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# FORMULATION DEVELOPMENT AND EVALUATION OF ONCE DAILY SUSTAINED RELEASE METFORMIN HYDROCHLORIDE TABLETS

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## ABSTRACT

Metformin hydrochloride has relatively short plasma half-life and low absolute bioavailability. The need of administration for two to three times a day when larger doses are required can decrease patient compliance. Sustained release formulation that would maintain plasma level for 20 h might be sufficient for daily dosing of metformin. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. The overall objective of this study was to develop an oral sustained release metformin hydrochloride tablet by using hydrophilic alone or its combination with hydrophobic as rate controlling factor. The tablets were prepared by granulation method. The *in vitro* dissolution study was carried out using USP 22 apparatus I, paddle method. The drug release study revealed that HPMC alone was unable to sustain the drug release. Combining HPMC & HEC and coting with a semi-permeable membrane with controlled release from an orifice, sustained the drug release for more than 20h.

**Keywords:** HPMC, HEC, Semipermeable membrane matrix tablets, Delivery orifice, Release kinetics.

## 1. INTRODUCTION

Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of type-II diabetes, a common disease that combines defects of both insulin secretion and insulin action [1]. Unlike other anti diabetic drugs, metformin HCl does not induce hypoglycemia at any reasonable dose, and hence it is called as an antihyperglycaemic rather than a hypoglycemic drug [2]. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability is reported to be of 50-60% [3, 4]. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occurs during the initial period of treatment. The compound has relatively short plasma half-life of 1.5-4.5 h and the low absolute bioavailability of 50-60% [5]. Side effects, short half-lives, low bioavailability and the need of the administration for two to three times a day when larger doses are required can decrease patient compliance. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. Matrix systems are widely used in oral controlled drug delivery because of their flexibility, cost effectiveness, low influence of the physiological variables on its release behavior and broad regulatory acceptance [6, 7]. Many researchers investigated various natural, semi-synthetic and synthetic polymeric materials. Cellulose ethers such as Hydroxypropylmethylcellulose, sodium carboxymethylcellulose, Eudragit (polymethacrylate) polymer [8, 9], ethyl cellulose [10] and some natural gums like guar gum and xanthan gum are widely used hydrophilic polymers as release retardants [11].

Methacrylic resins (Eudragit) appear particularly attractive due to their high chemical stability and compactility properties, and many literatures substantiate use in the development of control release matrix tablet [12, 13]. The hydrophilic polymer selected for the present study was HPMC, which provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms [14]. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs, it becomes essential to include combination of polymers in the matrix system [15], and coating with a semi-permeable membrane with a precise delivery orifice.

The natural materials have been extensively used in the field of drug delivery because they are readily available, cost-effective, eco-friendly, capable of multitude of

chemical modifications, potentially degradable and compatible due to their natural origin [16]. Gum copal (GC) and gum damar (GD) are natural resinous materials of plant *Bursera bipinnata* family Burseraceae and *Shorea wiesneri* family Dipterocarpaceae, respectively. The wide applications of GC and GD propose their strong hydrophobic nature, substantial binding property, compatibility with the physiologic environment [17] and their sustaining property [18]. The objective of this work was to prepare sustained release metformin HCl matrix tablets using synthetic hydrophilic polymer HPMC alone or in combination to evaluate the *in vitro* release characteristic and to predict and correlate the release behavior of metformin HCl from the matrices. The influence of the polymer concentration in the tablets was also investigated. The *in vitro* drug release profiles of the matrices are evaluated, and its release mechanism was studied.

Although HPMC has been widely used as sustained release material; to our knowledge, the property of its combination with HEC has not been evaluated. Hence, in the present work, an attempt has been made to formulate the extended-release matrix tablets of metformin HCl using hydrophilic polymer alone or in combination and the coating with semipermeable membrane to evaluate the *in vitro* release characteristics and to predict the release behavior through a controlled delivery orifice.

## 2. MATERIAL AND METHODS

Metformin HCl was obtained from Shrikrishna, India. Microcrystalline cellulose (MCC, Avicel pH 101) and ethyl cellulose were purchased from S. D. Fine Chem. Labs. (Mumbai, India), HPMC was obtained as gift samples from Dow chemicals (Mumbai, India). Cellulose Acetate Phthalate was procured from Eastman and all the other ingredients used throughout the study were of analytical grade and were used as received.

### 2.1. Study of physical interaction between drug and polymer

Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 $cm^{-1}$ using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer.

