obtained for the API I standard, USP tailing factor should not be more than 2.0.

Procedure:

Equilibrate the system with the mobile phase for sufficient time until stable baseline is observed. Inject dissolution medium as blank, standard preparation, sample preparation. Inject standard preparation as bracketing after six injections of sample preparation.

Calculation for percentage release of API I:

$$\% \text{ Drug release of API I} = \frac{AT_I}{AS_I} \times \frac{WS_I}{100} \times \frac{10}{100} \times \frac{900}{1} \times \frac{50}{3} \times \frac{100}{LC_I} \times \frac{P_I}{100}$$

Standard preparation for API II:

Weigh and transfer about 46.0mg of API II working standard (equivalent to 41.5 mg of pure form of API II) in to 100 ml volumetric flask. Add 70 ml of diluents and sonicate with intermittent shaking. Dilute this to 100 ml with diluent. Take 2 ml of this solution and dilute it to 100 ml with diluent. The concentration of API II would be 8.3 ppm.

Sample preparation for API II:

Set the dissolution apparatus as per the above conditions. Place one tablet in each bowl of dissolution apparatus. Rotate the paddle for 45 minutes with the paddle spped mentioned above. Perform dissolution and withdraw the sample aliquot at specified time interval. Collect the filtrate after discarding few ml of filtrate. The concentration of API II should be 8.3 ppm.

System suitability:

The standard is injected in to the system and the system suitability parameters are checked. The %RSD of five replicate injections of API I should not be more than 2.0. Number of USP theoretical plates should not be less than 1500. In the chromatograms obtained for the API I standard, USP tailing factor should not be more than 2.0.

Procedure:

Equilibrate the system with the mobile phase for sufficient time until stable baseline is observed. Inject dissolution medium as blank, standard preparation, sample preparation. Inject standard preparation as bracketing after six injections of sample preparation.

Calculation for percentage release of API I:

$$\% \text{ Drug release of API II} = \frac{AT_{II}}{AS_{II}} \times \frac{WS_{II}}{100} \times \frac{2}{100} \times \frac{900}{1} \times \frac{100}{LC_{II}} \times \frac{P_{II}}{100} \times \frac{356.54}{392.35}$$

- AT_I and AT_{II} are peak areas of API I and API II respectively obtained from their chromatograms.
- AS_I and AS_{II} are the average of peak areas of API I and API II respectively obtained from their chromatograms.
- WS_I and WS_{II} are the weights of working standards of API I and API II in mg.
- LC_I and LC_{II} are labelled claim amount of API I and API II in mg per tablet.
- P_I and P_{II} are percentage potency of APIs working standard potency.

Specifications for Drug release:

Drug	**Specification**
API I	After 1st hour 25% to 50% After 3rd hour 45% to 75% After 10th hour Not less than 80%
API II	Not less than 75% after 45 minutes.

Table 25 Specification for Dissolution of API I & API II

Data analysis[36, 37]:

The data obtained from the dissolution study were subjected for analysis to know the release pattern of the drug from the dosage form.

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi model, and Korsmeyer-Peppas model. Based on the r-value, the best-fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and No equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Where $Q_{t=}$ amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution and

K_o = zero order release constant.

First order kinetics:

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_o is the initial amount of drug in the solution and K_1 is the first order release constant.

Higuchi model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$\mathbf{F = K.t^{\frac{1}{2}}} \quad \textbf{or} \quad \mathbf{F = K.\sqrt{t}}$$

Where,

'F' is the amount of drug release, 'K' is the release rate constant, and 't' is the release time. When the data is plotted as a cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer and Peppas release model:

The release rate data were fitted to the following equation,

$$\frac{\mathbf{M_t}}{\mathbf{M_\infty}} = \mathbf{K.t^n}$$

Where, M_t / M_∞ is the fraction of drug release, 'K' is the release constant, 't' is the release time, and 'n' is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

When the data is plotted as Log fraction of drug released versus Log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y-intercept.

BLISTER PACKING OF DOSAGE FORM:

Packing of dosage forms is important for reasons like

- Protection
- Identification
- Elegance
- Ease of Shipping

Blister packing is done for the selected formulation before being charged for the stability studies.

Packaging of tablets:

Base foil and lidding foil were loaded in the machine .The tablets were loaded in the hopper. The base foil passes through the forming units with Teflon heads and cavities are formed. Tablets in the hopper coming down through inclined feeding channel and singling unit and are introduced into the cavities formed. The lidding foil is introduced and the sealing of the foils was done in the sealing station. The non-filled cavities are detected using non fill detecting system and are rejected by NFD rejection area. The cutting assembly and the trimming station cuts the blister into appropriate size.

STABILITY STUDIES[38]

Introduction:

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Objective of the Study:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.

ICH specifies the length of study and storage conditions.

Long-term Testing: $30^0C \pm 2^0C$ / 65 % RH ± 5 % for 12 Months.

Accelerated Testing: $40^0C \pm 2^0C$ / 75 % RH ± 5 % for 6 Months.

Method:

Stability studies were carried out at 30^0C / 65 % RH for 12 months and at 40^0C / 75 % RH for 6 months for the selected formulation.

The stability studies were done for the Formulation seven (F-7). This formulation was selected because of its reproducibility of the In *vitro* drug release of the drug from the sustained release layer of the Bi-layered tablets. The formulation was charged for stability at conditions 30°C/65% RH and 40°C/75%RH which are usually conditions for the Real time and Accelerated stability study.

The formulation was tested for parameters like appearance, assay, uniformity of weight, In *vitro* drug release.

Formulation	Stability condition	Testing frequency	Tested for
Selected Formulation	30°C/65% RH	3rd month 6thmonth 9th month 12th month	Appearance, Assay, Uniformity of weights, In *vitro* drug release.
	40°C/75%RH	1st month 2ndmonth 3rd month 6thmonth	

Table 26 Stability testing

Evaluation of Active pharmaceutical ingredients::

Physical parameters like Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's index and Solubility of the APIs were determined and were given here in the table below.

Parameter	API I	API II
Solubility	Freely soluble in water, practically insoluble in Acetone and methylene chloride.	Soluble in N,N Dimethyl formamide and methanol.
Angle of repose	32.00°	21.96°
Bulk density	0.223g/cc	0.532 g/cc
Tapped density	0.339g/cc	0.625g/cc
Compressibility index	34.21%	14.894%
Hausner's ratio	1.520	1.174
Loss on drying	0.25%	0.37%
Assay	99.55%	99.37%

Table 27 Results for Pre-formulation analysis of APIs

The solubility, Loss on drying, Assay of the drugs are found to be within the specifications. From the Compressibility index, Angle of repose values of API I, it can be concluded that the API I has a poor flow and this can be improved by granulation. Flow properties of API II can be inferred as good.

