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# DESIGN AND CHARACTERIZATION OF INLAY TABLET FOR TYPE 2 DIABETES MELLITUS (T2DM) - A NOVEL APPROACH IN DRUG DELIVERY

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## ABSTRACT

Any drug delivery system that enhances the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site is always invitable. Among various route of administration oral route is the most compact, painless, safest and least expensive, it is the one most often used. The present study aimed to develop a novel type of layered tablet consists of sitagliptin phosphate as immediate release layer and metformin hydrochloride as sustained release layer for T2DM. Immediate release layer was prepared by direct compression method using superdisintegrants such as sodium starch glycolate, crospovidone and croscarmellose sodium and sustained release layer of metformin hydrochloride was prepared by wet granulation process with HPMCK100M Premium as polymer. The blend and tablets were characterized for pre and post compression evaluations. The results found to be within standard limit. The immediate release layer consists of croscarmellose sodium produces better disintegration this may due to higher interaction of superdisintegrants with water. *In- vitro* percentage drug release results shown that higher concentration of hydrophilic polymer sustained the release of drug due to increase in viscosity of polymer. The *in-vitro* release kinetics profiles of drug from sustained release layer expressed by Higuchi's equation as the plots showed high linearity ($R^2$>0.991) and it indicates the release of drug from the tablet through diffusion dominated mechanism. In conclusion, a novel inlay tablet contains anti diabetic drugs resulted better release profile to control Type 2 DM (Diabetes Mellitus).

**KEYWORDS:** Inlay tablet, Diabetes Mellitus, Sitagliptin phosphate, Metformin hydrochloride HPMCK100M Premium.

## 1.0 INTRODUCTION

Diabetes mellitus (DM) is probably one of the oldest disease for clinicians since centuries. It was first reported in Egyptian manuscript about 3000 years ago.[1] In 1936, the distinction between type 1 and type 2 DM was clearly made.[2] Type 2 DM was first described as a component of metabolic syndrome in 1988.[3] Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.[4] Type 2 DM results from interaction between genetic, environmental and behavioral risk factors.[5,6]

Diabetes Mellitus is a group of syndrome. These syndromes are characterized by hyperglycemia, changed metabolism of lipids, proteins and carbohydrates. Further an increased risk of complication from vascular disease is seen. Hyperglycemia (increase in blood glucose in the body) is a condition in which blood glucose level is high and there is diminished action of insulin either because of decrease in the circulatory concentration of insulin (insulin deficiency) or due to a decrease in their response of peripheral tissue to insulin (insulin resistance). These abnormalities give use to altered metabolism of lipids, carbohydrate and amino acids. All these effects produce hyperglycemia.

Diabetes mellitus may arise occasionally from any disease, which results in extensively destruction of pancreatic islets. e.g. pancreatitis, certain drugs, iron over load, (hemochromatosis), tumors, certain acquired or genetic endrocrinopathies and surgical excision. Diabetes gives rise to long term complication in blood vessels, kidney, eyes, and nerves. These result in major causes of morbidity and death from diabetes.

Many aspects agents are of Diabetes needs to be explored with respect to physiological actions of insulin and the various clinical features of this disease such as tissue complication, since this is life style disease, so proper treatment in relation to diet and antidiabetic emphasized.[7]

Sitagliptin phosphate monohydrate (SP) chemically, (7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-

5,6,7,8-tetrahydro-3-(trifluoro methyl)- 1,2,4-triazolo[4,3-a] pyrazine phosphate monohydrate) [1] (DPP-IV inhibitor) is an oral hypoglycemic agent commonly prescribed drug for the treatment of patients with type II diabetes mellitus [1], is indicated for the improvement of glycemic control in patients with type II diabetes mellitus as monotherapy or combination therapy with metformin or a peroxisome proliferator activated receptor gamma (PPAR) agonist (e.g., thiazolidinediones) when the single agent does not provide adequate glycemic control.[8]

Metformin Hydrochloride (MET) is a biguanide class of antidiabetic drug, chemically is N, N-dimethylimido dicarbonimidicdiamide hydrochloride 2-7 It is an oral anti-diabetic drug from the biguanide class. It is the first-line drug for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function, and evidence suggests it may be the best choice for people with heart failure. It is also used in the treatment of polycystic ovary syndrome.[9] The absolute bioavailability of Metformin hydrochloride is 50-60% and has biological half-life of 6.2 hrs. Frequent dosing schedule leading to high GI side effects and high daily dose makes its use uncommon. Hence there is a need to formulate SR Metformin tablets to prolong its duration of action and to reduce total dose of drug administered as well as the incidence of adverse side effects.