### 2.2. Preparation of Metformin hydrochloride matrix tablets

Matrix tablets, each containing 1000 mg metformin HCl were prepared by a conventional direct compression and or wet granulation technique. The composition with respect to polymer combination was selected on the basis of trial preparation of tablets. In each formulation, the amount of the active ingredient is 1000 mg and the total weight of a tablet is 1480 mg. A batch of 30 tablets was prepared with each formula. The ingredients were passed through a 60-mesh sieve. A blend of all ingredients except glidant and lubricant was mixed, a particular attention had been given to ensure thorough mixing and phase homogenization. Granulation was done manually with a solution of PVP K 30 in purified water. The wet masses were passed through a 12 mesh sieve and the wet granules produced were first air dried for 10 min and finally at 45-50°C in a tray drier for 2 h. The dried granules were sized by a 16-mesh sieve after lubrication with magnesium stearate. Compression was carried out using 16x8 mm flat faced capsule shape punches into tablets on an eight station rotary press tablet compression machine (Rimek Minipress I Ahmedabad, India) at a constant compression force. Just before compression, the surfaces of the die and punches were lubricated with magnesium stearate. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

### 2.3. Wet Granulation

Wet granulation technique was adopted. All the API and excipients were sifted through # 40 mesh sieve (Table 1). Purified water with PVP K 30 was used as granulating solvent. Pre-sifted excipients were loaded into the stainless steel bowl of a rapid mixer granulator (Ganson Limited, India) and mixed for 10 min. Solution of Purified water and PVP K -30 was added into the dry mix slowly with the impeller on. Granulation was done in rapid mixer granulator till granules of good consistency were observed. The granules were dried at a temperature of 40°C in a Fluid Bed Drier till LOD of 1.5 to 3.0 % w/w was achieved. The dried granules were sifted through # 30 mesh sieve and loaded into the stainless steel bowl of blender. Magnesium stearate was sifted through # 60 mesh sieve and loaded into the bowl of blender mixed for 5 minutes at fast speed. Lubricated granules were compressed using plain, standard oval punches of (F3, F4 & F5).

### 2.4. Coating of wet granulated matrix tablets

A solution of mixture of cellulose acetate and hydroxypropyl methyl cellulose (HPMC 6cps) Triacetin solution was prepared by dissolving in acetone: IPA (9:1). The coating solution (5% w/w solid content) was sprayed in a Conventional Perforated Coating Pan. The Inlet temperature was 45°C. Coating solutions were also prepared by using methylene chloride: IPA (9:1) combination or acetone: IPA (9:1) solution.

### 2.5. Influence of pore diameter in coated wet granulated tablets

Coated tablets were drilled mechanically with an orifice of 0.4-0.7 mm with the help of a mechanical stirrer fitted with a needle. These tablets were subjected to the *In-vitro* dissolution studies to study the rate of release. Table 1 illustrates the formulation details of various compositions of monolayer matrix tablets formed by direct compression and wet granulation method.

**Table 1: Unit Composition of the Tablets formed by Wet Granulation Technology**

| S. No. | Ingredient | Mg/Tablet | | | | |
|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 |
| **Granulation/Direct Mixing** | | | | | | |
| 1 | Metformin Hydrochloride | 1000 | 1000 | 1000 | 1000 | 1000 |
| 2 | PVP K- 30 | - | 50 | 50 | 50 | 50 |
| 3 | Hydroxy Ethyl Cellulose (HEC 250) | 10 | 20 | 20 | **30** | **40** |
| 4 | Microcrystalline Cellulose | 410 | 340 | 340 | **330** | **320** |
| 5 | Purified Water | - | - | Q.S. | - | - |
| **Lubrication Step** | | | | | | |
| 6 | Sodium Lauryl Sulphate | - | - | - | - | - |
| 7 | Sodium Chloride | - | - | 20 | 20 | 20 |
| 8 | Magnesium Stearate | 10 | 10 | 10 | 10 | 10 |
| **Extended Release Coating** | | | | | | |
| 9 | Cellulose Acetate | 40 | 40 | 40 | 40 | 40 |
| 10 | HPMC 6 Cps | 7 | 7 | 7 | 7 | 7 |
| 11 | Triacetin | 3 | 3 | 3 | 3 | 3 |
| 12 | Acetone (90%)/Methylene Chloride | QS | QS | QS | QS | QS |
| 13 | IPA (10%) | QS | QS | QS | QS | QS |
| 14 | Purified Water (10%) | - | - | - | - | - |
| **Mechanical Drilling (Drilled on One Side Only)** | | | | | | |
| 15 | Mechanical Drill | Influence of Orifice Diameter was studied | | | | |

### 2.6. Drug content determination (Assay of coated tablets)

The Metformin Hydrochloride content of in core tablets (F1 to F5) was determined by employing the method as described in USP (Metformin Hydrochloride Extended Release Tablets).

