Biocompatible Interpolymer Complex Matrix Tablets – As a Drug Carrier for Class-III Antidiabetic Drug

OBJECTIVES

- Interpolymer complexes (IPCs) of chitosan (CH) and two different viscosity grades of hydroxypropyl methylcellulose - HPMC (K4M and K100M) at various ratios, say, 4:6, 2:8, and 1:9 respectively have been prepared.
- The physical properties and drug content of formulated tablets are evaluated. In addition, in vitro drug release kinetics is carried out at two different pH, say, 2 and 6.8.

2.1 INTRODUCTION

The aim of the present study is to design an adjustable drug carrier system in the form of interpolymer complexes (IPCs) for sustained release of highly water soluble metformin. Based on the literature survey, it is observed that the role of IPCs towards sustained release (SR) formulation is yet to be unequivocally proved.

Metformin is a hydrophilic drug, incompletely absorbed in gastro intestinal tract (Dunn and Peters, 1995) and need to be administered two or three times a day to maintain plasma levels of drug. A few reports confirm that oral absorption of metformin is mainly targeted at small intestine such as duodenum, jejunum and lesser extent to ileum (Vidon et al., 1988; Scheen, 1996; Marathe et al., 2000). The sustained release drug delivery is an ideal approach to prolong its activity, patient compliance (Dunn and Peters, 1995) and also facilitate complete drug release in small intestine and has been developed using different types and grades of polymer in IPC form.

A few literature reports on metformin indicate the use of polymers as a matrix to make it a sustained release. Nayak et al. (2014) developed novel mucoadhesive beads by using pectin and tamarind seed polysaccharide (TSP) polymer blend to prolong the metformin drug release in a sustained manner. Corti et al. (2007) used the blend of chitosan, hydroxypropyl cellulose, EudragitRL100-55 and other excipients for the sustained release
of Met dispersed in hydrophobic triacetyl-β-cyclodextrin. Wadher et al. (2011) reported the significance of combinations of hydrophobic polymer (ethyl cellulose) in the presence of hydrophilic polymer (Eudragit RSPO and RLPO) towards controlling the drug release rate of metformin as compared to individual hydrophilic polymers. Further, it has also been reported, based on comparison study of different grades of hydroxypropyl methyl cellulose, that HPMC K100M shows greater effect in controlling the metformin release due to its high viscosity. Only very few reports are available with respect to IPCs as a drug carrier and that too for other types of drugs and not for metformin. The chitosan/carbopol IPC shows pH-independent sustained release profile of theophylline from the tablets that contain different molecular weight chitosan (Park et al., 2008). Imwitor 900 K, a hydrophobic waxy retardant polymer used as an efficient matrix forming agent, with hydrophilic IPCs of chitosan/hyaluronate sodium, pectin and sodium alginate controls the release rate of nicorandil drug for about 8h (Abdelbary et al., 2008). From the above literature survey, it is obvious that IPCs have greater role as a drug carrier than individual polymers towards sustained release. In this regard, in the current study, IPCs matrix systems have been designed as a drug carrier for sustained release of metformin, hitherto, unreported.

2.2 EXPERIMENTAL

2.2.1 MATERIALS AND METHODS

Metformin hydrochloride and hydroxypropyl methylcellulose (HPMC K4M, Mn= 86000, viscosity 4000 cps and HPMC K100M, Mn= 150,000, viscosity 10,000 cps) were obtained from Cipla research laboratories, India. CH analytical research grade, low molecular weight, viscosity 20-300 cps was purchased from Sigma Aldrich and used as received. All other excipients were of analytical research grade and used as received.

2.2.2 PREPARATION OF CH/HPMC (K4M AND K100M) IPCs

A known quantity of CH was dissolved in acetic acid (1% v/v) under stirring condition for 2h until a clear bubble free solution was obtained. A known quantity of HPMC (K4M and K100M) solution was prepared separately by dispersing in distilled water (q.s) with
stirring for 2h. The prepared CH and HPMC solution were mixed and stirred for 3h at room temperature. The prepared solution was dried in hot air oven at 90°C. Dried samples were ground and sieved (no.80 mesh size). Collected IPCs were stored in desiccator for further study. CH/HPMC solution was mixed in different proportions (4:6, 2:8, 1:9) to prepare IPCs.