COMPATIBILITY STUDIES

Particulars		Ratio	Description	Parameters				Remarks
				25°C/60%RH		40°C/75%RH		
				15 days	30 days	15 days	30 days	Complies
API I	Dry Aqueous Non-aqueous	-	White crystalline powder and mass	No change	No change	No change	No change	Complies
API II	Dry Aqueous Non-aqueous	-	White crystalline powder and mass	No change	No change	No change	No change	Complies
API I + API II		2:1	White powder	No change	No change	No change	No change	Complies
API I + HPMC K 4M		1:1	White powder	No change	No change	No change	No change	Complies
API I + HPMC K 15M		1:1	White powder	No change	No change	No change	No change	Complies
API I + HPMC K 100M		1:1	white powder mixture	No change	No change	No change	No change	Complies
API I + HPMC 15 CPS		1:0.25	White powder	No change	No change	No change	No change	Complies
API I + S-CMC		1:0.50	white powder mixture	No change	No change	No change	No change	Complies
API I + Lactose monohydrate		1:1	White powder	No change	No change	No change	No change	Complies
API I + Dibasic Calcium phosphate		1:0.50	white powder	No change	No change	No change	No change	Complies
API I + Povidone		1:0.25	White powder mixture	No change	No change	No change	No change	Complies
API I + Aerosil		1:0.25	White powder	No change	No change	No change	No change	Complies
API I + Talc		1:0.25	White powder	No change	No change	No change	No change	Complies
API I + Magnesium stearate		1:0.25	White powder	No change	No change	No change	No change	Complies
API II + L.S. HPC (LH- 11)		1:1	Off white powder	No change	No change	No change	No change	Complies

COMPATIBILITY STUDIES

Particulars	Ratio	Description	Parameters				Remarks
			25°C/60%RH		40°C/75%RH		
			15 days	30 days	15 days	30 days	Complies
API II + CCS	1:1	Off white powder mixture	No change	No change	No change	No change	Complies
API II + Indigo caramine lake	1:0.50	Sky blue coloured powder	No change	No change	No change	No change	Complies
API II + Talc	1:0.5	White coloured powder	No change	No change	No change	No change	Complies
API II + Magnesium Stearate	1:0.5	White coloured powder	No change	No change	No change	No change	Complies

Table 28 Results of Compatibility studies

IR studies:

The samples that were charged in 45°C/75% RH stability chambers were analysed by IR spectroscopy after 30 days. The graphs of the samples were given below.

Figure 2 showing IR-graph of API I + HPMC 15 CPS.

