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# Dry Granulation by Slugging Method for Sustained Release of Model Drug

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**Keywords:** Co-processed excipients, slugging method, particle size, matrix tablet, MCC (PH102), HPMC (K4M)

**ABSTRACT**

The main objective of the present study was to develop directly compressible co-processed excipients by the slugging method for the sustained delivery of a model drug and to study the effect of particle size and concentration of polymer on the drug release by comparing *In-vitro* dissolution profile of a sustained-release tablet. The co-processed excipients were prepared by wet granulation technique by using MCC (PH102) and HPMC (K4M) in the ratio of 1:0.5, 1:1, 1:2 & 1:3 respectively by passing through different sieve number 18#, 20#, 30# and 40#. In the Preformulation study of co-processed excipients, it was found that a granule of size 18# has good flow properties and faster drug release as compared to the 20#, 30# &40#. As the concentration of HPMC (K4M) increases, the release of the drug from the tablet also get decreased but the difference was found to be insignificant (Tuckey test).

# 1. INTRODUCTION

## 1.1 Introduction to Sustained Release:

A sustained-release system includes a drug delivery system that "achieves slow release of a drug over an extended period." The term sustained release has become associated with those systems from which therapeutic agents may be automatically delivered over a long period. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities.

In conventional dosage form, multiple daily dosing is inconvenient to the patient and can result in missed doses, made up doses and patients in compliance with the therapeutic regimen. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized that the plasma level of a drug should be maintained within the safe margin and effective range, for these proper and calculated doses of the drug need to be given at different time intervals by conventional dosage form. To achieve and maintain the concentration of administered drugs within a therapeutically effective range, it is necessary to take drug dosage several times and thus results in a fluctuating drug level in plasma. Sustained drug delivery has been introduced to overcome the drawback of fluctuating drug levels associated with the conventional dosage form.

When a drug is delivered as a conventional dosage form such as a tablet, the dosing interval is much shorter than the half-life of the drug resulting in several limitations associated with such a conventional dosage form are poor patient compliance, the unavoidable fluctuations in the drug concentration may lead to under-medication or over medication as the Css values fall or rise beyond the therapeutic range, precipitation of adverse effect especially of a drug with small therapeutic index. [1, 2, 3]

Recent decades have seen tremendous strides in the designing of novel dosage forms, but tablets remain an attractive option for pharmaceutical scientists and clinicians because they offer advantages of accurate unit-dosing, better patient compliance, ease of large-scale manufacturing, low production cost and their stability compared with liquid and semi-solid presentations.[4] The development of pharmaceutical products for oral delivery, irrespective of its physical form, involves varying extent of optimization dosage form characteristics within the inherent constraints of GI physiology. Therefore the fundamental understanding of

various disciplines, including GI physiology, pharmacokinetic, pharmacodynamic and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater are the complexities in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

1. Physiochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.

2. The anatomical and physiological characteristics of the GIT.

3. Physiological characteristics and drug delivery mode of the dosage form to be designed.[2,3]

**Advantages of Oral SR Formulation:**

- The oscillating plasma drug level occurring in a conventional dosage form can be overcome by sustained release formulation that maximizes bioavailability, improves margin of safety, reduce toxicity, longer dose period improve patient convenience and compliance and improved efficacy of therapy.

- Reduction in health care costs through-improved therapy, Shorter treatment period, lower frequency of dosing, reduction in personnel time to dispense, administer and monitor patients.[5,6]

**Disadvantages of SR Formulation:**

- Possibility of dose dumping due to food, physiological, formulation variables or chewing or grinding of oral formulations by the patient thus, increased risk of toxicity.

- Retrieval of a drug is difficult in case of toxicity, poisoning, hypersensitivity reactions or immediate change in drug therapy. SR formulations are designed for the normal population, i.e. based on average drug biological half-lives. Consequently, disease states that alter drug disposition, significant patient variation, so forth are not accommodated. A physician has less flexibility in adjusting dosage regimens.

- Since more costly processes and equipment are involved in manufacturing many sustained-release forms that increase the cost. [5,6]

**1.2 Introduction to Co-processed Excipients:**

Co-processing of excipients in the pharmaceutical industry was introduced around the late 1980s as exemplified by co-processed microcrystalline cellulose and calcium carbonate, followed by Cellactose in 1990, a co-processed combination of silicified microcrystalline cellulose, lactose, and cellulose.

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding methods. The tablet is still the most frequently administered dosage form for medical applications. A wide range of materials from various sources have been developed and marketed as directly compressible (DC) vehicles such as starch, cellulose derivatives, inorganic substances, polyalcohol, spray-dried lactose, microcrystalline cellulose (MCC), granular dicalcium phosphate, crospovidone and pregelatinized starch have been introduced in the market but performance improvement was achieved only up to a limited extent, in addition to development of directly compressible excipients by the modification of a single substance(pre-processing).

Co-processing of two or more components could be applied to produce composite particles or co-processed excipients. co-processed excipients by combining properties of two different excipients fulfill the increasing demand of multifunctional excipients for direct compression.

The major challenge for tablets and capsule manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations contain excipients at a higher concentration than an active drug. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability. One such approach for improving the functionality of excipients is the co-processing of two or more excipients[7].

Excipients that have been combined synergistically and that are more beneficial than simple physical admixtures[8], or it can be defined as combining two or more established excipients by an appropriate process. Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical[9]. Co-

processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/ price[10,11]. Co-processing is primarily aimed at addressing the issues of flowability, compressibility, and disintegrating potential and most importantly, the development of filler-binder combination.

**Advantages of Co-processed excipients:**

**1) Improved Flow Properties:**

Controlled optical particle size and particle size distribution ensure superior flow properties of co-processed excipients without the need to add Glidant. The volumetric flow properties of SMCC were studied in comparison with MCC. The particle size range of these excipients was found to be similar to those of the parent excipients, but the flow of co-processed excipients was better than the flow of simple physical mixtures.

**2) Improved compressibility:**

Co-processed excipients have been used mainly in direct compression tableting because in this process there is a net increase in the flow properties and compressibility profiles and the excipients formed is a filler binder. The pressure-hardness relation of co-processed excipients when plotted and compared with simple physical mixture showed a marked improvement in the compressibility profile. The compressibility performance of excipients such as Cellactose SMCC and Ludipress are superior to the simple physical mixtures of their constituent excipients.

**3) Better dilution potential:**

Dilution potential is the ability of the excipients to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible, and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients.

**4) Fill weight variation:**

Material for direct compression tends to show high fill weight variation as a result of poor flow properties, but co-processed excipients, when compared with simple mixtures or parent material, have been shown fewer fill-weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surface and creates a near-optimal size distribution, causing better flow properties. Fill weight variation tend to be more prominent with high-speed compression machine. Fill-weight variation was studied with various machine speeds for SMCC and MCC, and SMCC showed less fill-weight variation than MCC.

**5) Reduced lubricant sensitivity:**

Most co-processed products consist of a relatively large amount of brittle material such as lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material. The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding. A large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

**6) Absence of chemical change:**

Detailed studies of excipients' chemical properties after co-processing have proven that these excipients do not show any chemical changes. Detailed studies of SMCC with X-ray diffraction analysis, solid-state nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and $C^{13}$ NMR spectroscopy have detected no chemical changes and indicate similarity to the physicochemical properties of MCC. This absence of chemical change helps reduce a company's regulatory concerns during the development phase.

**7) Other properties**:

Co-processed excipients offer the following additional advantages:

a) Manufacturers of the pharmaceutical company have the option of using single excipients with multiple functional properties, thereby reducing the number of excipients in inventory.

b) Improved organoleptic properties such as those in Avicel CE-15, which is a co-processed excipient of MCC and guar gum were shown to have distinctive advantages in chewable tablets in terms of reduced grittiness, reduced tooth packing, minimal chalkiness, better mouthfeel, and improved overall palatability.

c) The overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients.

d) Because they can retain functional advantages while selectively reducing disadvantages, co-processed excipients can be used to develop tailor-made designer excipients. This can help reduce the time required to develop formulations.

e) Co-processed excipients can be used as proprietary combinations, and in-house formularies can be maintained by pharmaceutical companies, which could help in developing a formulation that is difficult to reproduce and provides benefits in terms of intellectual property rights.[10, 11]

**1.3 Techniques for Co-processing:**

1. Dry granulation

2. Wet Granulation

3. Extrusion

**Granulation:**

Granulation is the act or process of forming or nucleating into grains. Granules typically have a size range between 0.2 to 4.0 mm depending on their subsequent use. Agglomeration processes or in a more general term particle size enlargement technologies are great tools to modify product properties. Agglomeration of powders is widely used to improve physical properties like wettability, flowability, bulk density, and product appearance.

**1) DRY GRANULATION:**

In the dry granulation process, the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. Dry granulation involves the compaction of the components of a tablet formulation using the tablet press or specially

designed machinery to obtain solid compacts, which are milling and screening into desired sized granules having better flow properties than that of the original powder mixture and then further compressed into a final tablet.

This method of dry granulation is also called "Slugging"[12].

The two basic procedures are to form a compact of material by compression are Slugging and Roller compaction. In slugging the powder is compressed and the resulting tablet or slugs were milled to yield the granules of the desired size. In the Roller compaction method, the powder is compressed with pressure rolls using a machine such as Chilosonator.

**Advantages of Dry granulation:-**

The main advantages of dry granulation are that it uses fewer equipment and space. It eliminates the need for binder solution, heavy mixing equipment, and the costly and time-consuming drying step required for wet granulation.

i) For moisture sensitive material

ii) For heat-sensitive material

iii) For improved disintegration, since powder particles are not bonded together by a binder.

**Disadvantages of Dry granulation:-**

i) It requires a specialized heavy-duty tablet press to form a slug.

ii) It does not permit uniform color distribution as can be.

iii) Achieved with wet granulation where the dye can be incorporated into binder liquid.

iv) The process tends to create more dust than wet granulation, increasing potential contamination.

**Two main dry granulation processes:**

**1) Slugging process:**

Slugging is a pre-compression process for the formation of extra-large tablets (slugs), usually of variable weight, due to poor flow of the drug powder. The accuracy or condition of the

slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling. Which are recompressed to obtain the final tablet, the procedure applies to the dry granulation of hydrolyzable drugs, such as Aspirin, Metformin which are not amenable to wet granulation.[13]

**Factors which determine how well a material may slug:**

i) Compressibility or cohesiveness of the matter

ii) The compression ratio of powder

iii) The density of the powder

iv) Machine type

v) Punch and die size

vi) Slug thickness

vii) Speed of compression

viii) The pressure used to produce slug

**2) Roller compaction:**

The compaction of powder using pressure roll can also be accomplished by a machine called Chilsonator. Unlike the tablet machine, the Chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production granules.