The combination of a DPP-4 Inhibitor with Metformin allows a broad and complementary spectrum of anti-diabetic actions. This combination does not increase the risk of hypoglycemia, does not promote weight gain, and does not cause adverse effect caused by various other oral anti diabetic combinations. Both the drugs have a complimentary and possibly additive effect on glycemic control and reduced glycosylated hemoglobin.[10]

Considering the above factors, the present study aimed to develop a novel and elegant pharmaceutical combination dosage form for simultaneous treatment of many patients with Type 2 diabetes with at high risk for coronary artery disease and associated co-morbidities. It deals with the combine formulation development and characterization of inlay tablet of DPP-4 inhibitor i.e., sitagliptin phosphate as immediate release and metformin hydrochloride as sustained release for better therapeutic compliance.

## 2.0 MATERIALS AND METHODS

### 2.1 Materials

Sitagliptin phosphate monohydrate (99.96% purity) was obtained from Alaris Pharmaceuticals (P) Ltd, Srilanka. Metformin hydrochloride (99.96% purity), Sodium starch glycolate and Magnesium stearate were concurred from Lalchand Bhimraj, Chennai. HPMC K100M Premium was concurred from Dow Chemicals, Chennai. Crospovidone was obtained from S Kesarimal, Chennai. Croscarmellose sodium and PVP K-30 were collected from Jain Impex (India). Microcrystalline cellulose was obtained from Castleline Organics Ltd, Chennai. Isopropyl alcohol was concurred from Kanchan agencies, Chennai. Iron oxide red was collected from Color Trendz, India. All others reagents and chemicals used were of analytical reagent grade.

### 2.2 Methods

#### 2.2.1 Preformulation studies

A preformulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as phase of research and development process of physical and chemical properties of a new drug substance alone and when provide a rational for formulation design, or support the need for molecular combined with excipients, in order to develop stable, safe and effective dosage form. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

A thorough understanding of physicochemical properties may ultimately modification or merely confirms that there are no significant barriers to the compounds development. The goals of the preformulation study are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.[11]

**Compatibility study**

The drug and the excipients chosen for the formulation were screened for compatibility by physical methods and Fourier Transform infrared spectrometric method (FTIR).

**Physical Compatibility study**

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and the excipients in the ratio of 1:1 and stored in air tight containers at room temperature and at $40^0$C and 75%RH. Any change in color of the physical mixture was observed visually.[12]

**Fourier transforms infrared spectrometry (FT-IR)**

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipient mixture was subjected to FTIR studies using Shimadzu FT-IR spectrometer model to investigate the Drug-excipient interactions. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide and the ratio of sample is 1:100.[13]

#### 2.2.2 Preparation of blends of immediate release layer of sitagliptin phosphate monohydrate

Immediate release layer of sitagliptin phosphate monohydrate (IR1 to IR3) were prepared by direct compression technique as per the composition given in

Table 1. Sitagliptin phosphate monohydrate and other excipient sifted through sieve no 40 # and thoroughly mixed in a blender approximately for 5 min. The color iron oxide red was passed through the sieve number # 100 and added with above mixer. Above mixer was lubricated for 2 min with Magnesium Stearate which was already passed through sieve 60. Immediate release layer was prepared using sodium starch glycolate, crospovidone and croscarmellose sodium as superdisintegrants.

**Table 1. Composition of immediate release layer**

| S.NO | INGREDIENTS | IR1 | IR2 | IR3 |
|---|---|---|---|---|
| | **Qty(mg)/tab** | | | |
| 1. | Sitagliptin phosphate monohydrate | 32.13 | 32.13 | 32.13 |
| 2. | Vivapur PH102 | 154.87 | 154.87 | 154.87 |
| 3. | Sodium starch glycolate | 10 | - | - |
| 4. | Crospovidone | - | 10 | - |
| 5. | Croscarmellose sodium | - | - | 10 |
| 6. | Magnesium stearate | 2 | 2 | 2 |
| 8. | Iron oxide red | 1 | 1 | 1 |
| **Total weight** | | 200 | 200 | 200 |