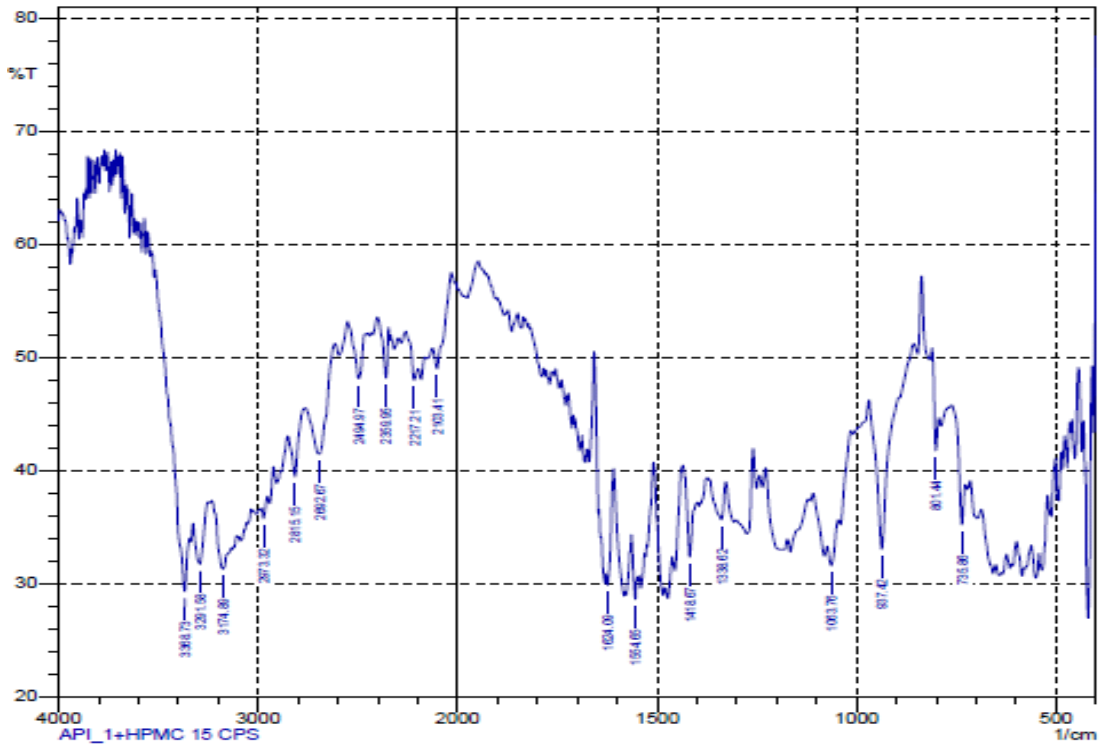


Figure 3 showing IR graph of API+ HPMC K 4M

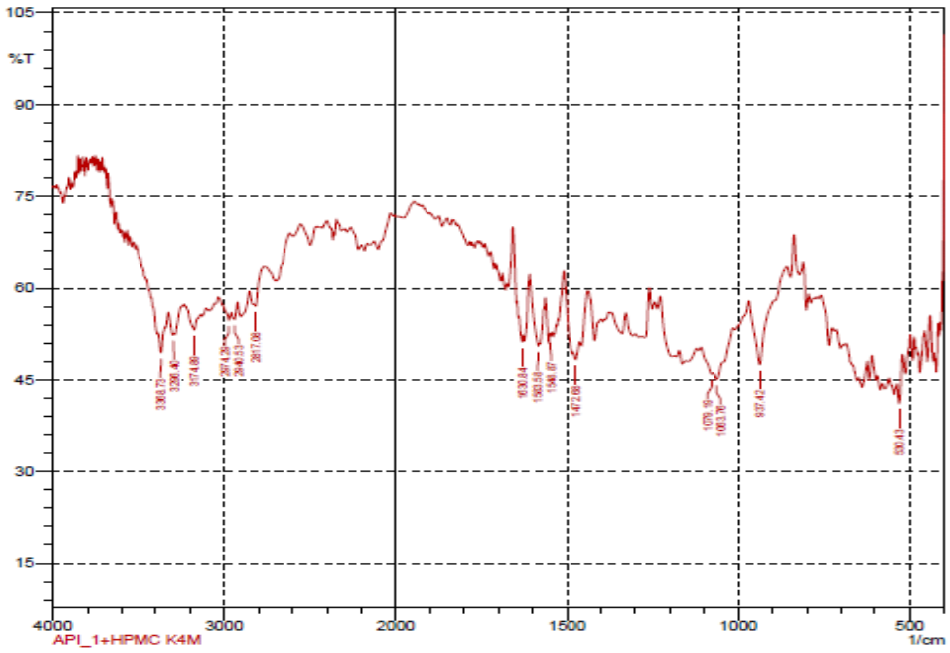


Figure 4 showing IR graph of API I + HPMC K 15M

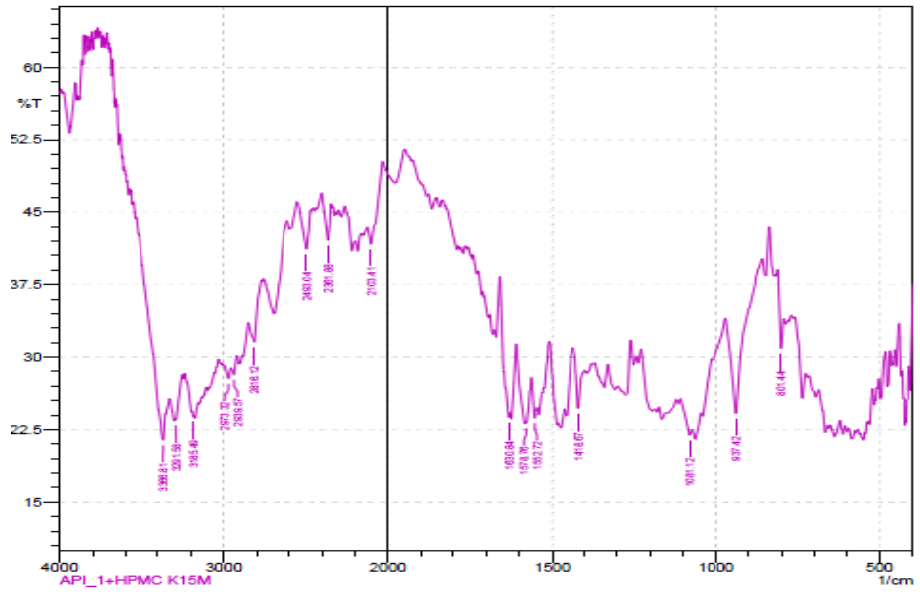


Figure 5 showing IR graph of API I + HPMC K 100M

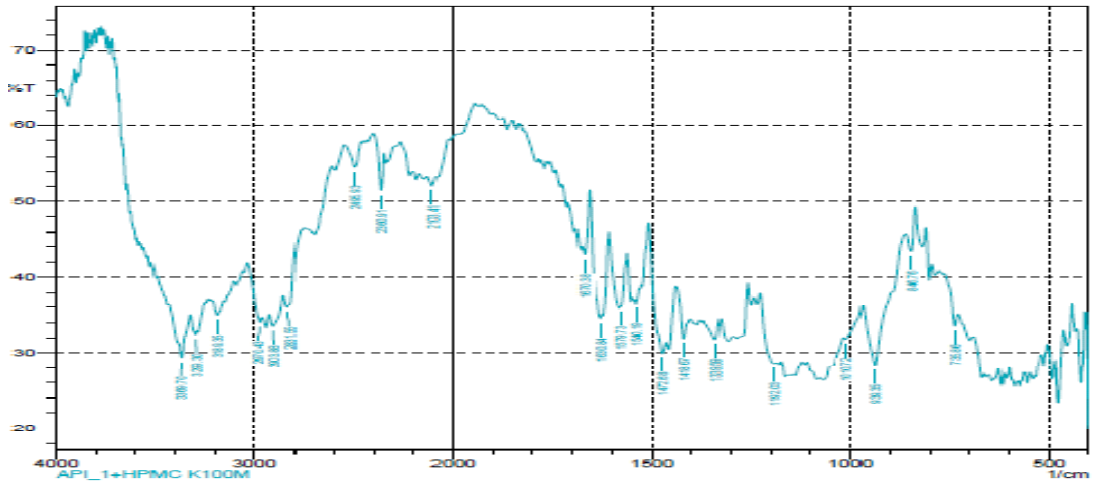


Figure 6 showing IR graph of API I + Sodium CMC

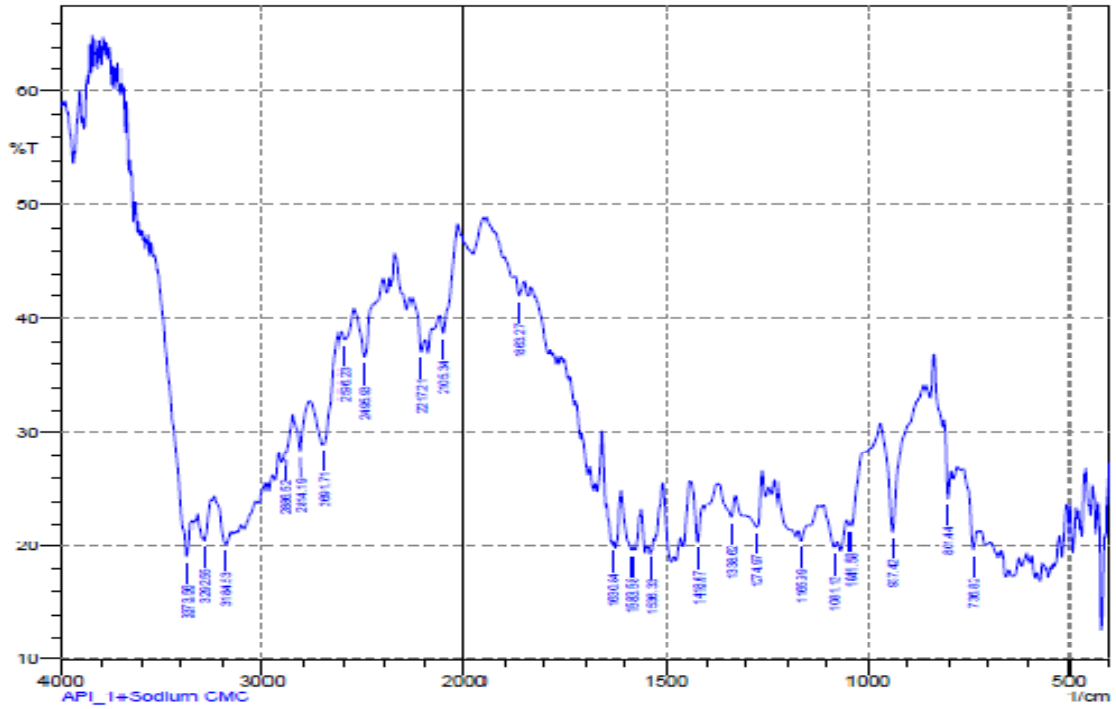


Figure 7 Showing IR graph of API II + L.S. HPC (LH-11)