Mobile phase: Acetonitrile Buffer solution (1:9), Diluent: 1.25% solution of acetonitrile in water, Standard solution: (L/4000) mg/mL of USP Metformin Hydrochloride RS in Diluent, where L is the labeled quantity, in mg, of metformin hydrochloride in each Tablet.

System suitability stock solution: 12.5 µg/mL each of USP Metformin Related Compound B RS and USP Metformin Related Compound CRS in Diluent.

System suitability solution: Diluted 0.5mL of the System suitability stock solution with the Standard solution to 50mL.

10 Tablets were finely powdered and the powder equivalent to the average tablet weight was transferred to a homogenization vessel, and 500mL of 10% acetonitrile solution was added. Allowed to soak, followed by Homogenization of the sample using five pulses, each of 5 s, at about 20,000 rpm, and allowed to soak for 2 min. These steps were repeated two additional times and passed a portion of the sample stock solution through a suitable filter of 0.45-µm pore size, discarding the first 3mL of filtrate. 25mL of the filtrate was transferred to a 200-mL volumetric flask, and diluted with water to volume. The following chromatographic condition were utilized for the sample, Mode LC, Detector UV 218, Column 3.9-mmx30-cm-10 micon Packaging L1, Column Temperature is 30°C, Flow rate 1mL/min, Injection Volume 10 µL, Run time Until after the elution locus of metformin related compound C.

### 2.7. *In-vitro* release rate determination (Dissolution Profiling)

The *In-vitro* release rate was determined by following the method mentioned in the USP monograph of Metformin Hydrochloride extended release tablets, the following was the method utilized for determining the rate of *in-vitro* release of Metformin Hydrochloride from the Sustained Release tablets of Metformin Hydrochloride.

**Table 2: Compositions of the investigational tablets containing different Grades of Control Release Polymer (Effect of Change of Grade of HEC and PVP K 90)**

| S. No. | Ingredient | Mg/Tablet | | | | |
|---|---|---|---|---|---|---|
| | | F6 | F7 | F8 | F9 | F10 |
| | **Granulation** | | | | | |
| 1 | Metformin Hydrochloride | 1000 | 1000 | 1000 | 1000 | 1000 |
| 2 | **PVP K- 90** | 30 | 30 | 30 | 30 | 30 |
| 3 | **Hydroxy Ethyl Cellulose (HEC 250 H)** | 10 | 20 | 20 | **30** | **40** |
| 4 | Microcrystalline Cellulose | 410 | 340 | 340 | **330** | **320** |
| 5 | Purified Water | - | - | Q.S. | - | - |
| | **Lubrication Step** | | | | | |
| 6 | Sodium Lauryl Sulphate | 20 | 20 | - | - | - |
| 7 | Sodium Chloride | - | - | 20 | 20 | 20 |
| 8 | Magnesium Stearate | 10 | 10 | 10 | 10 | 10 |
| | **Extended Release Coating** | | | | | |
| 9 | Cellulose Acetate | 40 | 40 | 40 | 40 | 40 |
| 10 | HPMC 6 Cps | 7 | 7 | 7 | 7 | 7 |
| 11 | Triacetin | 3 | 3 | 3 | 3 | 3 |
| 12 | Acetone (90%) | QS | QS | QS | QS | QS |
| 13 | IPA (10%) | QS | QS | QS | QS | QS |
| 14 | Purified Water (10%) | - | - | - | - | - |
| | **Mechanical Drilling (Drilled on One Side Only)** | | | | | |
| 15 | Mechanical Drill | Influence of Orifice Diameter was studied | | | | |

### 2.8. Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content [19]. Hardness of the tablets was tested using a Strong-Cobb hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method [20]. Drug content was analyzed by measuring the absorbance of standard and samples at $\lambda$=233 nm using UV/Vis spectrophotometer (Shimadzu 1601, Kyoto, Japan).

#### *2.8.1.* In vitro *drug release studies*

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at 37±0.5°C. The dissolution media used were 900 ml of pH 6.8 phosphate buffer solution for 24h. Sink condition was maintained for the whole experiment. Samples (10 ml) were withdrawn at regular intervals and the same volume of pre-warmed (37±0.5°C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm [21]. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

## 3. RESULTS AND DISCUSSION

Physical properties of the granules and tablets prepared by wet granulation are reported in the table 3.