**2. WET GRANULATION:**

Wet granulation is the most widely used process of agglomeration in the pharmaceutical industry. The wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing, and drying. The main advantage of wet granulation is that the poor compression and flow properties exhibited by many drug substances can be masked as a result of their incorporation into a granule.[4, 14]

### 1.4 Particle Properties Influencing Excipients Functionality:

The particle size of granules affects the various properties of the material, which is summarized in Table No: 1.1, Hence a study on particle size-dependent changes in tablet properties is a necessary parameter.

**Table No. 1: Particle property and excipients functionality affected**

| Sr. No. | Particle property | Excipients functionality affected |
|---|---|---|
| 1 | Particle size | Flow properties, content uniformity, compressibility, disintegration, and dissolution rate. |
| 2 | Particle size distribution | Segregation potential, |
| 3 | Particle shape | Flowability, content uniformity & compressibility. |
| 4 | Particle porosity | Compressibility, disintegration & dissolution rate. |
| 5 | Surface roughness | Flowability, segregation potential, dilution potential & lubricant Sensitivity. |

### 1.5 Comparison of Granulation Techniques:

Tablets are manufactured by mainly three techniques: wet granulation, dry granulation, and direct compression. In wet granulation and dry granulation techniques, various processing steps and manufacturing challenges are involved, leading to higher cost and time of tablet production. In contrast to this, the direct compression technique involves simply the compression of a dry blend of powders that comprises the drug and various excipients. The simplicity and cost-effectiveness of the direct compression process have positioned it as a preferred alternative.[14] all techniques are which summarized in the table: 1.2[15]

**Table No. 2: Comparisons of Granulation Techniques**

| Step | Direct compression | Dry Granulation | Wet granulation |
|---|---|---|---|
| 1 | Mixing/blending of API and adjuvants | Mixing/blending of API and adjuvants | Mixing/blending of API and adjuvants |
| | ↓ | ↓ | ↓ |
| 2 | Compression | Compression into slugs | Preparation of binder solution |
| | | ↓ | ↓ |
| 3 | | Size reduction of slugs and sieving | The massing of the binder solution of step 2 with a powder mixture of step 1. |
| | | ↓ | ↓ |
| 4 | | Mixing of granules with pharmaceutical aids | Wet screening of damp mass |
| | | ↓ | ↓ |
| 5 | | Compression | Drying of wet granules |
| | | | ↓ |
| 6 | | | Reshifting of dried granules and blending with pharmaceutical aids |
| | | | ↓ |
| 7 | | | Compression |

## 2.1 REVIEW OF LITERATURE:

- ***Kochar S K et.al***,[16] had developed slugs of microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP) and spray-dried lactose (SDL) compressed, either on their own or in various combinations, between 12.7 mm flat-faced punches on a single punch tableting machine at 10 different pressures. 10 tablets of each batch were compressed and the crushing strengths for five were determined. The remaining slugs were screened through an oscillating granulator and recompressed at the same pressure used initially. The crushing strengths of the final tablets were again determined. The results indicated that the hardest tablets were produced using 75% MCC: 25% DCP. Excipient systems containing MCC generally produced slugs with the greatest crushing strengths, which may be due to the plastic nature of MCC.

- ***Bozic D Z et.al***,[17] had studied the effect of dry granulation (roller compaction and slugging) on compactibility and tablet capping tendency in a formulation with macrolide antibiotic and microcrystalline cellulose (MCC) was investigated. Direct tableting of this formulation revealed a pronounced capping tendency. Both dry granulated systems exhibit better compatibility and significant reductions in capping tendency compared to direct tableting. The capping tendency was also reduced through the use of precompression during direct tableting. Mixture with dry granulated material slugged, Avicel PH 101 15% (w/w), and talc 2% (w/w) mixed, after the addition of 0.5% magnesium stearate. Slugging was performed on a rotary tableting machine. The slugs were crushed in a mill with a 1.5mm sieve opening. The resulting granules were mixed with amberlite and the rest of the talc. The particle size alone does not show a significant influence on tablet crushing strength but the process of dry granulation.

- ***Majha Santla et.al***,[18] investigated the influence of various powder agglomeration processes on tableting mixture flow and compaction properties. Four different granulation methods of the same model placebo formulation were tested at a semi-industrial scale and their properties were compared to those of the directly compressed mixture. The compactibility was considerably lower for the slugged mixture; however, the roller-compacted mixture produced tablets with unexpectedly high tensile strength. In conclusion, it was important to emphasize those general assumptions like higher porosity better compressibility or better compressibility better compatibility cannot be established for complex tableting mixture.

- ***Mitchell S A et.al***,[19] studied a technique to enhance the dissolution rate of poorly water-soluble drugs with hydroxypropyl methylcellulose (HPMC) without the use of solvent or heat addition. Three poorly water-soluble drugs, naproxen, nifedipine, and carbamazepine, were studied with low-viscosity HPMC USP Type 2208 (K3LV), HPMC USP Type 2910 (E3LV and E5LV), and methylcellulose. Polymer and drug were dry-blended, compressed into slugs on a tablet press or into ribbons on a roller compactor, and then milled into a granular powder physical mixtures of HPMC and one of the poorly water-soluble drugs Round, flat-faced punches with 22-mm diameter were used.

In conclusion, slugging/roll compaction combined with dry granulation was reported to be an easily scalable process, which requires neither solvents nor heat and it can effectively enhance the dissolution properties of the sparingly soluble drugs.

- ***Saravanan M et.al***,[20] produced HPMC based extended-release tablets for cephalexin and compared wet granulation with slugging/dry granulation. Tablets prepared with materials from dry granulation showed a slower release of cephalexin. A clear explanation was not provided. The authors suggested the presence of higher moisture in granules prepared by a dry granulation technique after wet-granulation resulted in faster swelling of the HPMC matrix. The addition of polysorbate 80 further reduced the dissolution of cephalexin which was again explained by the faster wetting and swelling of the HPMC matrix.

- ***Dixit R B et.al***[21] developed once-daily sustained-release matrix tablets of metformin HCl, an anti-diabetic agent. The tablets were prepared by the non-aqueous wet granulation method. Isopropyl alcohol solution of polyvinylpyrrolidone (PVPK30) was used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC) and locust bean gum (LBG). The tablets were subjected to thickness, weight variation test, drug content, hardness, friability, and in vitro release studies. All the tablet formulations showed acceptable pharmacy technical properties and complied within-house specifications for tested parameters. The results of dissolution studies indicated that formulation M5 (HPMC: LBG, 200:30 mg) could extend the drug release up to 8 hours. The successful formulation of the study exhibited satisfactory drug release (M5) was compared with the marketed formulation (Obimet SR™) and showed very close to a release profile which suggests a sustained release profile.

- ***Wadher K J et.al***[22] developed the formation of oral sustained release metformin tablets prepared by direct compression method, using hydrophilic hydroxyl propyl methylcellulose and Xanthan gum polymer as a rate-controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Mean dissolution time was used to characterize the drug release rate from a dosage form and indicated the drug release retarding efficiency of polymer. Hydrophilic matrix of HPMC alone could not control the Metformin release effectively for 12 h whereas when combined with Xanthan gum could slow down the release of a drug.

- ***M Rajesh et.al***[23] formulated dispersible tablets in pediatric, to overcome the drawbacks of conventional Cefuroxime Axetil tablets such as swallowing difficulty and bitter taste. Taste masking was done by adopting four taste-masking methods including the Addition of Flavors and Sweeteners, Granulation with Stearic acid by slugging process, Polymer coating method and Inclusion complexation with ß-Cyclodextrin. The blend was compressed as slugs in a

tablet machine using flat-faced punches (23.5mm round). The slugs were screened through sieve # 20 and 60 to produce granules. The slugging process was repeated to produce sufficient granules.

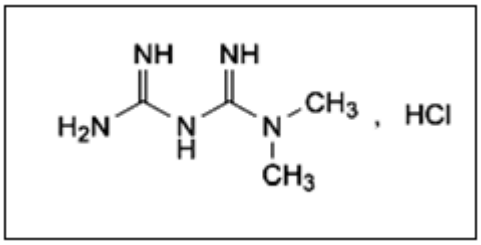
- ***Madishetty V K et.al***[24] developed the formulation of pseudoephedrine Hydrochloride (HCl) extended-release was prepared by using different polymers (HPMC and ethocel) and with different diluents (dibasic calcium phosphate anhydrous, dibasic calcium phosphate dihydrate, lactose anhydrous and DCL-15). The experimental work included preformulation studies, formulation development, and evaluation. The results of the present study pointed out that the type and level of excipients influence the rate and extent of pseudoephedrine HCL extended-release. The insoluble diluents especially dibasic calcium phosphate causes that the drug to be released at a slower rate and to a lesser extent than the soluble diluents (lactose) was investigated. Slugs were prepared by using a rotary tablet compression machine by using 12mm flat punches and reduce the size by using a cutter mill. #24 sieve, lubrication, compression.

- ***Yadav V B et.al***[25]developed a compaction technique to enhance the solubility, dissolution rate and other physicochemical properties of poorly water-soluble drug indomethacin (IM) with different polymers. The IM was compacted with the different polymers like hydroxypropyl methylcellulose (HPMC), Kollicoat IR, Chitosan, Polyvinyl Pyrrolidone without using any binder and solvent. Polymer and drug were dry-blended, compressed into slugs on a tablet press, and then milled into a granular powder. Slugs were prepared by compression of the resulting physical mixtures on a KBR Press with 30 second dwell time. Round, flat-faced punches with 13-mm diameter were used. A compression force of 1 tone was utilized for all slugs, and the range for slug weight was 500-800 mg. The resulting slugs were milled in mortar and pastel then passed through sieve no # 22 to form uniform compacted granules containing drug and polymers.

## 2.2 DRUG PROFILE:

**Metformin HCl** [26-29]

- **Structure:-**




- **Chemical name:-** Metformin HCL
- **Chemical formula:-**$C_4H_{11}N_5$
- **IUPAC name:-**1-carbamimidamido-N, N-dimethylmethanimidamide.
- **Molecular weight:-** 129.1636
- **Melting point:-** 223-226$^0$ c
- **Description:-** white crystalline powder; hygroscopic.
- **Solubility:-**freely soluble in water; slightly soluble in ethanol (95%); practically insoluble in acetone, chloroform.
- **Half-life:-** 1.5-3 hrs
- **Bioavailability:-** 50 to 60% under fasting conditions
- **Protein binding:-** Metformin is negligibly bound to plasma proteins.
- **Mechanism of action:-** Metformin's mechanism of action is different from other classes of oral anti-hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin 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 Metformin'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. AMPK probably also plays a role, as Metformin administration increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake.

- **Clearance route:-** Kidney.

- **Toxicity:-** adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise, and headache might be seen.