**2.2.3. Granulation of sustained release layer of metformin HCl**

Sustained release layer of Metformin HCl (SR1 to SR) was prepared by wet granulation technique with various excipients as per the formula given in Table 2. Metformin HCl, Microcrystalline cellulose PH 102, Lactose, HPMC K100M premium were sifted through Sieve no. # 40. Then the above sifted materials were mixed in Rapid Mixer Granulator for 5 min (RPM of Impeller- 150). PVP K- 30 was dissolved in mixture of IPA. Then above mixture with binder PVP K-30 solution was granulated at Impeller RPM 150 and kneading for 2 min (Impeller RPM 150 and chopper RPM 1500). The granules were dried in tray dryer at 65°C (LOD 1.5 to2.5 % w/w). The granules were passed through mesh no.# 20 in oscillating granulator. Finally, mixture was lubricated with magnesium stearate for 2 min in Cage blender. Sustained release layer was prepared using different ratio of HPMC K100M premium like 1: 2: 2.5: 3: 3.5 as polymer.[14]

**Table 2. Composition of sustained release granules**

| S.NO | INGREDIENTS | M1 | M2 | M3 | M4 | M5 |
|---|---|---|---|---|---|---|
| | **Qty(mg)/tab** | | | | | |
| 1. | Metformin hydrochloride | 500 | 500 | 500 | 500 | 500 |
| 2. | HPMC K100M Premium | 50 | 100 | 150 | 200 | 250 |
| 3. | Microcrystalline cellulose PH102 | 410 | 360 | 310 | 260 | 210 |
| 4. | PVP K-30 | 30 | 30 | 30 | 30 | 30 |
| 5. | Isopropyl alcohol | Q. S | Q.S | Q.S | Q.S | Q. S |
| 6. | Magnesium stearate | 10 | 10 | 10 | 10 | 10 |
| **Total weight** | | 1000 | 1000 | 1000 | 1000 | 1000 |

**2.2.4. Characterization of granules**

Prior to compression, blends of two layers were evaluated for their characteristic parameters like density, bulk density, tapped density, compressibility index and Hausner's Ratio. Carr's index was calculated from the bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd, India).

**2.2.5. Preparation of inlay tablet**

The tablet was compressed as inlay tablet using both Metformin HCl granules and sitagliptin phosphate monohydrate blend, it was selected from its best in characterization. Inlay tablets were compressed by as one layer only for Metformin HCl and second layer for sitagliptin phosphate monohydrate using 21 X 7.4 mm D tooling oblong shape punch in 21 station tablet compression machine (Cadmach, India). In this Metformin HCl granules were introduced first into the die cavity and a slight pre compression was made so that layer was uniformly distributed after that sitagliptin phosphate monohydrate blend was added and final compression was made.

**2.2.6. Physico - Chemical properties of Inlay tablet**

The prepared tablets were subjected to various evaluation tests like thickness, hardness, weight variation, friability, and drug content. Thickness of the tablets was determined by using Vernier calliper. Randomly 10 tablets were selected and used for determination of thickness. It is expressed in mm. Hardness is termed as the tablet crushing strength and it is the force required to break a tablet diametrically. Hardness of tablets was measured by selecting 6 tablets randomly and the hardness of each tablet was determined using digital hardness tester (Elchem, Mumbai). The hardness was noted. The hardness is usually measured in terms of $kg/cm^2$. The tablet friability is a measure of loss due to abrasion. The pre weighed tablets were exposed to repeat

shocks in friabilator (Esico, India) in which they are initially weighed (*W*0) and kept in a tumbling and rotating apparatus drum and were subjected to fall from 6 inches' height. After completion of 100 rotations, the tablets were reweighed (*Wf*) and the percent loss in weight or friability (*f*) was calculated by the formula given below

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Final weight of the tablets}} X100$$

For weight variation test individual weight of 20 tablets was taken; then their average weight and their mean and standard deviation were calculated and compared with the standards. The weight of the tablet being made is measured to ensure that it contains predetermined amount of drug. The percentage deviation of tablets was calculated and compared with the USP official limits given below.[15]

**USP limits for weight variation**

| Average weight of a tablet | Limits |
|---|---|
| 130 mg or less | ±10% |
| >130 mg and <324 mg | ±7.5% |
| more than 324 | ±5% |

**2.2.7. Drug content**

Twenty tablets were weighed and finely powdered. The powder equivalent to 500 mg of Metformin HCl and 32.13 mg of sitagliptin phosphate monohydrate were transferred to a 100 ml volumetric flask. Add about 50 ml of diluents and sonicate to dissolve. Make volume up to the mark with diluents and mix. Dilute 1.0 ml of this solution to 100.0 ml with diluents and mix. Acetonitrile was used as diluents. The total amount of drug within the tablets was analyzed by modified High performance chromatographic method (HPLC) and the chromatographic conditions were given below.