![Diagram]

**2.2.3 PREPARATION OF SUSTAINED RELEASE MATRIX TABLET**

Formulations F1-F9 was prepared by wet granulation technique. Weighed amount of all ingredients were passed through sieve no-44 and mixed uniformly except PVPK30. Then PVPK30 (binder) dissolved in isopropyl alcohol were added to the ingredients to form a dough mass. The dough mass was then passed through sieve no.10 and dried at 50°-60°C till loss on dry (LOD) is less than 1-2% w/w, and then passed through sieve no.16. The weighed amount of granules were taken for compression of tablet in a cadmach single punching machine (CMB4 D-27, Cadmach Engg, Ahmedabad, India) using 12 mm round biconcave punch. Each 850mg tablet contains 500 mg of metformin and other pharmaceutical excipients as listed in Table 3.
In the last three decades, sustained release dosages forms have made significant progress in the terms of clinical efficacy and patient compliance. The polymeric matrix plays a vital role in controlling the drug release pattern. All the formulations were formulated by wet granulation method to obtain a sustained release polymeric bound matrix tablets. Metformin and all other excipients compositions are constant in all formulations (F1-F9). CH and different viscosity grades of HPMC compositions are varied in each formulation.

2.3 EXCIPIENTS USED

An excipients is a natural or synthetic substance formulated with active ingredients of a medication to bulking-up formulations (referred as "bulking agents," "fillers," or "diluents") or enhancement of the therapeutic activity during absorption and solubility. These ingredients are added during the manufacturing process of pharmaceutical products such as tablets, capsules, suppositories, and injections. These excipients significantly facilitating powder flowability or non sticky properties in addition to increase in vitro
stability (shelf life). The selection of excipients depends upon the route of administration, dosage form, active ingredients etc.

2.3.1 LACTOSE

- Chemical Name – $O$-$\beta$-$D$-galactopyranosyl-(1$\rightarrow$4)-$\beta$-$D$-glucopyranose
- Empirical Formula – C12H22O11
- Molecular Weight – 342.30
- Functional Category – Anhydrous lactose is widely used in direct compression of tablet application and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.
- Description – Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous $\beta$-lactose and anhydrous $\alpha$-lactose. Anhydrous lactose typically contains 70–80% anhydrous $\beta$-lactose and 20–30% anhydrous $\alpha$-lactose.
- Melting Point – 223°C for anhydrous $\alpha$-lactose; 252°C for anhydrous $\beta$-lactose; 232°C (typical) for commercial anhydrous lactose
- Solubility – Soluble in water; sparingly soluble in ethanol (95%) and ether
- Stability and Storage Condition – Lactose anhydrous should be stored in a well-closed container in a cool, dry place.
- Safety – Lactose is widely used in pharmaceutical formulations as a diluent and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions of lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of solid dosage forms.

2.3.2 TALC

- Chemical Name – Talc
- Empirical formula – Mg$_6$(Si$_2$O$_5$)$_4$(OH)$_4$
- Molecular Weight – 379.27g
✓ Functional Category – Anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

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

✓ Melting point – Above 900°C

✓ Moisture content – Up to about 90%.

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

✓ Stability and storage condition – Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

✓ Safety – Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants.

2.3.3 MAGNESIUM STEARATE

✓ Chemical Name – Octadecanoic acid magnesium salt.

✓ Empirical Formula – C₃₆H₄₄MgO₄

✓ Molecular Weight – 591.27

✓ Structural Formula – [CH₃(CH₂)₁₆COO]₂Mg

✓ Functional Category – It is used as tablet and capsule lubricant. Used in Cosmetics, foods and pharmaceutical formulations. Primarily used in capsules and tablets manufacturing at a concentration in between 0.25% to 5.0%.
✓ Description – It is a fine, white, precipitated, greasy powder of low bulk density, having a faint, characteristics odour and taste. It readily adheres to the skin.

✓ Flow ability – It is a poorly flowing, cohesive powder

✓ Melting Point – 88.5\degree C

✓ Moisture Content – < 4%

✓ Solubility – Practically insoluble in ethanol (95%), ether and water. Slightly soluble in warm benzene and warm ethanol (95%)

✓ Stability and Storage Condition – It is incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials.