- **Contraindications:-**

Metformin hydrochloride extended-release tablets are contraindicated in patients with:

1. Renal disease or renal dysfunction

2. Congestive heart failure requiring pharmacologic treatment.

3. Known hypersensitivity to metformin hydrochloride.

4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function.

- **Dose:** -0.5-2gm

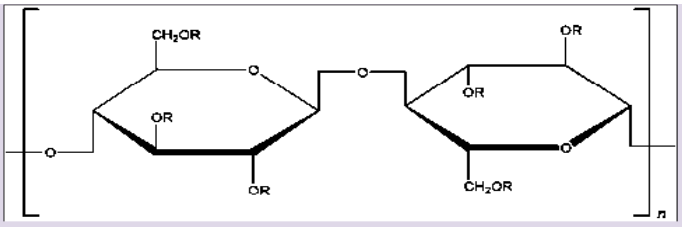
- **Dosing frequency:** -2-3 dose/day

- **Duration of action:** -6-8 hrs

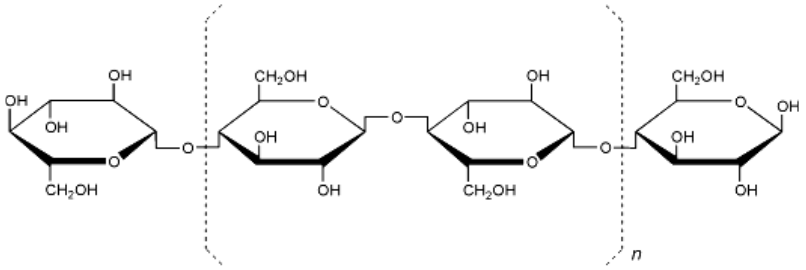
- **Dosage form:** - Tablet, extended release tablet.

## 2.3 EXCIPIENT PROFILE[30]:

### 2.3.1 Hydroxypropyl methylcellulose K4M:

| Sr. No. | Parameter | | Description |
|---|---|---|---|
| 1 | Name | : | Hydroxypropyl methylcellulose K4M |
| 2 | Nonproprietary Names | : | Hypromellose (BP),Hypromellose (USP), Hypromellose(PhEur). |
| 3 | Synonyms | : | HPMC, hypromellose, Methocel. |
| 4 | Chemical name | : | Cellulose 2-hydroxy propyl methyl ether |
| 5 | CAS Registry Number | : | 9004-65-3 |
| 6 | Molecular Weight | : | Approximately 10,000 – 15, 00, 000. |
| 7 | Structural Formula | : |  |
| 8 | Description | : | the odorless, tasteless, white or creamy white fibrous or granular powder |
| 9 | Viscosity | : | viscosity values for 2% (w/v)of methocel K4M aqueous solutions was 4000mPas |
| 10 | Functional category | : | Binder in tablet granulation (2-5%); high viscosity grades are used to retard the release of water-soluble drugs, emulsifying agents, suspending agents and stabilizers in gel and ointments, adhesive in plastic bandages. |
| 11 | Applications in Pharmaceutical Formulation | : | Used in oral, ophthalmic and topical pharmaceutical formulations. As tablet binder, film coating and as an extended-release tablet matrix. It is also used as suspending and thickening agent in topical formulations |
| 12 | Melting point | : | Browns at 190-200$^0$c; chars at 225-230$^0$C. |
| 13 | Solubility | : | Slightly soluble in 5% w/v NaOH solution; practically insoluble in water, dilute acids, and most organic solvents. |
| 14 | Stability &Storage | : | The powder is stable, although hygroscopic after drying. Hypromellose powder should be stored in a well-closed container, in a cool, dry place. |
| 15 | Incompatible | : | Incompatible with some oxidizing agents. |

### 2.3.2 Microcrystalline Cellulose PH102:

| Sr. No. | Parameter | | Description |
|---|---|---|---|
| 1 | Name | : | Microcrystalline cellulose PH102 |
| 2 | Nonproprietary Names | : | Microcrystalline cellulose (BP), Cellulose Microcrystalline ( PhEur) |
| 3 | Synonyms | : | Cellulose, Avicel PH 102 |
| 4 | Chemical Name | : | Cellulose |
| 5 | CAS Registry Number | : | 9004-34-6 |
| 6 | Molecular Formula | : | $(C_6H_{10}O_5)_n$ where n = 220. |
| 7 | Molecular Weight | : | ≈36000 |
| 8 | Structural Formula | : |  |
| 9 | Description | : | A white, odorless, tasteless, crystalline powder composed of porous particles. Commercially available in different particle sizes and moisture grades that have different properties and applications |
| 10 | Functional category | : | Adsorbent, suspending agent, tablet and capsule diluents, tablet disintegrant. |
| 11 | Applications in Pharmaceutical Formulation | : | As binder/diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and Disintegrants properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products. |
| 12 | Melting point | : | Chars at 260–270°C. |
| 13 | Solubility | : | Slightly soluble in 5% w/v NaOH solution, practically insoluble in water, dilute acids, and most organic solvents. |
| 14 | Stability &Storage | : | It is stable through hygroscopic material. It should be stored in a well-closed container in a cool, dry place. |
| 15 | Incompatible | : | Incompatible with strong oxidizing agents. |

**2.3.3 Colloidal silicon dioxide:**

| Sr. No. | Parameter | | Description |
|---|---|---|---|
| 1 | Name | : | Colloidal silicon dioxide |
| 2 | Nonproprietary Names | : | Colloidal Anhydrous Silica (BP),Colloidal silicon dioxide(USP-NF) |
| 3 | Synonyms | : | Aerosil, Cab-O-Sil, colloidal silica. |
| 4 | Chemical name | : | Silica |
| 5 | CAS Registry Number | : | 7631-86-9 |
| 6 | Molecular Formula | : | $SiO_2$ |
| 7 | Molecular Weight | : | 60.08 |
| 8 | Structural Formula | : | $SiO_2$ |
| 9 | Description | : | It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder. |
| 10 | Functional category | : | Adsorbent, anticaking agent, emulsion stabilizer, Glidant; suspending agent, tablet disintegrant; thermal stabilizer, viscosity-increasing agent. |
| 11 | Applications in Pharmaceutical Formulation | : | Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in several processes such as tableting. |
| 12 | Melting point | : | $1600^0C$ |
| 13 | Solubility | : | Practically insoluble in the organic solvent, water, and acid, soluble in a hot solution of alkali hydroxide. |
| 14 | Stability &Storage | : | Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. Store in a well-closed container in a dry place. |
| 15 | Incompatible | : | Incompatible with diethylstilbestrol preparations. |

### 2.3.4: Excipients Profile: Magnesium Stearate

| Sr. No. | Parameter | | Description |
|---|---|---|---|
| 1 | Name | : | MagnesiumStearate |
| 2 | Nonproprietary Names | : | Magnesium stearate(BP) (USPNF) (JP), Magnesii stearas(PhEur). |
| 3 | Synonyms | : | Dibasic magnesium stearate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt. |
| 4 | Chemical name | : | Octadecanoic acid magnesium salt. |
| 5 | CAS Registry Number | : | 557-04-0 |
| 6 | Molecular Formula | : | $C_{36}H_{70}MgO_4$ |
| 7 | Molecular Weight | : | 591.34 |
| 8 | Structural Formula | : | $[CH_3(CH_2)_{16}COO]2Mg$ |
| 9 | Description | : | 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. |
| 10 | Functional category | : | Tablet and capsule lubricant. |
| 11 | Applications in Pharmaceutical Formulation | : | Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations primarily with lubrication purposes. |
| 12 | Melting point | : | 117–150°C |
| 13 | Solubility | : | Insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%). |
| 14 | Storage | : | A well-closed container in a cool, dry place. |
| 15 | Incompatible | : | Strong acids, alkalis, iron salts. |

## 3. AIM AND OBJECTIVES OF PRESENT STUDY:

The present work aims to carry out the design and development of Co-processed excipients by the slugging method for direct compression of a model drug and co-processed excipients for sustained release tablets of model drugs by using HPMC K4M polymer. Also a comparative evaluation between granules of different particle sizes and different ratios of HPMC K4M and MCC PH102 on percent drug release.

**The objectives of the study:-**

1) Co-processed granulation of MCC PH102 and HPMC K4M by the slugging method.

2) To study the effect of polymer concentration on drug release from the SR tablet.

3) To study the effect of granules size on drug release.

4) To study the drug release pattern from the tablet prepared by the slugging method.

5) To study the effect of the drug to polymer ratio on drug release from the tablet.

## 4. SCOPE AND PLAN OF WORK

### 4.1 SCOPE:

➢ Now a day's tablets are the principal part among all the pharmaceutical formulations as it occupies 80% of all dosage forms administered to a human being. This is due to their ease of manufacture, the convenience of dosing and stability compared with liquid and semi-solid dosage forms.

➢ Wet granulation method is a widely used method for the manufacturing of tablets. But, wet granulation has the disadvantage that this method is not suitable for those drugs which are moisture sensitive and thermosensitive. So, for such drugs, dry granulation or direct compression methods are mostly used.

➢ Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates) and are compressed on a tablet press. This equipment offers a wide range of pressures to attain proper densification and granule formation. It is simpler than wet granulation. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may be added to the formulation to facilitate the formation of granules.

➢ Direct compression of the active ingredient with other appropriate excipients to form a tablet, for medium-to high-potency compounds where the drug content is less than 30% of

the formulation. The advantages of direct compression are well-known, the most important being fewer processing stages and the elimination of heat and moisture effects.

➢ Directly compressible excipients are the majority used for conventional tablets. So the main intention of the present work is to develop co-processed excipients which can be used for the formulation of the sustained-release tablet. Many drugs have shorter half-life so they need frequent administration that makes patient discomfort, this problem of the conventional tablet can be overcome by sustained release tablet formulation.

➢ The availability of handy co-processed excipients excluded rigorous safety testing of a completely new chemical. That is, excipients that have been combined synergistically and which are more beneficial than simple physical admixtures or it can be defined as combining two or more established excipients by an appropriate process.

➢ Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components.

➢ The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. Also in the preparation of a tablet, major time is required for the step of granulation but by using ready to use co-processed excipients one can get directly compressible excipients that eliminate the step of granulation.

➢ One of the major challenges of tablets and capsule manufacturing comes from the flow properties of the materials to be compressed. Hence by using this approach, we can increase the flow properties of compressible material.

**4.2 PLAN OF WORK:**

1) Literature Survey

2) Procurement of drug and chemicals

3) Analysis of Drug and Excipients

4) Preformulation study of Drug and Excipients

5) Formulation of the sustained released matrix of excipients by slugging method

6) Experimental work:

A) Preformulation study of the drug.

- Melting Point of the drug.
- Calibration curve of the drug.

B) Formulation of Co-processed excipients by slugging method and its Preformulation study:-

- The angle of repose.
- Bulk density.
- Tapped density.
- Carr's index.
- Hausner's ratio.
- Particle size distribution study.