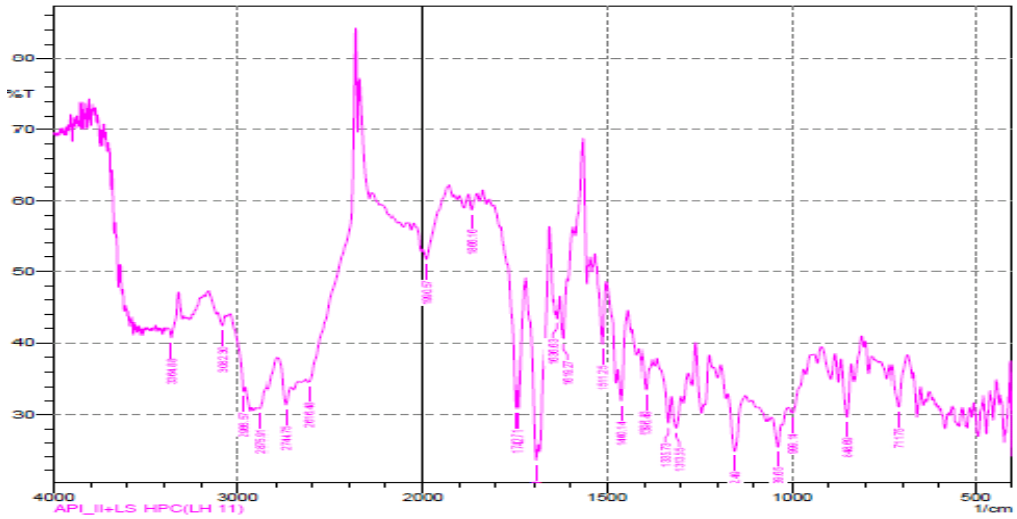


Figure 8 showing IR graph of API II + Lactose DCL 15

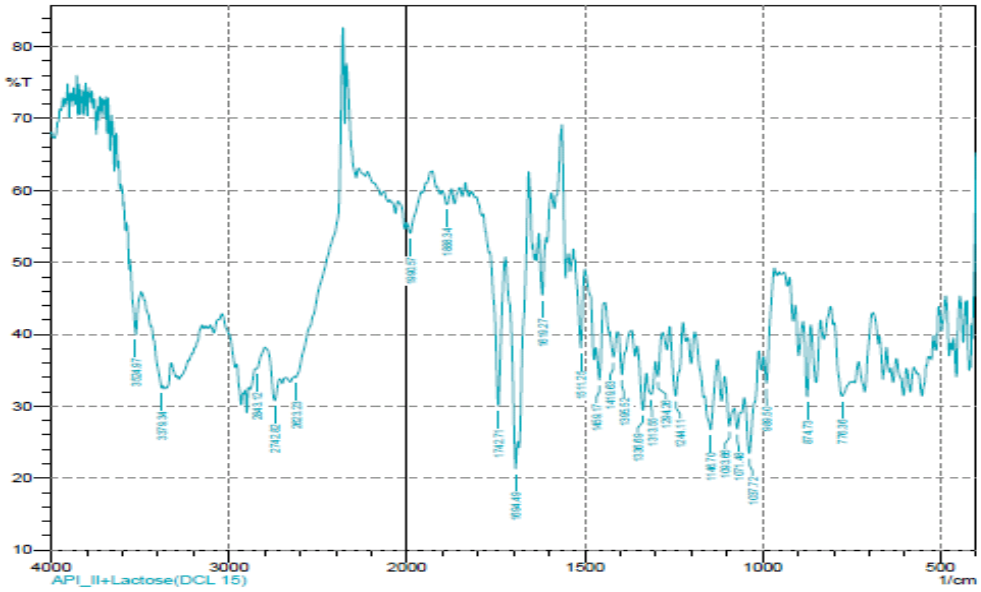
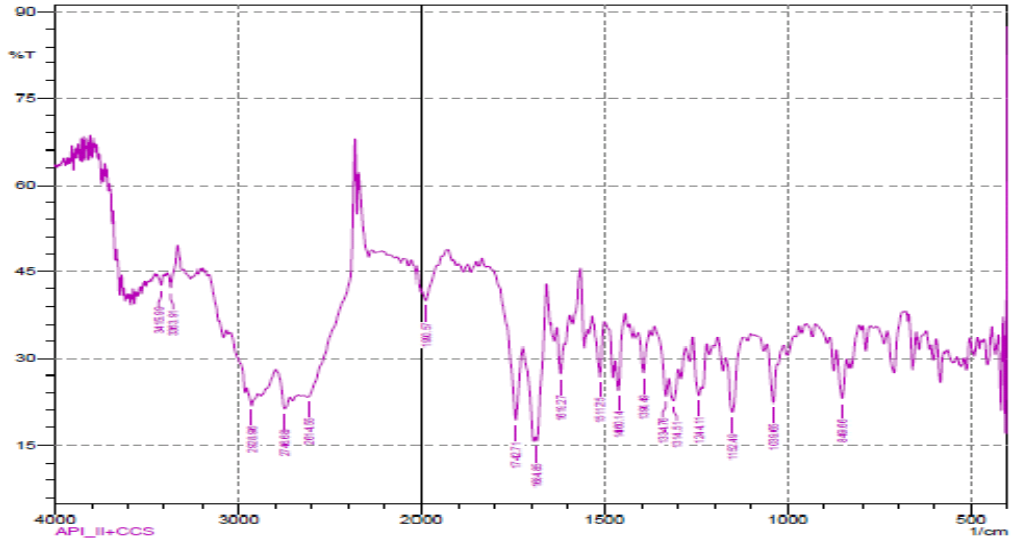


Figure 09 showing IR graph of API II + Croscaramellose Sodium



Discussion:

From the IR studies and Physical observation it can be concluded that there will be no possible chemical interaction between the excipients and the drugs. So these excipients were used for the formulation of the Bi-layered tablets.