### 3.1. Formulation development studies of Metformin Hydrochloride tablet formulation and *in-vitro* evaluation

Extended release tablets which have an osmotically active drug core surrounded by a semi permeable

membrane are known in the art. These osmotic dosage forms float freely in water, gastric or intestinal fluid and the drug in the core releases through one or more pores across the membrane. An elementary osmotic delivery system requires that the drug release follows zero order release kinetics in a controlled and predictable manner. The drug in solution gets released due to the osmotic gradient generated across the semi permeable membrane Keeping in view all these, formulation development for osmotic tablets were initiated which were designed to release the active drug Metformin Hydrochloride over a period of 24 hours.

### *3.1.1. Wet Granulation*

Wet Granulation study and the influence of Polymer quantity and impact of osmogen in uncoated matrix tablets is depicted in table 4.

**Table 3: Summary of the physical properties of the granules and tablets prepared by wet granulation and changing the grade of polymer**

| Process → | Wet Granulation(Grade of Polymer changed) | | | | |
|---|---|---|---|---|---|
| **Parameters** | **F1** | **F2** | **F3** | **F4** | **F5** |
| Bulk Density (g/mL) | 0.38-0.42 | 0.40-0.43 | 0.45-0.52 | 0.45-0.51 | 0.45-0.55 |
| Tapped Density | 0.52-0.63 | 0.52-0.63 | 0.61-0.63 | 0.61-0.63 | 0.61-0.63 |
| % Fines (<60#) | 55 | 48 | 50 | 58 | 53 |
| Hausner ratio | 1.5 | 1.5 | 1.3 | 1.3 | 1.3 |
| Angle of repose | 33 | 33 | 33 | 33 | 33 |
| Compressibility Index | 36 | 36 | 28 | 29 | 28 |
| Diameter (mm) | 0.12 | 0.19 | 0.20 | 0.18 | 0.21 |
| Weight (mg) | 1450 | 1450 | 1450 | 1450 | 1450 |
| Friability (%w/w) | 0.45 | 0.45 | 0.32 | 0.2 | 0.32 |
| Hardness (N) | 13 | 12 | 18 | 17 | 17 |
| Average Weight | 1450 | 1450 | 1450 | 1450 | 1450 |
| Coating Weight Gain (mg) | 72.5 | 72.5 | 72.5 | 72.5 | 72.5 |

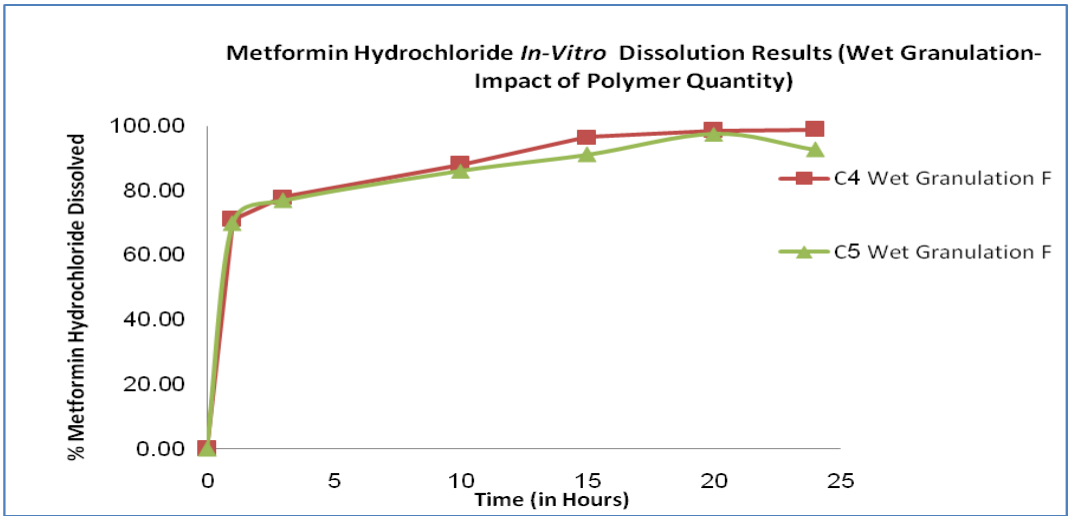


**Fig. 1: Influence of change in quantity of polymer on the release of Metformin HCL from wet granulated tablets in pH 6.8 Phosphate Buffer**

### *3.1.2. Coating of wet granulated matrix tablets*

Matrix tablets (F3/F4/F5) were coated with a semi-permeable membrane by employing cellulose acetate and hydroxypropyl methylcellulose. Table 5 shows % mean metformin released from 6 tablets i.e. from formulated tablets of F4 and F5. The coated tablets were driller with an orifice having a diameter of 0.6mm, this diameter has exhibited the diameter of choice with an optimum release of drug from the tablets.