**Chromatographic conditions**

Apparatus : High Performance Liquid Chromatography
Column : 250 mm x 4.6 mm, 5µm, C18, ODS
Flow Rate : 1.0 ml/min
Temp : 250° C
Injected Volume : 20 µl
Detector : UV at 267 nm
Retention time: About 2.5 min Metformin HCL and 8.6 min sitagliptin
*Buffer preparation:* Buffer was prepared by dissolving 2.72 g of potassium dihydrogen phosphate in 1 litre of water adjusted to pH 4.3 using phosphoric acid solutions.
*Diluent:* Acetonitrile was used as diluents
*Mobile phase***:** Filtered and degassed mixture of Buffer and Acetonitrile (60:40).[16]
The percentage of potency were calculated by given formula,

**Percentage of Sitagliptin Phosphate**

$$\frac{\text{Test Area}}{\text{Standard Area}} X \frac{\text{Std. wt}}{50} X \frac{5}{100} X \frac{250}{\text{Test Wt}} X \frac{20}{5} X \frac{407.52}{505.31} X \frac{P}{100} X \text{Avg. wt}$$

Where,

Std.Wt = Standard weight taken in mg
Test Wt = Test weight taken in g
Avg.wt = Average weight in g
P = Purity of Sitagliptin Phosphate
407.52 is the molecular weight of Sitagliptin
505.31 is the molecular weight of Sitagliptin phosphate

**Percentage of Metformin HCl**

$$\frac{\text{Test Area}}{\text{Standard Area}} X \frac{\text{Std. wt}}{100} X \frac{250}{\text{Test Wt}} X \frac{20}{5} X \frac{P}{100} X \text{Avg. wt}$$

Where,

Std.Wt = Standard weight taken in mg
Test Wt = Test weight taken in g
Avg.wt = Average weight in g
P = Purity of metformin Hydrochloride

***2.2.8 In-vitro* disintegration study for sitagliptin phosphate IR tablets**

The disintegration time was determined using disintegration test apparatus (Veego, Mumbai) containing a basket rack assembly with six glass tubes and the bottom of which consists of a #10 mesh sieve. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in water maintained at a temperature of 37 $\pm 2^0$C and the tablet remain 2.5cm from the bottom of medium, a standard motor driven device move the basket containing tablet up and down through a distance of 5 to 6cm at a frequency of 28 to 32

cycles per minute. The time taken for complete passage of tablet fragments through the mesh was considered as disintegration time of the tablet. All the experiments were repeated for three times and mean value was calculated.

### *2.2.9 In-vitro* dissolution study for metformin hydrochloride SR tablets

Release of Metformin hydrochloride was determined using a USP dissolution apparatus type II (Basket) at 100 rpm. The dissolution was studied using 1000ml of 6.8 phosphate buffer. The temperature was maintained at 37 ± 0.5°C.The sample (10 ml) was withdrawn from midpoint of apparatus at different time intervals, i.e., 1, 2, 3, 4, 5, 6, 8 and 10 hours, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Metformin hydrochloride content by UV-Visible Spectrophotometer at $\lambda_{max}$ 233nm. All the experiments were repeated for three times and mean value was calculated.[17]

### 2.2.10 *In-vitro* dissolution studies for inlay tablet

Release of sitagliptin phosphate monohydrate was determined using a USP dissolution apparatus type II (Basket) at 100 rpm. The dissolution was studied using 1000ml of 0.1 N Hydrochloric acid. The temperature was maintained at 37 ± 0.5°C. The sample (10ml) was withdrawn at different time intervals, i.e., 5, 15, 30 minutes, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for sitagliptin phosphate monohydrate content by UV-Visible Spectrophotometer at 267nm. Release of Metformin hydrochloride was continued with phosphate buffer pH 6.8 in same apparatus. The sample (10 ml) was withdrawn at different time intervals, i.e., 1, 2, 3, 4, 5, 6, 8 and 10 hours, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Metformin hydrochloride content by UV-Visible Spectrophotometer at $\lambda_{max}$ 233nm.All the experiments were repeated for three times and mean value was calculated.