TABLET BLEND ANALYSIS:

The results of the blend analysis performed for all the formulations are given here in the Table I and table II below for both the layers.

FOR LAYER I

Formulation	Angle of repose	Bulk density(g/cc)	Tapped density(g/cc)	Carr's index	Hausner's ratio
F-1	17.7	0.4969	0.5689	12.56	1.144
F-2	18.1	0.5290	0.5946	11.03	1.124
F-3	18.9	0.5156	0.5803	11.14	1.125
F-4	18.4	0.5109	0.5813	12.11	1.137
F-5	18.2	0.4555	0.5316	14.31	1.167
F-6	19.1	0.5076	0.5697	10.90	1.122
F-7	18.5	0.4925	0.5480	10.12	1.112

Table 29 Results of Tablet blend analysis of Layer I

FOR LAYER II

Parameter	Angle of repose	Bulk density(g/cc)	Tapped density(g/cc)	Carr's index	Hausner's ratio
F-1	16.9	0.5219	0.5882	11.27	1.12
F-2	16.7	0.5555	0.6125	9.30	1.10
F-3	17.5	0.5434	0.5995	9.35	1.10
F-4	16.3	0.5747	0.6354	9.55	1.10
F-5	16.9	0.5813	0.6403	9.21	1.10
F-6	16.5	0.5681	0.6260	9.24	1.10
F-7	17.1	0.5370	0.5930	9.44	1.10

Table 30 Results of Tablet blend analysis of Layer I

The powder characteristics of all the formulations (for Layer I & Layer II) were found to be good and have shown no problems during the process. The reason for this can be:

- Angle of repose was less than 20 that implies excellent flow properties of formulations.
- Carr's index and Hausner's ratio were also found to be in optimum range by which the blends can be concluded to be possessing good flow properties.

The use of the wet granulation technique for the Layer-I in all the formulations and suitable diluents, glidants and lubricants in optimum percentages for Layer-II resulted in tablet blends with optimum powder characteristics which are always important during processing of tablets.

TABLET EVALUATION:

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations. The values are indicated in below Table.

Table 31 Specifications for preliminary characterization of formulations

Parameters		Range
Hardness (kg/cm^2)		9-12
Thickness (mm)		7.00mm-7.30 mm
Weight variation (%)		±5%
% Friability		Not more than 1.0%
Assay (%)	API I	95.0-105.0
	API II	90.0-110.0

Results of preliminary characterization of tablets for all formulations were given below:

Parameters		F-1	F-2	F-3	F-3	F-5	F-6	F-7
Hardness (Kg/cm^2) (n = 10)		9.16	9.54	9.59	10.50	10.08	10.50	10.30
Thickness (mm) (n = 10)		7.08	7.01	7.04	7.10	7.02	7.05	7.12
Friability (%)		0.337	0.367	0.305	0.398	0.420	0.377	0.342
Weight variation		-1.9 to +2.7	-2.9 to +3.4	-2.9 to 3.9	-1.8 to 2.9	-4.1 to 3.2	-1.9 to 2.2	-2.4 to 2.8
% Drug content	API I	98.81	99.42	97.34	101.42	99.73	98.36	98.75
	API II	98.19	99.08	98.54	98.84	98.12	99.63	99.81

Table 32 Results of Tablet evaluation

Discussion:

From the results it can be concluded that the results of all the formulations were found to be within specifications. The tablets are subjected for In *vitro* dissolution study.

In-*VITRO* RELEASE STUDY

The Dissolution profiles of the formulations of Bi-layered tablets were obtained by the procedure reported earlier and the results were shown in following tables.

Dissolution profile of formulation 1 (F-1):

Layer I								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	64.3	65.4	64.9	63.0	69.1	65.0	65.2
	3rd	83.4	84.1	84.0	83.2	82.2	81.04	82.9
	10th	99.1	99.0	98.8	99.5	97.1	98.2	98.6
Layer II								
0.1N HCl	After 45 minutes	97.3	98.1	97.5	97.0	96.5	98.0	97.4

Table 33 Dissolution Profile of F-1

Discussion: The use of low viscosity polymer i.e. HPMC K 4M could not retard the release of drug as desired during the 1st and 3rd hours. So it was decided to use HPMC K 15M for the next trial. The drug from the immediate release layer released as desired.

Dissolution profile of formulation-2 (F-2)

Table 34 Dissolution Profile of F-2

Layer I								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	60.4	62.2	61.3	60.9	62.4	60.7	61.3
	3rd	78.8	77.6	78.3	79.0	78.2	79.5	78.5
	10th	99.1	98.9	98.4	99.2	100.10	99.4	99.2
Layer II								
0.1N HCl	After 45minutes	90.1	95.4.	93.3	94.1	95.1	96.1	94.0

Discussion: Although the percentage release of the drug at 1st and 3rd hour did retard after using HPMC K 15M instead of HPMC K 4M, the rate profile is not as desired. In the next trial it was decided to use HPMC K 100M as a release retardant polymer.