**Table 4: Metformin released from tablets containing HEC 250 prepared through wet granulation technique**

| Time (Hours) | Dissolution Conditions | %Release of Metformin from Wet Granulation Process (F-3) | % Release of Metformin from Wet Granulation Process (F-4) | % Release of Metformin from Wet Granulation Process (F-5) |
|---|---|---|---|---|
| 1 | pH 6.8 phosphate buffer solution;1000 mL | 78.30 | 71 | 69.8 |
| 3 | | 83.50 | 78 | 76.9 |
| 10 | | 90.50 | 88 | 86.0 |
| 15 | | 95 | 96.5 | 91.1 |
| 20 | | 98.6 | 98.6 | 97.5 |
| 24 | | 98.8 | 98.9 | 97.9 |
| Infinity | | - | - | - |

**Table 5: Metformin released from coated tablets, formulation F4 C& F5C with an orifice of 0.6 mm**

| Time (Hours) | Dissolution Conditions | % Release of Metformin from Wet Granulation Process (F-4C) | % Release of Metformin from Wet Granulation Process (F-5C) |
|---|---|---|---|
| 1 | pH 6.8 phosphate buffer solution; 1000 mL | 53.9 | 49.8 |
| 3 | | 68.2 | 63.5 |
| 10 | | 81.8 | 79.2 |
| 15 | | 96.5 | 88.6 |
| 20 | | 98.6 | 92.5 |
| 24 | | - | - |
| Infinity | | - | - |

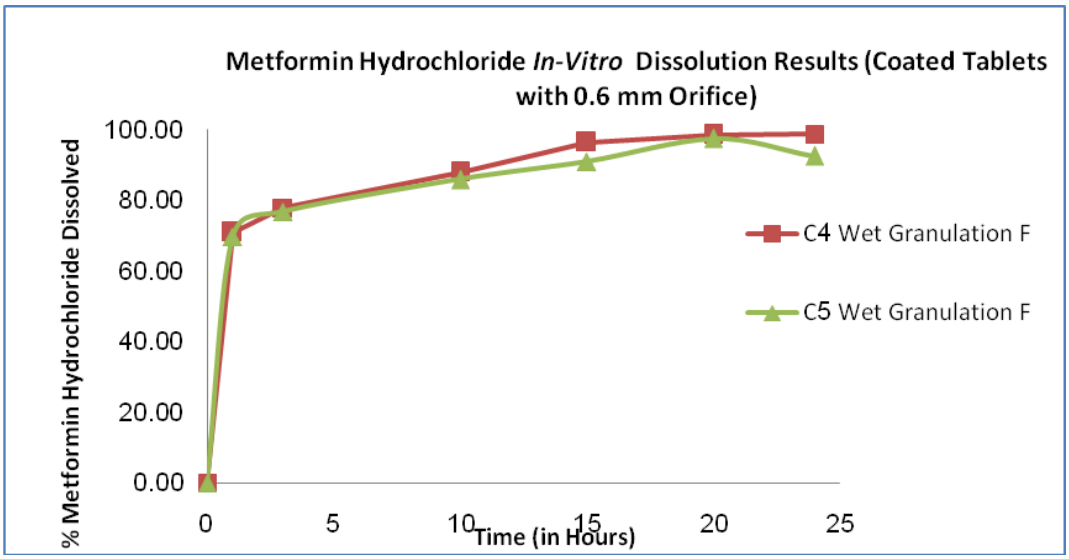


**Fig. 2: Influence of coating on the release of Metformin HCL from formulation F 4 C and F 5C in pH 6.8 phosphate buffer.**

### *3.1.3. Drug content determination*

The content of Metformin Hydrochloride in each sample of F4C and F5C was determined by performing the assay of the sample by HPLC method. The drug content in tablets of both batches was determined in triplicate. The results did not reveal more that 5% w/w variation in drug content indicating no significant degradation of metformin in the final formulation.

Impact of different polymer on the release of Metformin Hydrochloride from the hydrophilic Monolithic system is given in table 8.