✓ Safety – Most widely used pharmaceutical excipients and regarded as being non-toxic flowing oral administration. Oral Consumption of large quantities results in some laxative effect or mucosal irritation. Inhalation is harmful and resulted in fatalities.

2.3.4 ISO-PROPYL ALCOHOL

✓ Chemical Name – propane-2-ol

✓ Empirical formula – C_3H_8O

✓ Molecular Weight – 60.1

✓ Structural Formula – (CH\_2\_2CHOH

✓ Functional Category – Mainly used as disinfectant, and solvent. Application in pharmaceutical formulation. Used in cosmetics and pharmaceutical formulations as a solvent in topical preparation. Not recommended for oral use due to its toxicity. Also used as solvent both for tablet film coating and tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has some antimicrobial activity and 70%v/v solutions used as topical disinfectants.

✓ Description – It is clear, colourless, mobile, volatile, flammable liquid with a characteristic spirituous odour resembling that of a mixture of ethanol and acetone and has slightly bitter taste.

✓ Boiling point – 82.4\degree C
EXPLOSIVE LIMIT – 2.5 – 12.0% v/v in air.

FLAMMABILITY – Flammable

FREEZE POINT – 89.5°C

MELTING POINT – 89.5°C

MOISTURE CONTENT – 0.1 to 13%

SOLUBILITY – it is miscible with benzene, chloroform, ethanol, ether, glycerin, and water. Soluble in acetone. Insoluble in salt solution and forms a azeotrope with water containing 4% w/w isopropyl alcohol.

STABILITY AND STORAGE CONDITION – stored in an amber coloured air tight container in a cool, dry place.

SAFETY – Widely used in cosmetics and topical pharmaceutical preparation. Readily absorbed from G.I tract and may be slowly absorbed through intact skin. IPA is metabolized very slowly than ethanol, acetone. IPA and its metabolites excreted in urine. IPA is two time toxic than ethanol and thus shouldn’t be administered orally. It has unpleasant test. 20 ml IV administration diluted with water shows side effects such as sensation of heat and slight lowering of blood pressure and thus not commonly used in parenteral products. Mostly used in topical preparation where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

2.3.5 POLY VINYL PYRROLDIDONE (Povidone) (PVP K-30)

CHEMICAL NAME – 1-ethynyl-2-pyrolidone homopolymer.

EMPirical Formula – (C₆H₉NO)n

MOLECULAR WEIGHT – 2,500-3,000,000

FUNCTIONAL CATEGORY – Used as Suspending agent, tablet binder.

APPLICATION – Mainly used in solid dosage (tablet) form as a binder in wet granulation method. Also used as coating agent, suspending, stabilizing or viscosity increasing agent in a number of topical and oral suspension and solutions. Mixing with povidone can enhance the solubility of most poorly soluble active drugs.
✓ Description – It is a fine white to creamy white colour, odourless, hygroscopic powder.
✓ Hygroscopic – Highly hygroscopic
✓ Melting point – 150°C
✓ Dynamic viscosity – 5.5 to 8.5 mPa.s at 20°C
✓ Stability and storage condition – Under ordinary storage conditions, it undergoes decomposition or degradation. As it is hygroscopic, should be stored in an air tight container in a cool dry place.
✓ Incompatibilities – In solution state, it is compatible to wide range of inorganic salts, natural and synthetic resins and other chemicals. It forms molecular adducts with sulphathiazole, sodium salicilate, salicylic acid, Phenobarbital, tannin, and other compounds. Efficacy of some preservatives e.g. thiomersal, adversely effected by formation of complexes with povidone.
✓ Safety – Widely used and when consumed orally it is considered very non-toxic since it is not absorbed from GI tract or mucous membrane. It has no irritant effect on skin and causes no sensitization. Side effects are subcutaneous granulomas at injection sites of IM injection. Acceptable daily intake for povidone has been set by WHO up to 25 mg/kg body weight.