### 2.2.11 Characterization of the release profile

The experimental results of the release studies were fitted according to the exponential equation.

Zero order Release Equation:$Q = K_0t$

First Order Release Equation: $\text{Log } C = \log C0 - Kt / 2.303$[18,19]

Higuchi's Square Root of Time Equation:$Q = Kt_{1/2}$[20]

Korsmeyer Peppas Equation:$Mt / M\alpha = K_m t_n$[21]

Whereas, Q = Amount of drug release at time t, C = Amount of drug remained at time 't',C0 = Initial amount of drug, K = First – order rate constant (hr-1). Mt = drug release at time t, Mα = total amount of drug in dosage form, F = fraction of drug release at time t, K0 =zero order release rate constant, K = Higuchi square root of time release rate constant, Km = constant depend on geometry of dosage form, n = diffusion exponent indicating the mechanism of drug release where for cylinder value of n is <0.5 indicate Fickian diffusion, between 0.5 and 1.0 indicate Non-Fickian and > 1.0 indicate case-II transport.

## DISCUSSION

Type 2 diabetes mellitus (T2DM) is a chronic and escalating disease integrated with significant morbidity and mortality and that emerges from a complex pathophysiology includes insulin resistance, reduced insulin secretion and increased hepatic glucose excretion. Metformin, a biguanide agent, is widely prescribed first-line oral anti-hyperglycemic agent (AHA) as monotherapy and it primarily acts to lower hepatic glucose excretion.[22,23] It was reported that as with all AHAs, monotherapy with metformin is often unsuccessful in achieving or maintaining adequate glycemic control.[24-26] In addition, patients who initially desired with monotherapy often need additional agents over time in order to maintain glycemic control due to the progressive nature of T2DM.[25] There is good evidence showing that intensive glycemic control reduces the development and progression of complications. In order to achieve glycemic targets, patients often require a combination of oral therapy and/or insulin in addition to lifestyle modification especially in patients with moderate-to high HbA1c levels for which the use of initial combination therapy is considered a potential treatment option supported by practice guidelines.[27]

Sitagliptin is an oral, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients withT2DM.[28] Sitagliptin delays the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), the major incretins involved in glucose homeostasis, thereby increasing insulin release and lowering glucagon secretion in a glucose-dependent manner.[29,30] Treatment with sitagliptin 100 mg once daily leads to improvements in glycemic control in patients with T2DM, including reductions in fasting and postprandial glucose concentrations. Sitagliptin has not been associated with an increased risk of hypoglycemia when administered as either monotherapy or in combination with agents not known to cause hypoglycemia.[31-35] It shows combined use of sitagliptin and metformin is an effective method of lowering glucose levels in T2DM. Considering the above overview our research work attempted to prepare a combination therapy of sitagliptin phosphate monohydrate as immediate release and metformin hydrochloride as sustained release from a modified dosage form such as inlay tablet for the treatment of patients withT2DM.

The immediate release tablet of sitagliptin phosphate was prepared by direct compression method using sodium

starch glycolate, crospovidone and croscarmellose sodium as superdisintegrants in ratio of 10mg/tablet. Direct compression method is suitable to formulate immediate release tablet due to drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet and thus disintegrates easily when exposed to dissolution process.

The sustained release layer of metformin was formulated by wet granulation method using HPMC K100M premium. In this method the drug and excipients are granulated intragranularly thereby extending the release of drug in dissolution medium. Thus this method is suitable to prepare sustained release layer.[36]

The results of both physical and chemical compatibility studies shown there is no interaction between the drug and polymer which indicates that both drug and excipients were compatible with each other and stable at different temperature and humidity.

Estimation of Pre and post compression parameters in tablet is most important and the results were given Table 3. Evaluation of these properties will results the characteristics of powder ingredients before punch as a tablet and also reflect their withstanding capacity during transportation, content uniformity and drug release. The obtained result from pre-compression evaluations shown that the prepared powders were having well in their flow properties and within the accepted limits with low standard deviation and the result of post compression studies such as content uniformity, hardness, friability and weight variation shown within the official limits. It indicates all the prepared tablets were well in their physico-chemical properties.