C) Formulation of tablets.

- Preparation of sustained-release matrix tablet by direct compression using co-processed excipients with Metformin as a model drug.

D) Evaluation of Tablets:

- Weight variation test.
- Tablet dimensions.
- Hardness.
- Friability study.
- *In-vitro* dissolution studies.
- Drug release kinetic.
- Statistical analysis of data.

## 5 MATERIALS AND METHOD:

### 5.1 LIST OF MATERIAL USED:-

**Table No. 3: Name of the Excipients and Chemical and its supplier**

| Sr. No. | Material | Supplier |
|---|---|---|
| 1. | Metformin HCL | Piramal Health Care Baddi |
| 2. | Hydroxypropyl Methyl Cellulose K4M | Dow Chemical's the USA |
| 3. | Microcrystalline Cellulose PH102 | FMC Biopolymer, UK |
| 4. | Colloidal-silicon dioxide (Aerosil) | Loba chemicals, Mumbai |
| 5. | Magnesium stearate | Mallinckrodt, USA |
| 6. | Sodium hydroxide | Loba chemicals, Mumbai |
| 7. | Potassium Dihydrogen orthophosphate | Loba chemicals, Mumbai |

### 5.2 LIST OF INSTRUMENTS AND EQUIPMENT USED:-

**Table No. 4: Name of Instruments and Equipment and its manufacturer**

| Sr.No. | Name of equipment | Name of manufacturer |
|---|---|---|
| 1 | Electronic balance (sensitivity 0.001gm) | Shimadzu Corporation, Japan |
| 2 | UV-VIS double beam spectrophotometer 2203 | Systronic, Ahmedabad. |
| 3 | 8 station dissolution apparatus (USP) | Electrolab, Mumbai |
| 4 | 16 station multi tooling tablet compression machine. | Cadmach, Ahmedabad, India |
| 5 | Hardness tester (Monsanto type) | Rolex, Mumbai. |
| 6 | Bulk density apparatus | Dolphin, India |
| 7 | Mechanical sieve shaker | Dolphin, India |
| 8 | Friability test apparatus | Suprashesh, India |
| 9 | Ultrasonicator | Citizen, Digital Ultrasonic Cleaner |
| 10 | Micrometer Screw Gauge. (LC 10µm) | Insif India, Delhi |
| 11 | pH meter | Systronic 335 |

## 5.3 METHOD

### 5.4 5.3.1 Selection of drug and polymer:[22,26]

Metformin HCL is freely soluble in water. It has a half life of 1.5- 3 hrs and bioavailability 50-60%. Metformin HCl was mainly absorbed from the lower track of GIT. Thus, the absorption window is predominantly in the small intestine and follows a saturable dose-dependent mechanism. Metformin absorption following oral administration is therefore likely to be site specific. The immediate release products need to be administered 2 to 3 times daily. So, the Metformin HCL is a suitable drug for the formulation of sustained release tablet. Hydroxypropyl methylcellulose K4M is used as a matrix-forming agent.

**Table No. 5: List of ingredients and category**

| Sr. No. | Ingredient | Category |
|---|---|---|
| 1 | Metformin HCL | Active Pharmaceutical Ingredient |
| 2 | HPMC K4M | Matrix forming polymer |
| 3 | MCC PH102 | Polymer |
| 4 | Aerosil | Glidant |
| 5 | Magnesium stearate | Lubricant |

### 5.3.2 Identification of pure Metformin HCL:

#### 5.3.2.1 Description:

The sample of Metformin HCL was analyzed for physical appearance and powder nature.

#### 5.3.2.2 Determination of Melting Point: [31]

The melting point of the pure drug and excipients was determined by using the melting point apparatus. The thermometer used was previously calibrated (IP-1996). The method consists of placing the powdered compound in a capillary tube & heated in the Thiele apparatus. The temperature at which the sample starts melting is considered as the lower limit and at which completely melts is considered an upper limit of melting range. The obtained results compared with the values in literature.

**5.3.2.3 Study of UV-Visible Spectrophotometric Characteristics of Metformin HCL (Determination of $\lambda_{max}$)**

A known quantity of Metformin HCL was dissolved in phosphate buffer of pH 6.8 with sonication; further suitable dilution was made to get a 10µg/ml solution. The solution was scanned for range 200nm to 400nm in a UV double beam spectrophotometer to get the spectrum of the drug. Initially, cell matching was done by using a phosphate buffer of pH 6.8.

**5.3.2.4 Standard Calibration Curve of Metformin HCL**[32]

**Standard calibration curve of Metformin HCL in phosphate buffer (pH 6.8):-**

A stock solution of 100µg/ml was prepared and further dilution made to obtain varying concentration solutions. Absorbance was read at 232nm against phosphate buffer of pH 6.8 as blank.

**5.3.2.5 Assay of Metformin HCl:-**

For the assay, 20 tablets were crushed in mortar and pestle. 400 mg powder equivalent to 100 mg of Metformin HCl was added to 500 ml volumetric flask and volume made up to 500 ml with 10% methanol. This solution was sonicated for 30 minutes. After the sonication solution was filtered through a 0.45-micron membrane filter. Further, 5 ml of this filtrate was diluted to 100 ml with the same solvent and absorbance was taken[33].

**FORMULATION DESIGN:**

**Table No. 6: Formulation code and the ratio of MCC PH102 to HPMCK4M**

| Sr. No. | Ingredient | FA | | FB | | FC | | FD | |
|---|---|---|---|---|---|---|---|---|---|
| | | mg | w/w | mg | w/w | mg | w/w | mg | w/w |
| Intragranular | | | | | | | | | |
| 1 | HPMC K4M | 118.33 | 23.66 | 177.5 | 35.5 | 236.66 | 47.25 | 266.25 | 53.25 |
| 2 | MCC PH102 | 236.67 | 47.33 | 177.5 | 35.5 | 118.33 | 23.66 | 88.75 | 17.75 |
| Extra granular | | | | | | | | | |
| 3 | Metformin HCL | 125 | 25 | 125 | 25 | 125 | 25 | 125 | 25 |
| 4 | Aerosil | 15 | 3 | 15 | 3 | 15 | 3 | 15 | 3 |
| 5 | Magnesium stearate | 5 | 1 | 5 | 1 | 5 | 1 | 5 | 1 |
| **Total** | | 500 | 100 | 500 | 100 | 500 | 100 | 500 | 100 |

**Table No. 7: Formulation Table for each tablet**

| Sr. No. | Formulation Code | MCC PH102:HPMCK4M |
|---|---|---|
| 1 | FA | 1:0.5 |
| 2 | FB | 1:1 |
| 3 | FC | 1:2 |
| 4 | FD | 1:3 |

## 5.5 SELECTION OF EXCIPIENTS FOR CO-PROCESSING:

In the current research work, MCC PH 102 and HPMC K4M were used to manufacture co-processed excipients. HPMC K4M is used as a matrix forming agent where as MCC PH102 is used as a diluent. To retard the release of water soluble drug (Metformin HCL), hydrophobic diluents (MCC PH 102) and swellable matrix system (HPMC K4M) was used for the preparation of co-processed excipients.

## 5.6 PREPARATION OF CO-PROCESSED GRANULES:

### 5.6.1 Granulation by Slugging technique[16]:

For the preparation of co-processed granules, a different ratio of MCC PH102 and HPMC K4M was used (Table 6). MCC PH 102 and HPMC K4M were shifted through the sieve 40#. Then both excipients were mixed for 15 min in a glass mortar. Slugs were prepared on a tablet compression machine using a 12mm punch, weighing approximately 1gm. These slugs were crushed in mortar and pestle and passed through sieves of different mesh sizes like 18#, 20#, 30# and 40#, to obtain granules of different size. The granules passed through 18#, 20#, 30# and 40#were designated as 1, 2, 3 and 4 respectively.

## 5.7 EVALUATION OF GRANULES:

### 5.7.1Angle of repose:

The angle of repose is defined as the maximum angle possible between the surface of a pile of powder and a horizontal plane. The angle of repose has been used as an indirect method of quantifying powder flowability. The angle of repose for a blend of each formulation was determined by the fixed funnel method. The fixed funnel method employs a funnel that is secured with its tip at a given height, h, which is kept 2 cm, above graph paper that is placed

on a flat horizontal surface. With r, being the radius of the base of the conical pile, angle of repose can be determined using the following equation.[34, 35]

$$\tan \theta = h/r$$

Where; θ = Angle of repose

r = Radius of the base

h =Height from tip of funnel to the surface of graph paper.

**Table No. 8: Grading of powder flow property according to the angle of repose**

| Angle of repose | Flow Property |
|---|---|
| <25 | Excellent |
| 25 -30 | Good |
| 30 -40 | Passable |
| > 40 | Very poor |

**5.7.2. Bulk density:**

It is the ratio of mass to bulk volume. It is required to decide the appropriate packing of dosage forms. 20 gm powder/ granules were allowed to flow in a fine stream into a graduated cylinder and final volume was noted. The bulk density was obtained by dividing the weight of the sample in grams by final volume in $cm^3$ and it was determined by the equation given below[36, 37, 38]

**Bulk density = Mass/ Bulk volume**

**5.7.3. Tapped density:**

20 gm powder/ granules were allowed to flow in a fine stream into a graduated cylinder of a mechanical tapping device. The measuring cylinder was tapped for 100 times and final tapped volume was noted. The tapped density was obtained by dividing the weight of the sample in grams by final tapped volume in $cm^3$ and it was calculated by using the equation given below[39, 40,41]

**Tapped density = Mass/ Tapped volume**

### 5.7.4 Hausner's ratio:

Hausner found that the ratio tapped density/bulk density was related to inter particle friction as such, and could be used to predict powder flow properties. He showed that the powder with low interparticle friction had a ratio of approximately 1.2, whereas more cohesive less free-flowing powders have a Hauseners ratio greater than 1.6. Hausner's ratio of less than 1.25 indicates good flow.[40, 41, 42, 43]

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

**Table No. 9: Relationship between flowability and Hausner's ratio**

| Flow Character | Hausner's Ratio |
|---|---|
| Excellent | 1.00 - 1.11 |
| Good | 1.12 - 1.18 |
| Fair | 1.19 - 1.25 |
| Passable | 1.26 - 1.34 |
| Poor | 1.35 - 1.45 |
| Very poor | 1.46 - 1.59 |
| Very very poor | >1.60 |

### 5.7.5 Compressibility index:

It is also one of the simple methods to evaluate the flow property of powder by comparing the bulk density and tapped density. The percentage compressibility of powder was a direct measure of the potential powder arch or bridge strength and stability. It is also known as Carr's index. It can be calculated by the following equation. [40,42, 38,41]

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

**Table No. 10: Grading of compressibility of the powder according to Carr's index**

| Carr's Index | Flow Property |
|---|---|
| ≤10 | Excellent |
| 11 to 15 | Good |
| 16 to 20 | Fair |
| 21 to 25 | Passable |
| 26 to 31 | Poor |
| 32 to 37 | Very poor |
| > 38 | Very very poor |

### 5.7.6 Particle size distribution:

Granules were studied for particle size distribution using a mechanical sieve shaker. Each granulation formulation was evaluated for granule to fine ratio. The sieves used along with their opening diameter in mm are given below. [44,45, 46]

Granules which retained above sieve 60# were considered as granules and which passed through sieve 60# were considered as fine.