Table 3 Formulation of metformin HCl tablets (850mg) and their composition (mg)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug</th>
<th>CH</th>
<th>HPMC CH/K4M</th>
<th>CH/K100M IPC</th>
<th>CH/K4M IPC</th>
<th>Lactose</th>
<th>PVP-K30</th>
<th>Mg Stearate</th>
<th>Talc</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>500</td>
<td>227</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F2</td>
<td>500</td>
<td>-</td>
<td>227</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>500</td>
<td>-</td>
<td>227(4:6)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F4</td>
<td>500</td>
<td>-</td>
<td>227(2:8)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F5</td>
<td>500</td>
<td>-</td>
<td>227(1:9)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F6</td>
<td>500</td>
<td>-</td>
<td>227(4:6)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F7</td>
<td>500</td>
<td>-</td>
<td>227(2:8)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F8</td>
<td>500</td>
<td>-</td>
<td>227(1:9)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>F9</td>
<td>500</td>
<td>-</td>
<td>227(4:6)</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>
2.4 CHARACTERIZATION/RESULTS AND DISCUSSION

2.4.1 EVALUATION OF SUSTAINED RELEASE TABLET

2.4.1.1 WEIGHT VARIATION TEST

Twenty tablets were selected randomly from each formulation and weighed individually using digital balance (Shimadzu AUY 220, Uni Bloc, Germany). The average weights were calculated and mean values were determined. It should not deviate more than ± 5% as per the Indian Pharmacopeia (IP).

2.4.1.2 TABLET THICKNESS TEST

To determine the uniformity and physical dimension of tablet, thickness is measured by vernier calipers for randomly selected 20 tablets from each formulation.
2.4.1.3 HARDNESS TEST

Hardness is determined to measure the strength of a tablet, for randomly selected 10 tablets from each formulation using Monsanto Hardness Tester (Lachmann and Liberman, 2009).

![Monsanto Hardness Tester](image1.jpg)

2.4.1.4 TABLET FRIABILITY

Previously weighed 10 tablets were placed in the Roche’s friabilator for 4min/100 rpm. The tablets were de-dusted and accurately weighed. The % loss was calculated as per IP. It is expected to be less than 1%.

![Roche’s Friabilator](image2.jpg)
2.4.1.5 DRUG CONTENT UNIFORMITY

Ten tablets from each formulation were crushed and dissolved in water. The solution was filtered and the drug content was determined by UV spectrophotometer (Jasco V-670, Japan) at 232 nm with a suitable dilution.

Metformin tablets (Formulation F1-F9) were evaluated for their physicochemical properties that play a vital role in the drug release pattern. A comparison of physicochemical properties of all the formulations is listed in Table 4. The weight variation was found to be within the limit of ± 5%. The average weight for all formulations was found to be in the range of 847 to 850 mg. The uniform thickness was in the range of 5.17 to 5.68 mm. The formulated tablets passed through the hardness and friability tests as per the standard limits, the hardness ranging from 6.02 to 7 and percentage of friability obtained below 1%. The drug content for different formulations was found to be within the standard limit of 97.5 to 100.5. The prepared tablets are thus mechanically stable for further study.

Table 4 Physical properties of Metformin HCl (850mg) tablets Formulation F1-F9

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tablet Weight variation (mg)</th>
<th>Tablet Thickness (mm)</th>
<th>Tablet Hardness (kg/cm²)</th>
<th>Tablet Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>847.31±1.31</td>
<td>5.31±0.72</td>
<td>6.02±0.17</td>
<td>0.47±0.02</td>
<td>100.49±1.78</td>
</tr>
<tr>
<td>F2</td>
<td>848.11±1.3</td>
<td>5.58±0.69</td>
<td>6.42±0.14</td>
<td>0.31±0.32</td>
<td>98.36±0.32</td>
</tr>
<tr>
<td>F3</td>
<td>847.53±1.9</td>
<td>5.63±0.09</td>
<td>7±0.85</td>
<td>0.28±0.61</td>
<td>98.17±0.71</td>
</tr>
<tr>
<td>F4</td>
<td>848.37±1.32</td>
<td>5.17±0.35</td>
<td>6.37±0.03</td>
<td>0.56±0.14</td>
<td>99.09±1.39</td>
</tr>
<tr>
<td>F5</td>
<td>849.23±1.06</td>
<td>5.19±0.04</td>
<td>6.43±0.83</td>
<td>0.47±0.33</td>
<td>98.95±0.33</td>
</tr>
<tr>
<td>F6</td>
<td>850.37±1.09</td>
<td>5.27±0.48</td>
<td>6.59±0.33</td>
<td>0.46±0.57</td>
<td>97.46±0.91</td>
</tr>
<tr>
<td>F7</td>
<td>849.27±1.31</td>
<td>5.31±0.05</td>
<td>6.49±0.91</td>
<td>0.37±0.28</td>
<td>99.95±0.01</td>
</tr>
<tr>
<td>F8</td>
<td>850.39±1.75</td>
<td>5.68±0.15</td>
<td>6.72±0.57</td>
<td>0.17±0.11</td>
<td>98.31±1.05</td>
</tr>
<tr>
<td>F9</td>
<td>850.79±1.03</td>
<td>5.59±0.39</td>
<td>6.73±0.38</td>
<td>0.14±0.31</td>
<td>99.37±0.69</td>
</tr>
</tbody>
</table>