**Table 3. Pre-compression studies on drug and blend, Mean± S.D, n=3**

| Formula code | Angle of repose (°) | Bulk density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Carr's index(%) | Hausner's ratio |
|---|---|---|---|---|---|
| IR1 | 29.15±0.122 | 0.286±0.00 | 0.33±0.004 | 13.33±0.902 | 1.154±0.013 |
| IR2 | 27.79±0.237 | 0.28±0.002 | 0.319±0.009 | 11.99±0.814 | 1.137±0.011 |
| IR3 | 28.18±0.236 | 0.27±0.005 | 0.317±0.003 | 11.81±0.177 | 1.13±0.004 |
| SR1 | 23.77±0.457 | 0.442±0.01 | 0.526±0.008 | 16.08±0.984 | 1.19±0.016 |
| SR2 | 20.74±0.200 | 0.51±0.008 | 0.628±0.002 | 18.78±1.253 | 1.23±0.021 |
| SR3 | 27.32±0.233 | 0.432±0.00 | 0.542±0.001 | 20.24±0.917 | 1.246±0.004 |
| SR4 | 25.34±0.244 | 0.412±0.01 | 0.514±0.012 | 19.92±0.740 | 1.247±0.013 |
| SR5 | 24.16±0.104 | 0.432±0.00 | 0.543±0.007 | 20.46±0.389 | 1.256±0.007 |

**Table 4. Post compression parameters of Inlay tablets, Mean± S.D, n=3**

| Formula code | Thickness (mm) | Hardness ($kg/cm^2$) | Friability (%) | Weight Variation(mg) | Drug content (%) |
|---|---|---|---|---|---|
| IR1 | 4.02±0.012 | 3.19±0.110 | 0.18±0.024 | 201.2±0.002 | 109.7±0.004 |
| IR2 | 4.09±0.004 | 3.45±0.303 | 0.12±0.014 | 198.0±0.004 | 109.46±0.002 |
| IR3 | 4.04±0.009 | 3.45±0.376 | 0.10±0.004 | 203.2±0.015 | 110.17±0.025 |
| SR1 | 6.27±0.004 | 5.15±0.449 | 0.53±0.045 | 1000.5±0.026 | 99.14±0.048 |
| SR2 | 6.32±0.020 | 5.03±0.555 | 0.42±0.016 | 1005.5±0.041 | 102.17±0.010 |
| SR3 | 6.33±0.024 | 5.63±0.476 | 0.41±0.028 | 1002.8±0.03 | 101.46±0.019 |
| SR4 | 6.31±0.012 | 6.89±0.098 | 0.38±0.020 | 1006±0.007 | 101.35±0.001 |
| SR5 | 6.28±0.016 | 7.17±0.481 | 0.32±0.016 | 1016±0.016 | 106.76±0.071 |
| Inlay Tablet | 7.40±0.009 | 10.46±0.490 | 0.16±0.004 | 1199.5±0.008 | 105.54±0.042(IR) 108.34±0.048(SR) |

Disintegrants are an essential component to tablet formulations. A disintegrant used in this type of formulation, simply has to break the tablet apart to expose the drug substance for dissolution. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action. The results of disintegration study on sitagliptin tablet shown in the Table 5 and it varied according to the superdisintegrants used. Formulation IR3 consist of croscarmellose sodium was considered as best due to its fast release such as 6 seconds compared to other two formulations such as 12, 17sec for sodium starch glycolate and crospovidone. Previous study reveal croscarmellose sodium has better ability to strongly interact with water compare to other superdisintegrants.[37] Hence in our study we select IR3 as best formulation to prepare inlay tablet.

**Table 5. *In vitro* disintegration study for sitagliptin phosphate IR tablets, Mean± S.D, n=3**

| Formula code | Disintegration time(seconds) |
|---|---|
| IR1 | 12.33±0.4714 |
| IR2 | 16.67±0.4714 |
| IR3 | 6±0.4714 |
| Inlay tablet | 7±0.4714 |

*In-vitro* dissolution study was performed on sustained release formulations such as SR1, SR2, SR3, SR4, SR5 containing metformin hydrochloride to estimate the percentage of drug release from the formulations into the dissolution medium and the results were given in Table 6 and Fig.1. Metformin hydrochloride sustained release formulations were prepared using HPMC K100M Premium as polymer with different ratio like 50:100:150:200:250mg to find out the release behavior of polymer with different concentration in dissolution medium. The concentration of polymer was selected from its optimum standard value obtained in pharmacopoeia. The results obtained shown formulation SR5 released 93.02% of drug at $10^{th}$ hour. The % release of other formulations such as SR1, SR2, SR3, SR4 are 100.1,100. It shows that higher concentration of polymer sustained the release of drug from its formulation to the environment compare to lower one. Thus in our study we have selected SR5 as best formulation to prepare inlay tablet.