**Table No. 11: Sieve no. along with the opening diameter**

| Sr. No. | Sieve No. | Opening(mm) |
|---|---|---|
| 1 | 20 | 0.850 |
| 2 | 40 | 0.425 |
| 3 | 60 | 0.25 |
| 4 | 88 | 0.177 |
| 5 | 120 | 0.125 |

## 5.8 PREPARATION OF TABLET FORMULATION

Batch size of 100 tablets, were prepared by direct compression method. Drug, lubricant, and Glidant are first sifted through the sieve no. 40#. After that, drug Metformin and co-processed granules were mixed for 20-30 minutes in a polythene bag. After thorough mixing, the lubricant and Glidant were also mixed. Then this mixture was compressed into tablets using concave faced punches of 11mm diameter by keeping hardness between 6 to 9 kg/cm$^2$.

## 5.9 EVALUATION OF TABLETS:

Prepared tablets were evaluated for various physicochemical properties, such as hardness, thickness, diameter, weight variation, uniformity of content and *in-vitro* dissolution study, etc.

### 5.9.1. Uniformity of weight:

The weight of the tablet is measured to ensure that a tablet contains the proper amount of drugs. Weight variation test was performed as per IP 2007. Twenty tablets were selected randomly and weighed. The average weight of the tablet was determined. Not more than two of the individual weights should deviate from the average weight by more than the appropriate percentage deviation as specified in I.P.2007 [47].

**Table No. 12: IP standards for uniformity of weight[42]**

| Sr. No. | The average weight of the tablet | Percentage deviation |
|---|---|---|
| 1 | 80 mg or less | ± 10 |
| 2 | 80 mg to 250 mg | ±7.5 |
| 3 | 250 mg or more than 250 mg | ±5 |

### 5.9.2 Dimensions:

Any variation in tablet thickness within a particular lot of tablets or between manufacture's lots should not be apparent to unaided eyes for consumer acceptance of the product. Also, thickness and diameter must be controlled to facilitate packaging. Thus thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of tablets were measured using a micrometer screw gauge (Rolex Scientific Engineers Limited). The study was carried out in a triplicate [48].

### 5.9.3 Hardness:

Tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. Monsanto hardness tester (Rolex Scientific Engineers Limited) was used to determine the hardness of the tablet. It is expressed in $kg/cm^2$. The mean hardness of each formulation was determined. The study was carried out in the replicate of five. [49,50].

**5.9.4 Friability:**

Tablet hardness is not an absolute indicator of strength since some formulations compressed into very hard tablets tend to cap on attrition losing their crown portions. Therefore another measure of tablet's strengths, its friability is often measured. For a tablet with an average weight of 0.65gm or less take a sample of whole tablets corresponding to about 6.5gm and for a tablet with an average weight of more than 0.65gm take a sample of 10 whole tablets. Thirteen tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After 100 revolutions the tablets were dedusted and weighed again. Percentage friability was calculated from the loss in weight as given in the equation below. The weight loss should not be more than 1 % [51].

**% Friability = Initial weight - Final weight / Initial weight X 100**

**5.10 *IN-VITRO* DRUG RELEASE STUDIES:**

According to the USP monograph of ER metformin HCl tablet, USP- II Paddle type was used for dissolution. The parameters for dissolution are as follows[52],

- USP apparatus:- Type-II (Paddle)
- Paddle RPM:- 100
- Buffer Volume:- 900ml
- Sampling Volume:- 5ml
- Buffer Replacement:- replace 5ml
- Buffer: - 6.8 Phosphate Buffer.
- Temperature of bath:- $37 \pm 0.5^0$ C temp
- Sampling time:- 0.5 hr, 1hr, 3hr, 5hr, 8hr and 10 hr

**5.11 RELEASE KINETIC OF DRUG[53]:**

All the formulations were subjected to study the release kinetics. The drug release profile of all the batches was fitted to zero-order kinetics, first-order kinetics, Higuchi model and

Korsmeyer-Peppas model to ascertain the kinetic modeling of drug release and the model with the higher correlation coefficient was considered to be the best fit model.

**Fitting Kinetic Models To The Drug Release Data:** [54,55,56]

To analyze drug release kinetics from each of the prepared matrices, the following mathematical models were fitted to the release data:

(i) Zero-order Kinetics (Xu & Sunada, 1995; Singla & Medirata, 1988)

(ii) First-order Kinetics (Xu & Sunada, 1995; Singla & Medirata, 1988)

(iii) Higuchi's Square Root of Time Equation (diffusion model) (Higuchi, 1963)

(iv) Power Law Equation (diffusion/relaxation model) (Ritger & Peppas, 1987)

**Table No. 13: Fitting Kinetic Models to the Drug Release Data**

| Kinetic Model Name | Plot | Equation | Parameter definition |
|---|---|---|---|
| Zero Order - Kinetics | Time Vs Cumulative %Drug Release. | $C = K_o t$ | $K_o$ =zero order rate constant<br>t = time |
| First Order - Kinetics | Time Vs Log Cumulative % Drug Remaining. | $\log C = \log C_o - K_1 t/2.303$ | $C_o$ = initial concentration of drug<br>$K_1$ = first order constant |
| Higuchi's Square Root of Time (diffusion model) | Square Root of Time (SQRT) Vs Cumulative %Drug Release. | $Q = K_H t^{1/2}$ | $K_H$ = constant reflecting the design variables of the system |
| Korsmeyer - Peppas Power Law (diffusion/relaxation model) | Log Time Vs Log Cumulative %Drug Release. | $M_t / M_\infty = Kt^n$ | $M_t / M_\infty$ is fraction if drug released at time t<br>K = release rate constant<br>n = release exponent( Table 1) |

**Table No. 14: Diffusion exponent and solute release mechanism**

| Diffusion exponent (n) | Overall solute diffusion mechanism |
|---|---|
| 0.45 | Fickian diffusion |
| $0.45 < n < 0.89$ | Anomalous (non-Fickian) diffusion |
| 0.89 | Case-II transport |
| $n > 0.89$ | Super case-II transport |

**5.12 STATISTICAL ANALYSIS:**

All the formulations were compared for dissolution using GraphPad Instat Version 3.10. The significance values were determined by the Tukey test of significance.

**RESULTS AND DISCUSSION:**

**6.1 Introduction to the model drug:**

**Metformin Hydrochloride:**

The present work was aimed at the development of directly compressible, ready to use co-processed excipients of HPMC K4M and MCC PH102 for the formulation of a sustained release tablet of a model drug. The model drug used in this study was Metformin HCL.

A formulation of Metformin Hydrochloride Sustained release tablets containing 125 mg of Metformin hydrochloride were prepared by direct compression of co-processed excipients and Metformin HCL on a single stroke Cadmach machine. The tablets were evaluated for hardness, friability, weight variation, dimensions, and *In-vitro* release. Metformin HCl sustained-release tablets are now official in USP 31 effective from May 1, 2008. It is a blockbuster molecule in the treatment of diabetes mellitus and has very good market potential. It has a very good therapeutic value.

**6.2 Physical evaluation Metformin HCL:**

**Table No. 15: Physical Evaluation of Metformin HCL**

| **Test** | **Specification** | **Results** |
|---|---|---|
| **1.Organoleptic evaluation** | Colour-<br>Odor-<br>Taste-<br>Physical state- | White<br>no characteristic odor<br>slightly bitter<br>crystalline solid |
| **2 .Density** | | |
| Bulk density | - | 0.857gm/ml |
| Tap density | - | 0.5896gm/ml |
| Carr's index | An index of 5-15 indicates free-flowing granules while a ratio of 15-21indicates a fair flow whereas a ratio above indicates a bad flow. | 31.20% |
| Hausner's ratio | Powders with low interparticle friction such as coarse spheres have a ratio of approximately 1.2 whereas more cohesive, less free-flowing powders such as flakes have ratios greater than 1.6. | 1.45 |
| **3. Angle of repose** | Powders with an Angle of repose greater than 50° indicate unsatisfactory flow properties whereas those from 25°-30° indicate good flow properties. | $51.70^0$ |
| **4.Melting Point** | As per USP NF M.P. in the range of $223^0$C to $226^0$C | $224^0$C |

**6.3 Determination of $\lambda_{max}$ of Metformin HCL:**

As per USP NF, the reported λmax for Metformin HCL was 233nm. After doing a scan, the standard solution of Metformin HCL (10 µg/ml) shows maximum absorbance at 232 nm wavelengths in a phosphate buffer solution of pH6.8.