Results are expressed as of mean ±SD (n=3)
The formulated tablets are characterized using FTIR, Powder XRD and Thermal analysis.

2.4.2 FTIR

Figure 2(a, b) shows the FTIR spectra of CH, HPMC K4M/HPMC K100M and their IPCs respectively. A high intense stretching frequency occurring at 1655 cm\(^{-1}\) correspond to \(-\text{NH}_3^+\) groups present in CH and on the other hand spectrum of HPMC shows peak at 3444 cm\(^{-1}\) assigned to \(-\text{OH}\) groups. In case of IPCs, the broadening of bands at 3444 cm\(^{-1}\) can be inferred due to inter-molecular H-bonding between CH/HPMC polymers (Abdelbary and Tadros, 2008; Park et al., 2008).

![Figure 2 FT-IR spectra of a) CH, K4M and IPCs of CH/K4M (4:6, 2:8, 1:9 ratios) and b) CH, K100M and IPCs of CH/K100M(4:6, 2:8, 1:9 ratios)](image)

The FTIR spectrum in figure 3 reveals that there is no shifting or change in metformin spectra when it is in combination with pure polymers (CH, HPMCK4M and HPMC K100M) or with their IPCs.
2.4.3 XRD ANALYSIS

In the similar way, XRD pattern in figure 4 confirms that metformin has shown an intense sharp peak that corresponds to the crystalline state whereas pure CH and HPMC (K4M and K100M) shows a broad peak confirms amorphous nature of polymers. From the figure, it has been observed that individual polymers and their IPCs (1:9 ratio) with metformin have shown sharp intense peak which reveals that there is no significant change in peak intensity and peak position. This proves that individual polymers and their IPCs are compatible with the drug metformin.
Figure 4 X-ray, diffraction pattern of metformin hydrochloride pure polymers (CH, HPMC K4M/K100M) and metformin hydrochloride with pure polymers and their IPCs in (1:9) ratio

2.4.4 THERMO GRAVIMETRIC ANALYSIS

Figure 5 reveals two stages of thermal degradation for CH, K100M and IPCs of CH: K100M (1:9). The first stage of thermal degradation is due to the presence of moisture in the compound at 80-100°C. The second stage of thermal degradation for CH, K100M and CH:K100M (1:9) IPC is due to the depolymerisation of CH chains (Ritthidej et al., 2002; Wanjun et al., 2005; Haque and sheela, 2014), cellulose ethers dehydration and degradation of unsaturated CH and K100M in IPC respectively. IPC shows its characteristic thermal behaviour different from that of individual polymers.
2.5 DRUG RELEASE PROFILE

2.5.1 IN VITRO DISSOLUTION TEST

Drug release studies for all formulations were determined using single bucket USP type-I basket apparatus (Secor India Lab) at 100rpm bearing 900 ml of pH 2 or pH 6.8 medium at 37 ± 0.5°C. At regular intervals of time, 5ml sample were withdrawn and replaced by fresh solution and the absorbance was measured at 232 nm after a suitable dilution. The obtained absorbance used in calibration curve equation of metformin to further calculate the % of drug release at different interval of time.
In vitro dissolution time for formulations F1 to F9 tablets show variations in release period ranging from 30 min to 12 h shown in Table 5. This may be attributed to the nature of polymer and their grades used in various proportions in IPC. The cross linking nature of high viscosity grade HPMC forming complex matrix network with CH may also be due to the intermolecular –H bonding between CH/HPMC. The gel like matrix acts as a barrier retarding the rate of diffusion of drug molecule. Formulation F1 showed immediate release of metformin (98.26%) at pH-2 within 30 min as it disintegrates rapidly favouring immediate release. Formulations F2 and F3 have shown relatively slower rate of drug release of 99.87% and 96.37% within 6 h and 8 h respectively attributed to the presence of different viscosity grade of HPMC. Formulations F4, F5 and F6 have shown 97.19%, 95.11% and 99.39% within 6 h, 8 h and 9 h respectively. Formulations F7 and F8 have shown 95.7% and 98.19% of drug release with in 9 h and 11 h respectively due to the gradual increase in the concentration of HPMC K100M. In case of F9, the higher viscosity grade HPMC K100M present in highest concentration favoured retarded drug release of 97.94% till 12 h. Figure 6 shows drug release pattern for different formulations (F1- F9).