**Table 6. *In vitro* dissolution study for metformin hydrochloride SR tablets, Mean± S.D, n=3**

| Time (hrs) | Cumulative % drug release(n=3) | | | | |
|---|---|---|---|---|---|
| | SR1 | SR2 | SR3 | SR4 | SR5 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 40.28±0.34 | 37.96±0.39 | 31.67±0.47 | 27.46±2.46 | 24.07±1.41 |
| 2 | 50.56±0.20 | 47.57±0.37 | 43.19±1.93 | 39.30±0.55 | 36.16±2.18 |
| 3 | 68.52±0.26 | 65.12±0.20 | 51.88±2.67 | 50.88±1.71 | 46.96±1.96 |
| 4 | 76.78±0.53 | 72.15±1.66 | 61.81±0.34 | 57.37±2.53 | 52.04±2.32 |
| 6 | 98.21±0.48 | 86.32±1.47 | 78.56±0.35 | 73.85±2.25 | 68.84±3.56 |
| 8 | 104.51±0.90 | 99.71±0.28 | 97.68±0.34 | 82.48±3.35 | 77.78±1.90 |
| 10 | | 103.13±1.04 | 102.13±0.96 | 99.54±1.64 | 93.02±2.30* |

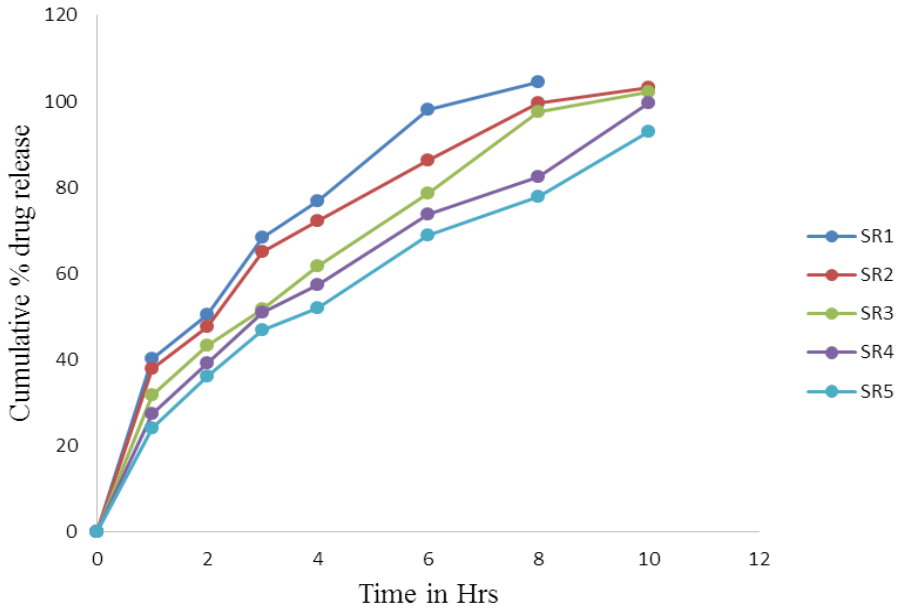


**Fig.1 *In vitro* dissolution study for metformin hydrochloride SR tablets**

***In-vitro* percentage drug release study for inlay tablet**

This study was performed on inlay tablet prepared using best formulation of IR and SR such as IR3 and SR5 and the results are shown in Table 7 and Fig.2. The % disintegration was achieved within 7 secs from the formulation in 0.1N HCL as medium and it was continued with pH 6.8 phosphate buffer to study the release of sustained layer. The % drug release from formulation was achieved as 98.40. It shows there is no significant change in release pattern after compression as inlay tablet and also it confirms that no influence in release due to tablet processing factor when compared with individual tablet.

The result suggested that HPMC K100MPremium with concentration of 250mg is suitable to formulate highly water soluble drug such as metformin hydrochloride to produce sustained release and incorporation of immediate release layer using superdisintegrants will give beneficial effect in the treatment of T2DM. The release data further indicates that the IR and SR layers incorporated in inlay tablet can produce sustained release followed by initial burst effect.