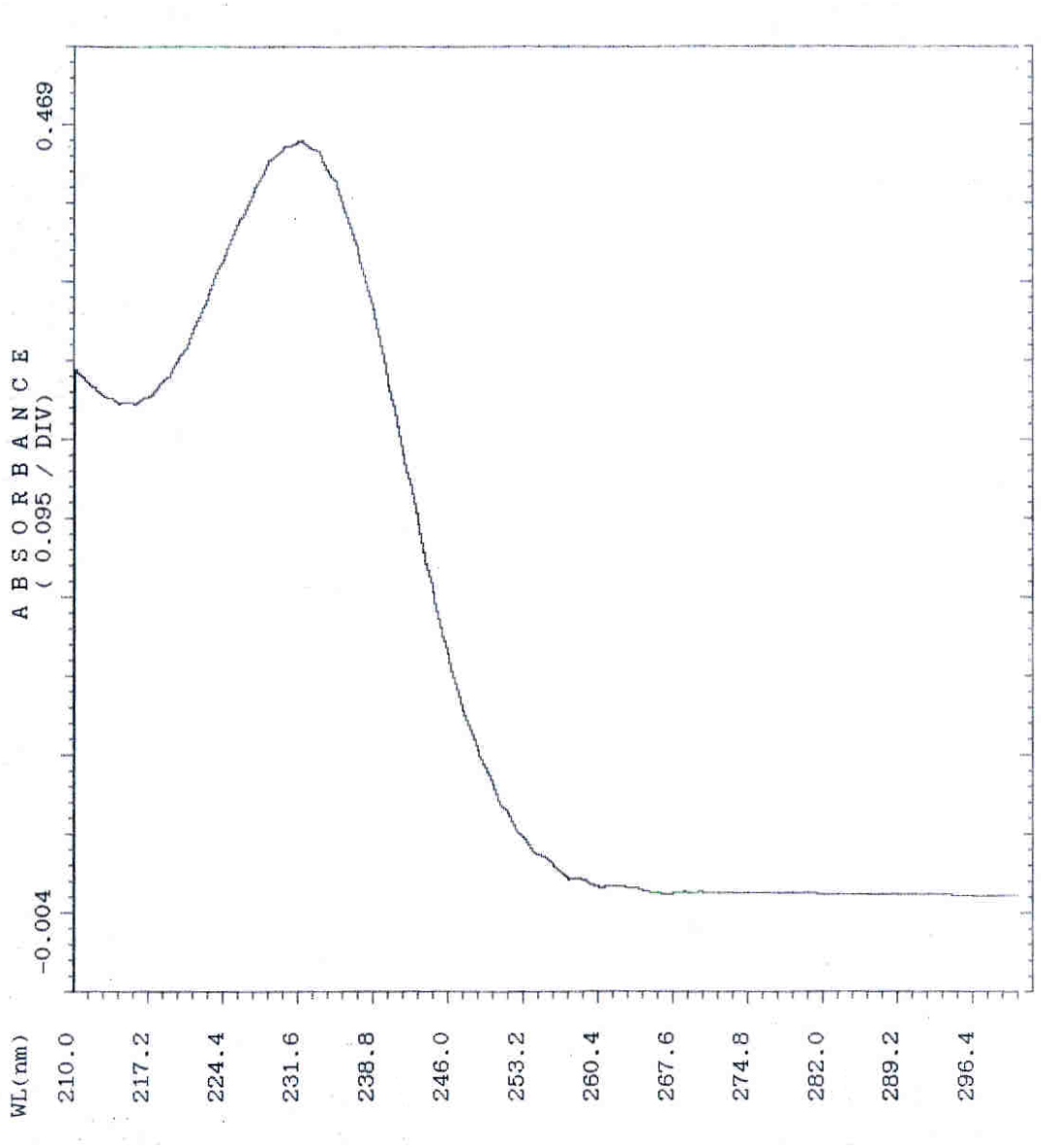



**Figure No. 1: Spectrum scan of Metformin HCL**

### 6.4 Calibration curve of Metformin HCL:

The absorbance data for the calibration curve of Metformin HCL in Phosphate buffer solution pH 6.8 is shown in Table No.6.2 The calibration curve followed linearity over the range of 2-20 µg /ml as shown in Graph No.6.1.

**Table No. 16: Data for the calibration curve of Metformin HCL in phosphate buffer of pH 6.8**

| Sr. No. | Concentration in µgm/ml | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.140 |
| 3 | 4 | 0.246 |
| 4 | 6 | 0.381 |
| 5 | 8 | 0.499 |
| 6 | 10 | 0.625 |
| 7 | 15 | 0.944 |
| 8 | 20 | 1.233 |

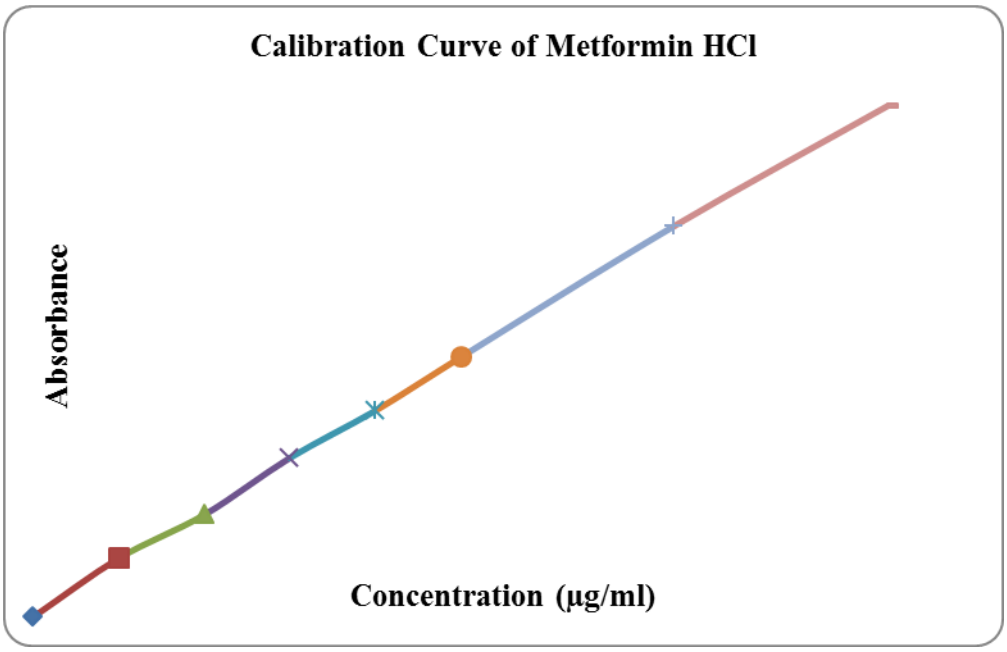



**Figure No. 2: Calibration curve for the Metformin HCL in phosphate pH 6.8**

**Table No. 17: Regression and slope value of Metformin calibration curve**

| | |
|---|---|
| Regression value ($R^2$) | 0.999 |
| Slope (n) | 0.061 |

**6.5 Evaluation of Formulation Parameters:**

The evaluation was divided in mainly-

- Pre-compression Parameters.

- Post-compression Parameters.

**PRECOMPRESSION STUDY:**

**Table No. 18: Results of flow properties**

| BATCH | ANGLE OF REPOSE(º) | BULK DENSITY (gm/ml) | TAPPED DENSITY (gm/ml) | CARR'S INDEX (%) | HAUSNER'S RATIO |
|---|---|---|---|---|---|
| **FA1** | 25.5 | 0.554 | 0.678 | 18.36 | 1.2 |
| **FA2** | 30.9 | 0.534 | 0.633 | 15.63 | 1.1 |
| **FA3** | 25.5 | 0.569 | 0.68 | 16.27 | 1.19 |
| **FA4** | 31.2 | 0.597 | 0.677 | 14 | 1.13 |
| **FB1** | 26.7 | 0.636 | 0.682 | 12.6 | 1.1 |
| **FB2** | 24.3 | 0.638 | 0.777 | 9.54 | 1.22 |
| **FB3** | 39.5 | 0.462 | 0.806 | 18.14 | 1.74 |
| **FB4** | 35.5 | 0.51 | 0.616 | 22.06 | 1.58 |
| **FC1** | 29.6 | 0.518 | 0.624 | 22.08 | 1.17 |
| **FC2** | 28.4 | 0.484 | 0.628 | 15.21 | 1.29 |
| **FC3** | 27.2 | 0.485 | 0.649 | 22.05 | 1.29 |
| **FC4** | 28.3 | 0.485 | 0.627 | 22.72 | 1.39 |
| **FD1** | 27.6 | 0.495 | 0.615 | 19.51 | 1.24 |
| **FD2** | 24.8 | 0.555 | 0.645 | 13.95 | 1.16 |
| **FD3** | 29.2 | 0.56 | 0.671 | 16.54 | 1.98 |
| **FD4** | 28.1 | 0.575 | 0.683 | 15.81 | 1.18 |

The formulated granules were characterized concerning the angle of repose, bulk density, and tapped density. All different granules show excellent flow property.

Carr's index and Hausner's ratio was found in all batches shown in table no.6.4.

**Particle size distribution study:-**

**Table No. 19: Particle size distribution of batch FA, FB, FC, FD**

| FA | | | | |
|---|---|---|---|---|
| Batch No. | 1 | 2 | 3 | 4 |
| % Granules | 60.28 | 62.57 | 64.75 | 61.62 |
| % Fine | 39.72 | 37.43 | 35.25 | 38.38 |

| FB | | | | |
|---|---|---|---|---|
| Batch No. | 1 | 2 | 3 | 4 |
| % Granules | 64.85 | 63.09 | 64.53 | 65.74 |
| % Fine | 35.15 | 36.61 | 35.47 | 34.26 |

| FC | | | | |
|---|---|---|---|---|
| Batch No. | 1 | 2 | 3 | 4 |
| % Granules | 70.35 | 68.57 | 67.57 | 69.25 |
| % Fine | 29.65 | 31.43 | 32.43 | 30.75 |

| FD | | | | |
|---|---|---|---|---|
| Batch No. | 1 | 2 | 3 | 4 |
| % Granules | 72.43 | 74.79 | 73.79 | 75.85 |
| % Fine | 27.57 | 25.21 | 26.21 | 24.15 |

From the particle size distribution data it was observed that as the concentration of polymer increases, the percentage of granules also increases for all the formulation batches. This is due to HPMC K4M which itself acts as a binder and having viscosity 4000mPas.

**POST- COMPRESSION PARAMETERS:**

**Weight Variation Test:**

Weight variation test revealed that the tablets were within the range of Pharmacopoeial specifications of weight variation and none of the tablets was found to deviate from the average weight of all the tablets. Thus all the formulations were found to comply with the weight variation test.

**Table No. 20: Weight variation of batch FA, FB, FC and FD**

| Batch | Max.Wt (mg) | Min. Wt (mg) | Avg. Wt(mg) | % Weight Variation | ± SD | % RSD |
|---|---|---|---|---|---|---|
| **FA1** | 0.526 | 0.493 | 0.507 | 0.1013 | 0.0096 | 1.90 |
| **FA2** | 0.520 | 0.480 | 0.503 | 0.1006 | 0.0104 | 2.08 |
| **FA3** | 0.515 | 0.479 | 0.497 | 0.0993 | 0.0101 | 2.03 |
| **FA4** | 0.519 | 0.475 | 0.500 | 0.1001 | 0.0136 | 2.72 |
| **FB1** | 0.503 | 0.493 | 0.500 | 0.0999 | 0.0023 | 0.47 |
| **FB2** | 0.505 | 0.495 | 0.500 | 0.1000 | 0.0027 | 0.55 |
| **FB3** | 0.505 | 0.495 | 0.499 | 0.0998 | 0.0031 | 0.63 |
| **FB4** | 0.516 | 0.480 | 0.500 | 0.0999 | 0.0079 | 1.59 |
| **FC1** | 0.520 | 0.479 | 0.497 | 0.0995 | 0.0102 | 2.06 |
| **FC2** | 0.507 | 0.482 | 0.497 | 0.0995 | 0.0080 | 1.61 |
| **FC3** | 0.522 | 0.485 | 0.509 | 0.1017 | 0.0108 | 2.12 |
| **FC4** | 0.520 | 0.470 | 0.497 | 0.0994 | 0.0151 | 3.04 |
| **FD1** | 0.514 | 0.490 | 0.500 | 0.0999 | 0.0065 | 1.30 |
| **FD2** | 0.516 | 0.473 | 0.495 | 0.0989 | 0.0115 | 2.33 |
| **FD3** | 0.515 | 0.493 | 0.503 | 0.1007 | 0.0065 | 1.28 |
| **FD4** | 0.530 | 0.492 | 0.506 | 0.1012 | 0.0089 | 1.76 |

**The thickness of Tablets:**

The diameter of the tablet is determined by the diameter of die and thickness is by the amount of fill permitted to enter the die, the compaction characteristic of the fill material and the force applied during compression. Thickness is not an official parameter. The thickness of the tablets was found to be in the range of **4.882 mm to 5.08 mm.**

**The hardness of Tablet:**

Tablet hardness has an influence on the tablet density and porosity that result in different release pattern of the drug. It also affects the rate of penetration of dissolution fluid in the tablet. The hardness of the sustained release tablet was found to be in the range of **6.50 kg/cm$^2$ to 7.75 kg/cm$^2$.**

**Friability:**

All the tablets have acceptable friability as none of the formulations had a percentage loss in tablet weights that exceed 1%. Maximum friability among all the batches was **0.9%.** Friability below 1% is an indication of the good mechanical resistance of the tablets. This ensures that tablets could withstand the pressure, shocks during handling, transportation and manufacturing processes.