Table 5 In vitro dissolution profile for metformin hydrochloride tablet (Formulation F1-F9)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min (1h)</th>
<th>120 min (2h)</th>
<th>180 min (3h)</th>
<th>240 min (4h)</th>
<th>300 min (5h)</th>
<th>360 min (6h)</th>
<th>420 min (7h)</th>
<th>480 min (8h)</th>
<th>540 min (9h)</th>
<th>600 min (10h)</th>
<th>660 min (11h)</th>
<th>720 min (12h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>75.31</td>
<td>98.26</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>11.85</td>
<td>20.32</td>
<td>31.53</td>
<td>40.71</td>
<td>54.41</td>
<td>66.73</td>
<td>83.79</td>
<td>99.87</td>
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</tr>
<tr>
<td>F3</td>
<td>10.25</td>
<td>19.44</td>
<td>28.63</td>
<td>41.94</td>
<td>56.72</td>
<td>68.83</td>
<td>77.88</td>
<td>85.31</td>
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</tr>
<tr>
<td>F4</td>
<td>15.15</td>
<td>22.31</td>
<td>33.91</td>
<td>46.74</td>
<td>58.95</td>
<td>69.39</td>
<td>84.99</td>
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</tr>
<tr>
<td>F5</td>
<td>14.23</td>
<td>22.92</td>
<td>31.24</td>
<td>45.71</td>
<td>55.39</td>
<td>64.97</td>
<td>73.89</td>
<td>81.21</td>
<td>88.26</td>
<td>95.11</td>
<td>-</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td>F6</td>
<td>14.67</td>
<td>19.36</td>
<td>30.59</td>
<td>43.47</td>
<td>55.33</td>
<td>63.71</td>
<td>71.27</td>
<td>80.39</td>
<td>87.92</td>
<td>93.84</td>
<td>99.39</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>F7</td>
<td>15.88</td>
<td>21.32</td>
<td>32.94</td>
<td>44.54</td>
<td>53.71</td>
<td>62.39</td>
<td>70.73</td>
<td>77.92</td>
<td>84.22</td>
<td>88.98</td>
<td>95.7</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>F8</td>
<td>13.59</td>
<td>20.36</td>
<td>28.78</td>
<td>40.71</td>
<td>49.48</td>
<td>58.73</td>
<td>67.93</td>
<td>74.29</td>
<td>81.19</td>
<td>86.38</td>
<td>91.11</td>
<td>96.49</td>
<td>98.19</td>
<td></td>
</tr>
<tr>
<td>F9</td>
<td>13.83</td>
<td>18.88</td>
<td>24.49</td>
<td>37.72</td>
<td>45.33</td>
<td>53.95</td>
<td>59.99</td>
<td>67.39</td>
<td>74.92</td>
<td>81.81</td>
<td>87.69</td>
<td>91.39</td>
<td>95.68</td>
<td>97.94</td>
</tr>
</tbody>
</table>

Results are expressed as of mean ±SD (n=3)
Figure 6 *In vitro* drug release of metformin from different polymer matrices a) metformin release from polymer Chitosan, HPMC K4M and HPMC K100M b) metformin release from IPCs of CH/HPMC K4M in (4:6, 2:8 and 1:9 ratios) c) metformin release from IPCs of CH/HPMC K100M in (4:6, 2:8 and 1:9 ratios)

2.5.2 KINETICS OF DRUG RELEASE

- The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets.
- The model that best fits the release data is selected based on the correlation coefficient (r) value in various models.
- The model that gives high ‘r’ value is considered as the best fit to the release data.