**Table 7. *In vitro* dissolution study for inlay tablet, Mean± S.D, n=3**

| Time (hrs.) | % Drug Release |
|---|---|
| 0 | 0 |
| 1 | 25.86±2.88 |
| 2 | 37.07±3.04 |
| 3 | 48.27±1.60 |
| 4 | 54.82±2.15 |
| 6 | 70.69±2.11 |
| 8 | 81.35±2.56 |
| 10 | 98.40±2.44* |

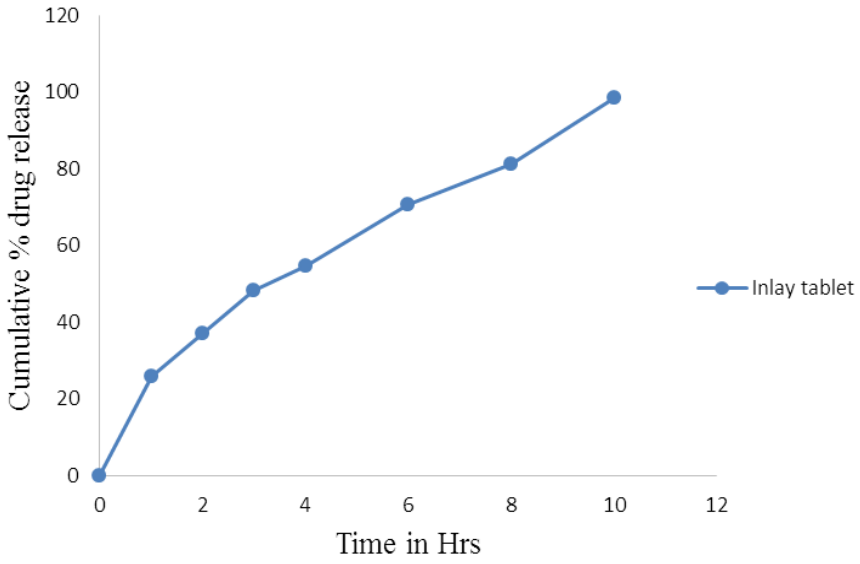


**Fig.2 *In vitro* dissolution studies for inlay tablet**

**Kinetic modeling of drug release**

The experimental results of the release studies from sustained release were fitted according to the exponential equation and the results were given Table 8. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity ($R^2$>0.991). Release of the drug from the sustained release tablets containing hydrophilic polymers generally involves factors of diffusion. To confirm the diffusion mechanism, the data was fitted into Korsmeyer- Peppas equation, with slope (n) value is 1.259. This result suggests that, the release of drug follows Case-II transport and it indicates the release of drug from the tablet through diffusion dominated mechanism.

**Table 8. The Regression co-efficient values for different formulations**

| Code | Zero order ($R^2$) | First order ($R^2$) | Higuchi Plot ($R^2$) | Korsmeyer Peppa's plot | | Hixson crowell ($R^2$) | Possible mechanism of drug release |
|---|---|---|---|---|---|---|---|
| | | | | ($R^2$) | n | | |
| SR1 | 0.885 | 0.879 | 0.993 | 0.492 | 1.398 | 0.928 | Zero order Case II transport |
| SR2 | 0.863 | 0.811 | 0.991 | 0.502 | 1.228 | 0.939 | Zero order Case II transport |
| SR3 | 0.929 | 0.918 | 0.993 | 0.543 | 1.257 | 0.894 | Zero order Case II transport |
| SR4 | 0.935 | 0.756 | 0.994 | 0.559 | 1.255 | 0.920 | Zero order Case II transport |
| SR5 | 0.943 | 0.939 | 0.993 | 0.576 | 1.254 | 0.978 | Zero order Case II transport |
| Inlay Tablet | 0.948 | 0.824 | 0.991 | 0.571 | 1.259 | 0.941 | Zero order Case II transport |

## CONCLUSION

In conclusion, the present study reveals that combination of sitagliptin phosphate as immediate release layer and metformin Hcl as sustained release layer in inlay tablet resulted better release profile in dissolution medium to control type II diabetes mellitus. Further work such as *in-vivo* release study may help to characterize *in vitro–in vivo* correlation.

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