**Table No. 21: Evaluation of tablet Thickness, Hardness, and Friability**

| Batch No. | Avg. Thickness ± SD ( mm) | Avg. Hardness ± SD ($kg/cm^2$) | Friability (%) |
|---|---|---|---|
| **FA1** | 4.927 ± 0.161 | 6.5 ± 0.275 | 0.22% |
| **FA2** | 4.936 ± 0.035 | 6.63 ± 0.414 | 0.19% |
| **FA3** | 4.882 ± 0.018 | 6.62 ± 0.539 | 0.18% |
| **FA4** | 4.995 ± 0.051 | 6.84 ± 0.855 | 0.18% |
| **FB1** | 4.917 ± 0.086 | 6.97 ± 0.550 | 0.16% |
| **FB2** | 4.964 ± 0.019 | 6.86 ± 0.277 | 0.09% |
| **FB3** | 4.926 ± 0.047 | 6.68 ± 0.856 | 0.12% |
| **FB4** | 0.427 ± 0.091 | 7.02 ± 0.400 | 0.90% |
| **FC1** | 5.080 ± 0.071 | 6.85 ± 0.310 | 0.51% |
| **FC2** | 4.991 ± 0.075 | 6.73 ± 0.674 | 0.62% |
| **FC3** | 4.976 ± 0.069 | 6.50 ± 0.85 | 0.13% |
| **FC4** | 4.982 ± 0.045 | 6.61 ± 0.500 | 0.09% |
| **FD1** | 4.923 ± 0.084 | 7.75 ± 0.250 | 0.08% |
| **FD2** | 4.995 ± 0.027 | 6.5 ± 0.450 | 0.07% |
| **FD3** | 4.965 ± 0.026 | 7.36 ± 0.390 | 0.04% |
| **FD4** | 4.957 ± 0.035 | 7.08 ± 0.250 | 0.14% |

n=10 n=5

**Assay of Metformin HCl tablets/ Drug Content:**

**Table No. 22: Percent assay of Metformin HCL**

| Batch No. | Sub batches of the assay in % | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| FA | 98.53 | 102.06 | 101.45 | 102.04 |
| FB | 100.43 | 100.57 | 99.91 | 101.30 |
| FC | 99.52 | 99.98 | 102.13 | 102.84 |
| FD | 101.75 | 101.64 | 99.16 | 102.77 |

All the batches showed results of DC in the range of **98.53 to 102.84 %**

***IN-VITRO* DRUG RELEASE STUDY:**

**Table No. 23: *In-vitro* release profile of formulation $FA_1$, $FA_2$, $FA_3$, $FA_4$**

| TIME (hr) | FA1 | ± SD | FA2 | ± SD | FA3 | ± SD | FA4 | ± SD |
|---|---|---|---|---|---|---|---|---|
| 0.5 | 33.0 | ± 1.55 | 27.0 | ± 0.1 | 33.2 | ± 1.1 | 29.0 | ± 0.22 |
| 1 | 40.1 | ± 0.61 | 35.4 | ± 0.82 | 36.2 | ± 0.71 | 36.9 | ± 0.28 |
| 3 | 60.6 | ± 0.55 | 55.2 | ± 0.32 | 55.1 | ± 0.21 | 56.1 | ± 0.38 |
| 5 | 81.9 | ± 1.02 | 68.6 | ± 0.71 | 70.0 | ± 0.32 | 70.8 | ± 0.01 |
| 8 | 93.3 | ± 0.48 | 80.3 | ± 0.21 | 87.2 | ± 0.40 | 87.8 | ± 0.31 |
| 10 | 98.8 | ± 0.72 | 98.5 | ± 0.61 | 98.2 | ± 0.28 | 96.7 | ± 0.22 |

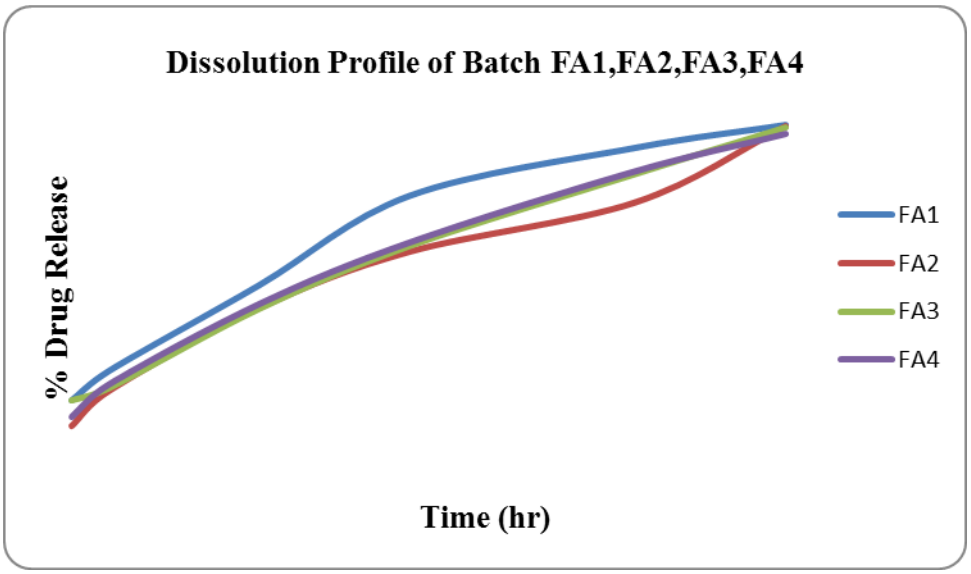



**Figure No. 3: *In-vitro* release profile of formulation $FA_1$, $FA_2$, $FA_3$, $FA_4$**

**Table No. 24: *In-vitro* release profile of formulation $FB_1$, $FB_2$, $FB_3$, $FB_4$**

| TIME (hr) | FB1 | ± SD | FB2 | ± SD | FB3 | ± SD | F4 | ± SD |
|---|---|---|---|---|---|---|---|---|
| 0.5 | 41.90 | ± 0.72 | 36.15 | ± 0.21 | 25.23 | ± 0.54 | 26.75 | ± 0.54 |
| 1 | 45.88 | ± 0.53 | 42.92 | ± 0.23 | 35.89 | ± 0.89 | 37.76 | ± 0.18 |
| 3 | 62.90 | ± 0.92 | 63.07 | ± 0.82 | 50.37 | ± 0.49 | 65.10 | ± 0.43 |
| 5 | 77.97 | ± 0.38 | 69.59 | ± 0.31 | 71.11 | ± 0.17 | 75.26 | ± 0.76 |
| 8 | 94.98 | ± 0.65 | 86.94 | ± 0.20 | 89.14 | ± 0.76 | 87.11 | ± 0.92 |
| 10 | 99.72 | ± 0.01 | 99.22 | ± 0.52 | 98.62 | ± 0.42 | 99.89 | ± 0.42 |

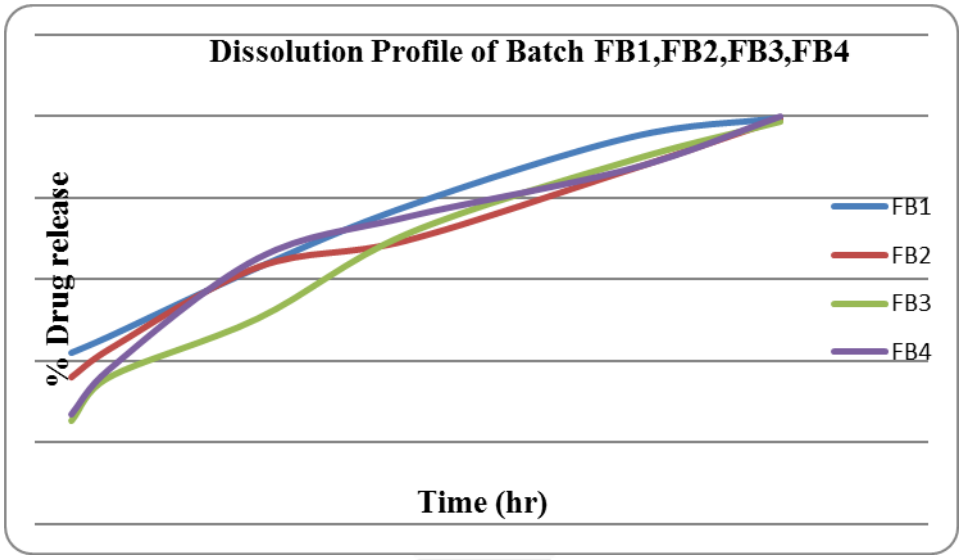



**Figure No. 4: *In-vitro* release profile of formulation $FB_1$, $FB_2$, $FB_3$, $FB_4$**

**Table No. 25: *In-vitro* release profile of formulation $FC_1$, $FC_2$, $FC_3$, $FC_4$**

| TIME(hr) | FC1 | ± SD | FC2 | ± SD | FC3 | ± SD | FC4 | ± SD |
|---|---|---|---|---|---|---|---|---|
| 0.5 | 30.81 | ± 0.72 | 36.40 | ± 0.72 | 29.30 | ± 0.72 | 25.65 | ± 0.72 |
| 1 | 40.89 | ± 0.53 | 49.02 | ± 0.53 | 40.83 | ± 0.53 | 32.30 | ± 0.53 |
| 3 | 63.75 | ± 0.92 | 68.32 | ± 0.92 | 62.08 | ± 0.92 | 61.61 | ± 0.92 |
| 5 | 79.75 | ± 0.38 | 90.16 | ± 0.38 | 81.44 | ± 0.38 | 80.65 | ± 0.38 |
| 8 | 93.97 | ± 0.65 | 96.47 | ± 0.65 | 91.89 | ± 0.65 | 92.77 | ± 0.65 |
| 10 | 99.98 | ± 0.01 | 99.59 | ± 0.01 | 98.53 | ± 0.01 | 100.79 | ± 0.01 |