**Table 6: Assay of Metformin in tablets**

| S. No. | % Assay of Metformin (F-4C) | % Assay of Metformin (F-5C) | % Assay of Metformin (F-8C) | % Assay of Metformin (F-9C) | % Assay of Metformin (F-10C) |
|---|---|---|---|---|---|
| 1 | 100.1 | 99.60 | 101.2 | 96.8 | 100.2 |
| 2 | 99.68 | 97.5 | 97.5 | 97.4 | 101.6 |
| 3 | 100.23 | 102.3 | 98.5 | 100.2 | 94.5 |
| Average Assay Value | 100.03 | 99.80 | 99.06 | 98.13 | 98.76 |

**Table 7: Metformin released from tablets containing HEC 250 H (change in grade of polymer) and sodium chloride as and osmogen**

| Time (Hours) | Dissolution Conditions | % Release of Metformin from wet granulation process | | | | |
|---|---|---|---|---|---|---|
| | | F-6 | F-7 | F-8 | F-9 | F-10 |
| 1 | pH 6.8 phosphate buffer solution; 1000 mL | 50.8 | 51.2 | 48 | 47 | 42.3 |
| 3 | | 65.1 | 69.7 | 65 | 61.6 | 59 |
| 10 | | 81.8 | 82.4 | 72.8 | 68 | 71.8 |
| 15 | | 86.3 | 98.6 | 81 | 77 | 76 |
| 20 | | 89.2 | 95 | 89 | 84 | 88.9 |
| 24 | | 101.2 | 102 | 98 | 85 | 89.7 |
| Infinity | | | 102.5 | 102 | 89 | 91.3 |

**Table 8: Compositions of the investigational tablets containing different Control Release Polymer**

| S. No. | Ingredient | Mg/Tablet | | | | |
|---|---|---|---|---|---|---|
| | | F11 | F12 | F13 | F14 | F15 |
| | **Granulation/Direct Mixing** | | | | | |
| 1 | Metformin Hydrochloride | 1000 | 1000 | 1000 | 1000 | 1000 |
| 2 | PVP K- 90 | - | 50 | 50 | 50 | 50 |
| 3 | **Hydroxy Propyl Methyl Cellulose (HPMC K 100M CR)** | 10 | 20 | 20 | **30** | **40** |
| 4 | Microcrystalline Cellulose | 410 | 340 | 340 | **330** | **320** |
| 5 | Purified Water | - | - | Q.S. | - | - |
| | **Lubrication Step** | | | | | |
| 6 | Sodium Lauryl Sulphate | 20 | 20 | - | - | - |
| 7 | Sodium Chloride | - | - | 20 | 20 | 20 |
| 8 | Magnesium Stearate | 10 | 10 | 10 | 10 | 10 |
| | **Extended Release Coating** | | | | | |
| 9 | Cellulose Acetate | 40 | 40 | 40 | 40 | 40 |
| 10 | HPMC 6 Cps | 7 | 7 | 7 | 7 | 7 |
| 11 | Triacetin | 3 | 3 | 3 | 3 | 3 |
| 12 | Acetone (90%) | QS | QS | QS | QS | QS |
| 13 | IPA (10%) | QS | QS | QS | QS | QS |
| 14 | Purified Water (10%) | - | - | - | - | - |
| | **Mechanical Drilling (Drilled on One Side Only)** | | | | | |
| 15 | Mechanical Drill | Influence of Orifice Diameter was studied | | | | |

**Table 9: Metformin released from tablets containing HPMC K 100 M CR (change in polymer) and sodium chloride as and osmogen**

| Time (Hours) | Dissolution Conditions | % Release of Metformin from Wet Granulation Process using HPMC K 100 M CR | | | | |
|---|---|---|---|---|---|---|
| | | F-11 | F-12 | F-13 | F-14 | F-15 |
| 1 | pH 6.8 phosphate buffer solution; 1000 mL | 45.2 | 42.5 | 43.5 | 36.5 | 28.6 |
| 3 | | 51.5 | 43.8 | 45.5 | 42.2 | 40.5 |
| 10 | | 79.8 | 51.2 | 52.5 | 50.8 | 51.8 |
| 15 | | 86.3 | 65.5 | 84.5 | 77.5 | 76 |
| 20 | | 87.2 | 78.2 | 89.8 | 84.5 | 88.9 |
| 24 | | 98.8 | 85.3 | 98.8 | 89 | 89.7 |
| Infinity | | | 100.5 | 102.2 | 90.5 | 91.3 |