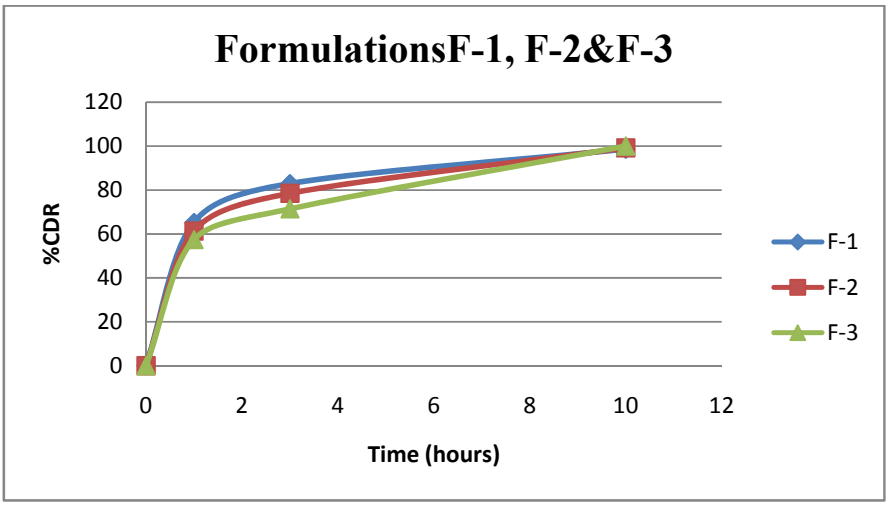
Dissolution profile of formulation-3 (F-3)

Layer I								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	56.7	58.5	57.2	56.9	57.7	58.0	57.4
	3rd	76.3	75.5	76.0	77.1	75.9	76.3	76.1
	10th	99.8	98.7	100.1	101.4	99.5	100.7	100.0
Layer II								
0.1N HCl	After 45minutes	94.1	93.5	90.9	94.8	92.1	92.8	93.03

Table 35 Dissolution Profile of F-3

Discussion: The release rate of the drug in the SR layer did not come within specifications here in the 3rd formulation also after using high viscosity HPMC. But there was a reduction in the rate of release of the drug when compared to formulation-2. In the next trial it was decided to incorporate HPMC 15 CPS as an adjuvant to HPMC K 100M.

Figure 13 Showing Dissolution profile of API I from Formulations 1, 2 & 3



Dissolution profile of formulation-4 (F-4)

Layer								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	50.1	53.2	52.9	54.1	51.1	53.6	52.5
	3rd	74.9	75.0	75.9	74.7	76.1	75.4	75.3
	10th	98.7	99.8	98.2	99.5	98.6	99.1	99.9
Layer II								
0.1N HCl	After 45minutes	94.2	93.3	92.8	93.9	95.1	94.8	94.01

Table 36 Dissolution profileof F-4

Discussion: The use of HPMC 15 CPS inhibited the release of the drug as expected, which is shown by the difference between release rates of the previous formulation and this formulation. But the release rate did not come under specifications. So a trial was decided with an increase of the HPMC K 100M than formulation-4.

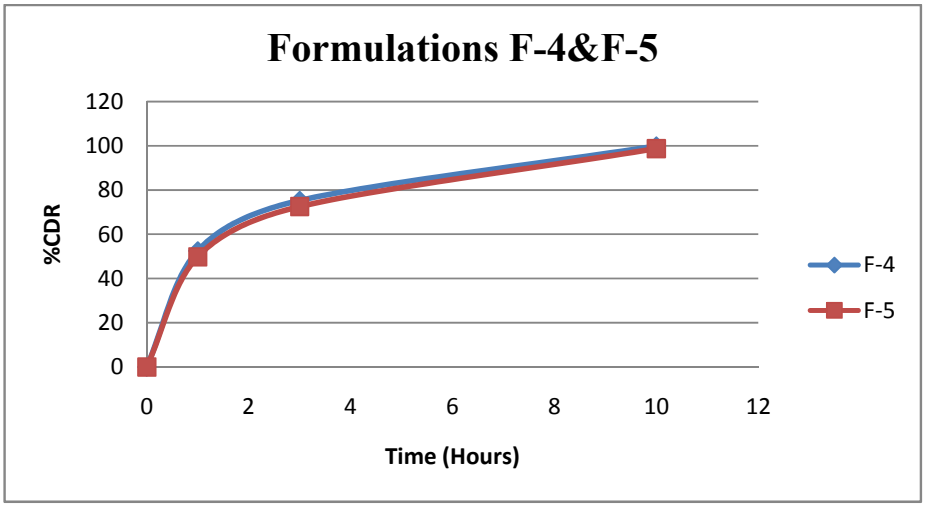
Dissolution profile of Formulation-5 (F-5)

Layer I								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	47.8	49.4	51.2	48.9	50.4	51.2	49.8
	3rd	71.5	71.9	73.4	72.9	71.3	73.9	72.5
	10th	98.6	99.1	99.7	99.4	97.4	97.9	98.7
Layer II								
0.1N HCl	After 45minutes	93.7	94.1	94.9	92.9	96.1	95.4	94.5

Table 37 Dissolution Profile of F-5

Discussion: The release rate of the drug could be reduced with an increase in the concentration of the polymer and is almost within the specification. To improve the release profile better than that of this formulation, a trial was taken by incorporating HPMC K 100M extra-granularly in formulation-6 (F-6)

Figure 14 Dissolution Profile of API I from Formulation 4 & 5



Dissolution profile of formulation-6 (F-6)

Layer I								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	36.4	36.5	37.8	37.2	36.9	37.5	37.0
	3rd	68.0	70.1	71.9	68.7	70.5	69.5	69.7
	10th	100.6	100.0	100.5	100.4	101.9	101.2	101.7
Layer II								
0.1N HCl	After 45minutes	93.3	93.9	94.1	93.9	94.4	94.7	94.0

Table 38 Dissolution profile of F-6

Discussion: Extra-granularly added HPMC K 100M has helped in obtaining the desired release profile of the drug in SR layer at 1st and 3rd hours. A reproducibility trial was planned with same formula as F-6, to check the consistency of the formulation.

Dissolution profile of formulation-7

Layer I								
Medium	**Time (Hours)**	**Cumulative Percentage release**						**Average**
		Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	
pH 6.8 buffer	1st	39.9	38.7	39.2	37.7	37.5	39.2	38.7
	3rd	71.3	72.0	71.9	70.8	70.6	71.9	71.4
	10th	98.9	98.3	101.5	99.7	98.6	99.9	99.5
Layer II								
0.1N HCl	After 45minutes	94.2	93.9	95.2	93.9	96.8	95.0	94.83

Table 39 Dissolution profile of F-7

Discussion: The release profile of the F-7 was found to be similar to that of the F-6 that is within specification.

Figure 15 Dissolution Profile of API I F-6 & 7.