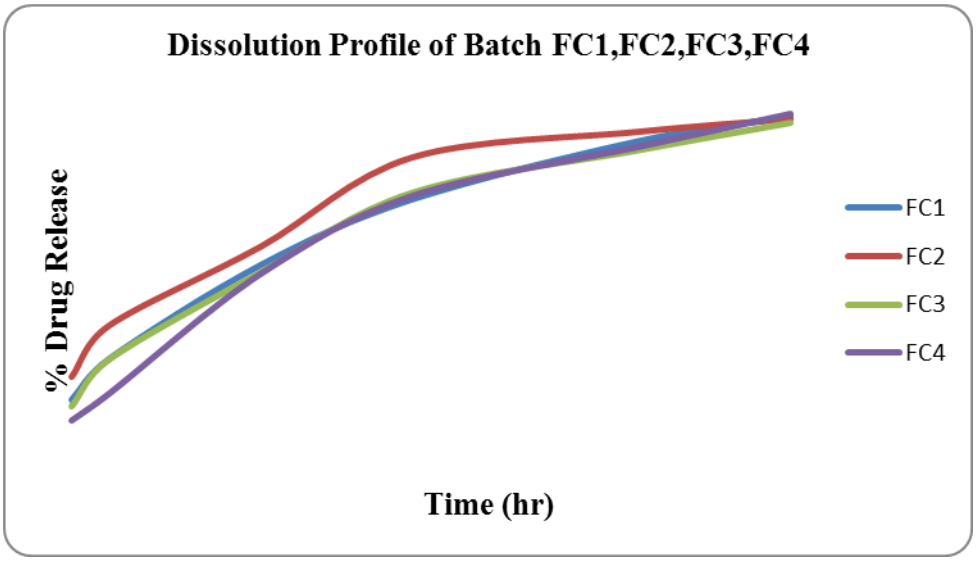



**Figure No. 5: *In-vitro* release profile of formulation $FC_1$, $FC_2$, $FC_3$, $FC_4$**

**Table No. 26: *In-vitro* release profile of formulation $FD_1$, $FD_2$, $FD_3$, $FD_4$**

| TIME(hr) | FD1 | ± SD | FD2 | ± SD | FD3 | ± SD | FD4 | ± SD |
|---|---|---|---|---|---|---|---|---|
| 0.5 | 35.00 | ± 0.56 | 25.70 | ± 0.42 | 25.00 | ± 0.54 | 24.50 | ± 0.46 |
| 1 | 43.22 | ± 0.32 | 36.40 | ± 0.22 | 31.70 | ± 0.64 | 31.50 | ± 0.80 |
| 3 | 66.80 | ± 0.08 | 60.00 | ± 0.71 | 58.20 | ± 0.16 | 54.60 | ± 0.23 |
| 5 | 83.30 | ± 0.01 | 75.80 | ± 0.67 | 76.20 | ± 0.86 | 73.70 | ± 0.75 |
| 8 | 93.30 | ± 0.41 | 91.40 | ± 0.35 | 93.20 | ± 0.28 | 92.20 | ± 0.24 |
| 10 | 97.80 | ± 0.99 | 95.80 | ± 0.04 | 94.80 | ± 0.01 | 97.30 | ± 0.78 |

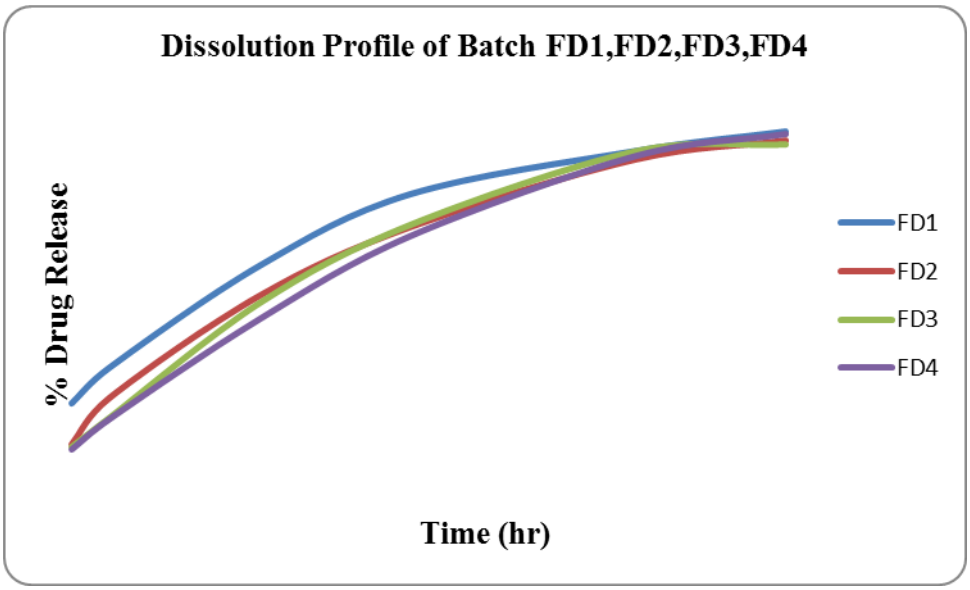



**Figure No. 6: *In-vitro* release profile of formulation $FD_1$, $FD_2$, $FD_3$, $FD_4$**

**Release kinetics of drug:**

**Table No. 27: Model fitting data of all the formulation**

| Batch | Sub Batch | $R^2$ values | | | |
|---|---|---|---|---|---|
| | | ZERO order | FIRST order | HIGUCHI | KP |
| FA | 1 | 0.956 | 0.989 | **0.989** | 0.989 |
| | 2 | 0.949 | 0.997 | **0.999** | 0.996 |
| | 3 | 0.989 | 0.983 | **0.991** | 0.972 |
| | 4 | 0.978 | 0.988 | **0.999** | 0.997 |
| FB | 1 | 0.991 | 0.948 | **0.991** | 0.97 |
| | 2 | 0.961 | 0.978 | **0.991** | 0.991 |
| | 3 | 0.982 | 0.974 | **0.988** | 0.986 |
| | 4 | 0.903 | 0.977 | **0.991** | 0.989 |
| FC | 1 | 0.952 | 0.987 | **0.999** | 0.996 |
| | 2 | 0.931 | 0.934 | **0.991** | 0.983 |
| | 3 | 0.935 | 0.988 | **0.996** | 0.995 |
| | 4 | 0.936 | 0.987 | **0.997** | 0.99 |
| FD | 1 | 0.932 | 0.988 | **0.998** | 0.995 |
| | 2 | 0.954 | 0.991 | **0.999** | 0.997 |
| | 3 | 0.965 | 0.981 | **0.997** | 0.995 |
| | 4 | 0.979 | 0.975 | **0.997** | 0.995 |

**DISCUSSION**

From the plot of percentage drug release Vs time of all the formulation batches, it was observed that the tablet formulated with granules of 18# passed showed higher drug release as compared with tablet formulated with 20#, 30#, 40# passed granules i.e as the sieve no increase drug release get decreased. But the value was insignificant. This might be due to the formation of a more compact matrix tablet of HPMC K4M due to granules. With a change in particle size, it was observed that there is no significant change in drug release pattern.

Table no 6.13 shows the $R^2$ values of all the formulation. It was observed that all the formulations follow Higuchi release model. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time-dependent. This relation can be used to describe the drug dissolution from a matrix tablet with a water-soluble drug.

With the change in HPMC K4M concentration, it was observed that there is no significant change in the Drug Release pattern, tested by the Tukey Test. This may be due to solubility

of drug which results in the formation of pores in swelled tablets giving the drug release almost in a similar pattern without any effect of HPMC concentration.

**SUMMARY**

Metformin hydrochloride an **anti-diabetic** agent used in the treatment of diabetes, Metformin hydrochloride has a short biological half-life 5 to 6 hours and 50% protein binding with a daily in divided doses. Because of the high frequency of administration and short biological half-life with low plasma protein binding, Metformin hydrochloride is an ideal drug for designing a sustained release formulation.

The use of natural and synthetic hydrophilic polymers is currently the most applied method in controlling the release of drugs from oral pharmaceutical dosage forms.

In the present study, co-processed excipients for SR of the model drug were prepared by the slugging method using MCC (PH102) as diluents and HPMC (K4M) as a matrix-forming polymer in the ratio of 1:0.5, 1:1, 1:2 & 1:3. Co-processed granules of slugs were prepared by passing them through 18#, 20#, 30# and 40# respectively.

These granules were evaluated for Bulk density, Tapped density, angle of repose, Carr's index, Hausner's ratio, and particle size distribution study and it was observed that co-processed excipients were having good flow properties. Sustained-release tablets of Metformin HCL were prepared by directly compressing the co-processed excipients along with the drug, lubricant, and Glidant.

IPQC test for a tablet-like weight variation, hardness, thickness, and friability was done which are in limits as per the official book. *In-vitro* dissolution study was done as per USP monograph for Metformin HCl ER tablet. The statistical test was applied to evaluate the effect of various parameters like Drug, polymer concentration and granules particle size on percent drug release. Drug release data also evaluated for kinetic models like zero order, first order Higuchi equation and Korsmeyer-Peppas Model and it was found that all the formulations followed the Higuchi equation.

## CONCLUSION

From the present study, the following conclusions can be drawn:

✓ Co-processed excipients by the slugging method were successfully developed using simple laboratory techniques.

✓ Physical modification of the excipients resulted in the improvement of functionality as can be used as directly compressible grade material.

✓ The slugging method was used for the preparation of co-processed excipients for sustained delivery of a model drug by using the matrix-forming polymer HPMC K4M and diluents MCC PH102.

✓ Bulk density and tapped density of granules were found to be independent on polymer concentration and particle size.

✓ Co-processed excipients were having good flow properties as compared to the direct compression blend.

✓ Using Co-processed excipients and Metformin HCL, a sustained release tablet was prepared which shows the desired release profile as per USP.

✓ It can be concluded that as the concentration of polymer increases the percentage retention of granules on 60# also increase.

✓ The minimum concentration of HPMC K4M required to retard drug release was 1:1 (MCC PH102: HPMC K4M respectively).

✓ There was no significant difference found in drug release with an increase or decrease in polymer concentration and particle size.

## RECOMMENDATION

Future studies involving their suitability for other dosage form applications, shelf-life determination, bioavailability, and clinical investigations, they are as follows.

- *In-vivo* Studies

- Scale up studies of the optimized formulation
- Bioavailability studies [pre-clinical and clinical trials]
- *In-vivo-in-vitro* Correlation.

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