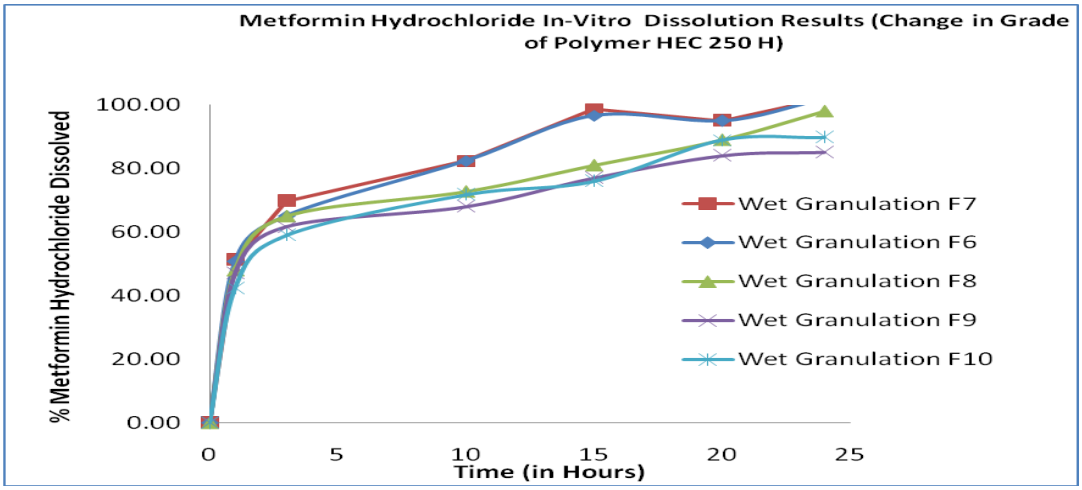


**Fig. 3: Influence of change of grade of polymer on the release of Metformin HCL from formulation F 6-F 10 in pH 6.8 phosphate buffer**

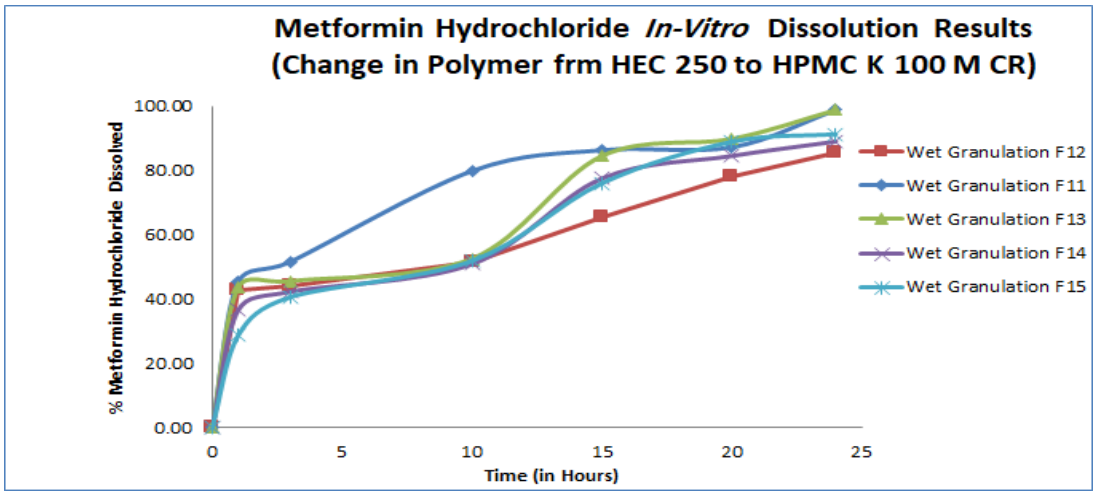


**Fig. 4: Influence of change of polymer on the release of Metformin HCL from formulation F 11-F 15 in pH 6.8 phosphate buffer**