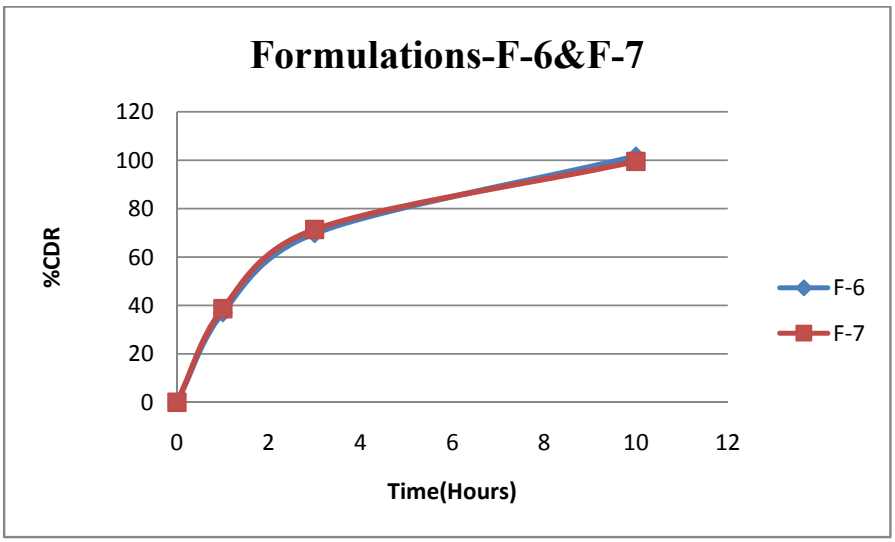
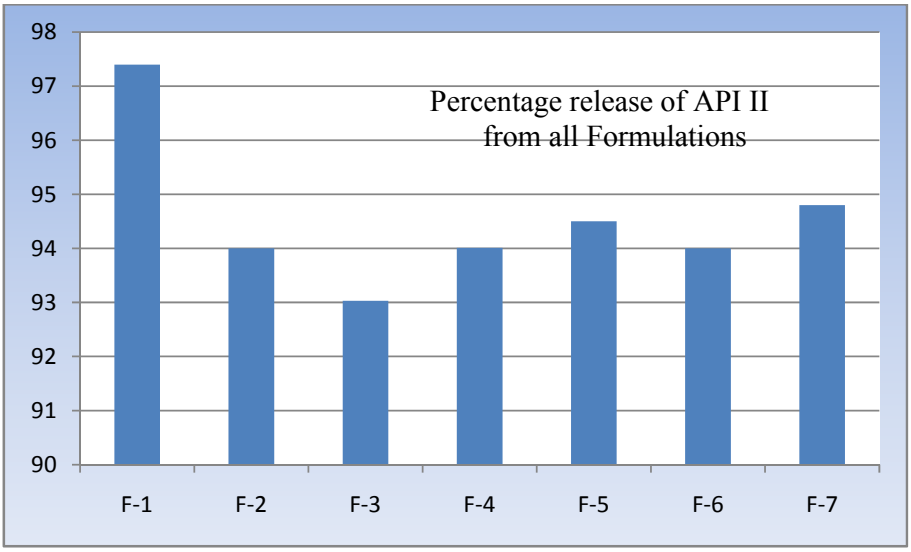


Figure 16 Shows Dissolution Profile of API II in all Formulations



Discussion: There was no change in formula of Layer-II as there was good and consistent release of the API II in all the formulations. The immediate disintegration of the layer within 45 minutes can be posed as the reason for the complete release of the API II withi45 minutes.

Time	F-1	F-2	F-3	F-4	F-5	F-6	F-7
1st hour	65.2	61.3	57.4	52.5	49.8	37.0	38.7
3rdhour	82.9	78.5	76.1	75.3	72.5	69.7	71.4
10th hour	98.6	99.2	100.0	99.9	98.7	101.7	99.5

Time	F-1	F-2	F-3	F-4	F-5	F-6	F-7
After 45 minutes	97.4	94.0	93.03	94.01	94.5	94.0	94.83

Table 40 Dissolution profiles of all the formulations

Kinetic study:

Formulation-7 was found to be giving the desired In*vitro* dissolution rate, so this formulation was selected for determining the nature of release of drug from dosage form.

Time (in hours)	Square root of time	Log Time	% CDR	Log(100% - CDR)	Log %CDR
0	0	-	0	2	0
1	1	0	38.7	1.78	1.58
3	1.73	0.47	71.41	1.45	1.85
10	3.16	1	99.45	-0.259	1.99

Table 41 Graphs for the different Kinetic models were plotted as per above values.

Formulation	Zero-order kinetics		First-order kinetics		Higuchi's kinetics		Korsmeyer-Peppas	
	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
F-7	8.425	0.786	0.227	0.996	31.65	0.964	-0.406	0.954

Table 42 Regression coefficients and Slopes from all the Kinetic model graphs

Discussion: The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release.

Based on the data analysis the drug release was found to follow First order release kinetics, the drug release mechanism was best explained by first order, as the plots showed the highest linearity. This model indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process.

STABILITY STUDY DATA

The samples from the stability chambers that were packed in PVC Blister packing were subjected to following analysis.

Table 43 Stability Data for the samples stored at condition 30° C/65 %RH

Parameter		Specifications		Initial	3 months
Appearance		White/Blue oblong shaped Bi-layered tablets		No change	No change
Average Weight (n= 20)		1300 mg ± 5 %		1311.2 mg	1312.5 mg
Weight variation		± 5%		-2.0% to +1.9%	-3.0% to 4.1%
Assay API I		90.0% to 110.0% of stated amount of API I		98.35% of API I	98.70% of API I
Assay API II		90.0%to 110.0% of stated amount of API II		99.33% of API II	99.6% of API II
In *vitro* drug release study	API I	1st Hour	25% to 50 %	36.3% to 40.9%	35.9% to 40.6%
		3rd Hour	45% to 75 %	66.8 to 72.6%	68.0 to 69.3%
		10th hour	NLT 80%	90.0% to 96.7%	98.3% to 100.5%
	API II	Within 15minutes NLT 75%		93.0%	94.6%

Table 44 Stability data for the samples stored at condition 40°C/75%RH

Parameter		Specifications		First month	Second month	Third month
Appearance		White/Blue oblong shaped Bi-layered tablets		No change	No change	No change
Average Weight (n= 20)		1300 mg ± 5 %		1296.9mg	1300.4	1306.5 mg
Weight variation		± 5%		-2.1% to +3.1%	-3.5% to +3.2%	-2.2% to +3.8%
Assay API I		90.0% to 110.0% of stated amount of API I		98.5% of API I	99.17% of API I	98.8% of API I
Assay API II		90.0%to 110.0% of stated amount of API II		99.33% of API II	99.6% of API II	99.06% of API II
In *vitro* drug release study	API I	1^{st} Hour	25% to 50 %	33.8% to 35.9%	34.5% to 39.5%	35.2% to 37.0%
		3^{rd} Hour	45% to 75 %	65.5% to 67.6%	64.8% to 71.6%	67.1% to 69.9%
		10^{th} hour	NLT 80%	97.9% to 99.6%	97.9% to 99.3%	99.0% to 100.8%
	API II	Within 15minutes NLT 75%		95.0%	94.2%	97.6%

Discussion: From the stability data provided above, it can be concluded that the Formulation was stable at both the conditions. This is because all parameters checked were within specifications.