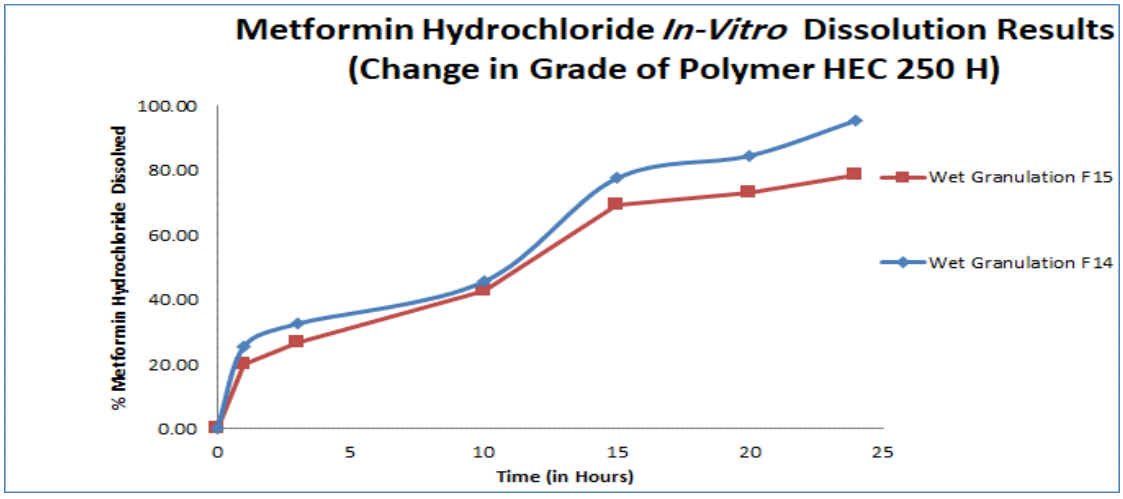


**Fig. 5: Influence of coating and change of grade of polymer on the release of Metformin HCL from formulation F 6-F 10 in pH 6.8 phosphate buffer**

**Table 10: Metformin released from coated tablets, formulation F14 & F 15 with an orifice of 0.6 mm. (coated tablets with change in polymer in core tablets)**

| Time (Hours) | Dissolution Conditions | % Release of Metformin from Wet Granulation Process (F-14C) | % Release of Metformin from Wet Granulation Process (F-15C) |
|---|---|---|---|
| 1 | pH 6.8 phosphate buffer solution; 1000 mL | 25.5 | 19.8 |
| 3 | | 32.5 | 26.5 |
| 10 | | 45.5 | 42.6 |
| 15 | | 77.5 | 69.4 |
| 20 | | 84.5 | 73.2 |
| 24 | | 95.5 | 78.6 |
| Infinity | | | |

### *3.1.4. Drug content determination*

The content of Metformin Hydrochloride in each sample of F14C and F15C was determined by performing the assay of the sample by HPLC method. The drug content in tablets of both batches was determined in triplicate. The results did not reveal more that 5% w/w variation in drug content indicating no significant degradation of metformin in the final formulation.

The experiments done with change in the quantity of polymer, retarded the release of Metformin from the core and the coated tablets, however the release was not as desired, hence it was decided to evaluate the change in the grade of polymer to HEC 250 H. This resulted in consolidation of metformin hydrochloride and other excipients to form a granular mass. Thus, tablets consisting of osmogen, polymer and other excipients were formed. Composition of the formulations where HEC 250H and sodium chloride was used as osmogen. Table shows the granules formed by change in grade of polymer exhibited better bulk density (0.42-0.55gm/ml) that can be expected to impart better fill volume inside the die cavity [21-24].

The failure in releasing metformin hydrochloride by osmogen and polymers alone or their combination prompted to find a suitable water swellable viscous polymer that would be helpful in releasing metformin from the designed dosage form in a predetermined manner. HPMC K 100 M CR is reported to sustain the drug release in a predictable manner. Alone HEC with low viscosity and sodium chloride (osmogen), or their combination thereof, did not exhibit the ability to push the dissolved metformin out of the semipermeable compartment and hence the higher viscosity grades of the polymer shall be evaluated and impact on the rate and extent of drug release shall be studied. The change in the type of polymer helped us to achieve the desired release pattern from the Investigational Extended release tablets, however single polymer monolithic systems exhibited the retardation of the release to a greater extent than desired and hence it was further decided to evaluate the influence of polymer combination to have the desired release pattern.

The release profiles of Metformin Hydrochloride from the tablets of batch F15C were found to be almost similar in different buffers (pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.5 intestinal fluid without pancreatin). These similar dissolution profiles suggest that Metformin Hydrochloride release was not influenced by the pH of the dissolution media. The results strongly indicated that the formulated osmotic tablets can be envisaged to release Metformin Hydrochloride at predetermined rate without being influenced by the gastric motility and emptying time.

## 4. CONCLUSION

It can be concluded that a combination of hydrophilic and hydrophobic polymer can be used for extending the release of Metformin hydrochloride for the period of 24hours. The osmotic pressure inside the sustained release core is the driving force for the sustained release of Metformin Hydrochloride from the osmotic pump system. Optimized formulation containing HPMC and HEC had successfully sustained the drug release up to 24 hours. Thus the matrix tablet of Metformin hydrochloride can be formulated, evaluated and found to be suitable candidate for prolonging the release of Metformin hydrochloride.

### *Conflict of interest*

None declared

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