9. SUMMARY

Tablets are oral solid dosage forms which are formed by compressing fixed volumes of powder particles comprising of the active pharmaceutical ingredients and other excipients. Tablets are most used dosage forms than other oral dosage forms. There are of different types based on the nature of administration, manufacturing. Bi-layered tablets are one of a kind of tablets which are manufactured when there is need of separation of two or for releasing a drug in different manner i.e. as sustained release and immediate release. These are generally manufactured in specially designed tablet presses. Bi-layered tablets can have two drugs in which one can release immediately and the other will be sustained for longer durations.

Diabetes is chronic metabolic disorder in which there would be increased glucose levels in the body. It is of two types' Insulin-Dependent diabetes and Non-Insulin Dependent diabetes. Diabetes is generally treated by using Insulin and Oral-Hypoglycemic drugs. Biguanides, Sulfonylureas, Thiazoliddinediones, Meglitinides, Alpha-Glucosidase inhibitors are the five classes of the Oral-Hypoglycemic drugs. These act by decreasing Insulin resistance of cells. Biguanides and Thiazolidinediones are used in combination when therapy with single Oral-Hypoglyemic agent is not satisfying.

In the present study a Biguanide and a Thiazolidinedione are selected for the designing Bi-layered tablets with the Biguanide in SR layer and Thiazolidinedione in IR layer. Pre-formulation studies were done with APIs. Compatibility was analysed before choosing the excipients for the study with physical observation and IR studies. The samples were charged in stability chambers of conditions 25°C/60%RH and 40°C/75%RH for 30 days. All the pre-formulation studies and compatibility studies are found to be satisfactory and so formulation trails were started with the selected excipeints.

Blend for SR layer was prepared by wet granulation and IR layer blend is prepared by dry mixing. HPMC K 4M, HPMC K 15M and HPMC K 100M were used as release retarding polymers for Layer I for trials in optimizing the formula. Other excipients include Sodium CMC, HPMC 15 CPS and Di-basic Calcium Phosphate, Colloidal Silicon Dioxide, Talc and Magnesium stearate.

Seven trials were done to optimize the release of API I in SR layer to be within specifications. F- 6 is the optimized formula with 12% of HPMC K 100M intra-granularly and 2.5% of same polymer extra-granularly. A reproducibility trail as F-7 was done which also gave results as F-6. For the IR layer, formula is kept constant as there is sufficient release of the drug was observed from the second trial. Direct mixing is done with Croscaramellose as super-disintegrant. Other excipients include Low substituted HPC (LH-11) as binder, Lactose DCL 15 as diluent, Talc and Magnesium stearate.

Post-Compression analysis of all formulations like Hardness, Weight variation, Friability and Assay were optimum for all the formulations. In-*vitro* dissolution studies revealed that for the formulation F-6 the sustained release layer released the drug as per the specifications. The same was reproduced in the formulation F-7. Stability studies were initiated for F-7 at conditions 30°C/45%RH and 40°C/75%RH for a period 12 months and 6 months respectively. The results obtained after 3 months for samples at both the conditions were found to be satisfactory and so the product is stable.

Kinetic Model fitting was done by plotting graphs for Zero-Order kinetics, First-Order kinetics, Higuchi's Kinetic model and Korsemeyer-Peppas kinetic model. The formulation selected was F-7 which has shown the release rate of the drug is by First order kinetics. The release mechanism is both by erosion and diffusion mechanism.

10. CONCLUSION

The aim of the study is to design and develop immediate release and sustained release bi-layered matrix tablets of Oral-Hypoglycemic drugs. A Biguanide and a Thiazolidinedione were selected for the sake of study. HPMC, water swell able polymer and Croscaramellose sodium a superdisintegrant were selected for the sustained release of API I and Immediate release of API II respectively.

The formulation was optimized to obtain the release of API I for a sustained period (within specification). In the initial trials HPMC low viscosity polymer is selected to check the feasibility of the polymer to sustain the release of API I. In later trials HPMC high viscosity grades were employed, which gave the desired release of the API I.

With low viscosity polymers like HPMC K 4M did not sustain the release of API I to the desired level. Use of HPMC K 15M did reduce the release of drug in the layer I compared to that of formulation with HPMC K 4M. But that was not an optimum profile. So a still high viscous polymer HPMC K 100M was used in the formulations F-3 to F-7. To enhance the activity of the Polymer, HPMC 15 CPS is used that effectively reduced the release rate. The incorporation of the Polymer intra-granularly and extra-granularly at concentration 12% and 2.5% respectively gave an optimum release profile within specifications. From this it can be conclude on increasing the polymer concentration, the release rate of the drug sustains. We can also conclude that the use of HPMC 15 CPS worked as an adjuvant to the sustained effect shown by HPMC K 100M.

The release of API II was constant all through the formulation. This concludes that the superdisintegrant played good role in disintegrating the Layer II.

From graphs plotted for various Kinetic models, it can be concluded that the F-7 is following First-order kinetic as the plots of that model had shown higher regression values (R^2=0.9960). The release mechanism can be concluded both by diffusion and erosion mechanisms.

From the stability studies completed for 3 months, it can be concluded that the formulation is stable one, as all the parameters like Appearance, assay of the drugs and Consistency in dissolution studies were found to be intact, even after simulating extreme conditions during their storage. Further, the stability studies would be continued in Micro Labs Ltd.

From this can be concluded that Bi-layered matrix tablets comprising Oral-Hypoglycemic drugs in immediate release layer and sustained release layer are a good means in promising a combination therapy, while achieving patient compliance for Diabetic Mellitus.

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