Mathematical models are:

1) ZERO ORDER RELEASE KINETICS

The zero order process can be defined as the one whose rate is independent of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of the reactants.

The equation for zero order release is

\[ Q_t = Q_0 + K_0t \]

Where

- \( Q_0 \) = Initial amount of drug
- \( Q_t \) = Cumulative amount of drug release at time “t”
- \( K_0 \) = Zero order release constant
- \( t \) = Time in hours
2) FIRST ORDER RELEASE KINETICS

The first order equation describes the release from the systems where release rate is concentration dependent.

The equation for first order release is
\[ \log Q_t = \log Q_0 + \frac{Kt}{2.303} \]

Where
- \( Q_0 \) = Initial amount of drug
- \( Q_t \) = Cumulative amount of drug release at time “t”
- \( K \) = First order release constant
- \( t \) = Time in hours

3) HIXSON – CROWELL RELEASE KINETICS

It describes the drug release by dissolution and with the changes in surface area and diameter of the particles or tablets.

The equation for Hixson-crowell release is
\[ 3\sqrt{Q_0} - 3\sqrt{Q_0} = K_{HC}t \]

Where
- \( Q_0 \) = Initial amount of drug
- \( Q_t \) = Cumulative amount of drug release at time “t”
- \( K_{HC} \) = Hixson-crowell release constant
- \( t \) = Time in hours

4) HIGUCHI RELEASE KINETICS

The Higuchi kinetics suggests that the drug release by diffusion.

The equation for Higuchi release is
\[ Q = K_H t^{1/2} \]

Where
- \( Q \) = Cumulative amount of drug release at time “t”
- \( K_H \) = Higuchi release constant
- \( t \) = Time in hours
5) KORSMEYER-PEPPAS RELEASE KINETICS

Korsmeyer-Peppas equation is
\[ F = \left( \frac{M_t}{M} \right) = K_m t^n \]

Where
- \( F \) = Fraction of drug release at time “t”
- \( M_t \) = Amount of drug release at time “t”
- \( M \) = Total amount of drug in dosage form
- \( K_m \) = Kinetic constant
- \( n \) = Diffusion or release exponent
- \( t \) = Time in hours

‘n’ is estimated from linear regression of log \( (M_t/M) \) versus log \( t \)

The *in vitro* release data of all formulations were applied to various kinetics models to predict the release kinetic mechanism.

Formulation F1 has shown insufficient data due to its immediate release pattern, so we could not plot whereas for all other formulations (F2-F9) shown below.

DR = Drug release
ARA = Amount remaining to absorb
\( Q_o \) = Initial amount of drug
\( Q_t \) = Drug release at time “t”
Release kinetic study of Formulation F2

Zero order

First order

Hixson-Crawell

Higuchi Release

Korsmeyer-Peppas
Release kinetic study of Formulation F3

**Zero order**

\[ R^2 = 0.977 \]

**First order**

\[ R^2 = 0.9887 \]

**Hixson-Crowell**

\[ R^2 = 0.9816 \]

**Higuchi Release**

\[ R^2 = 0.9899 \]

**Korsmeyer-Peppas**

\[ R^2 = 0.9916 \]
Release kinetic study of Formulation F4

Zero order

First order

Hixson-Crowell

Higuchi Release

Korsmeyer-Peppas
Release kinetic study of Formulation F5
Release kinetic study of Formulation F6

**Zero order**

- $R^2 = 0.976$

**First order**

- $R^2 = 0.7949$

**Hixson-Crowell**

- $R^2 = 0.9514$

**Higuchi Release**

- $R^2 = 0.5657$

**Korsmeyer-Peppas**

- $R^2 = 0.9798$
Release kinetic study of Formulation F7
Release kinetic study of Formulation F8

Zero order

First order

Hixson-Crowell

Higuchi Release

Korsmeyer-Peppas

\[ R^2 = 0.9325 \]

\[ R^2 = 0.9315 \]

\[ R^2 = 0.9907 \]

\[ R^2 = 0.9796 \]

\[ R^2 = 0.9835 \]
Release kinetic study of Formulation F9

The parameters obtained in all the release mechanism of the drug, applied to mathematical models of drug release are shown in Table 6. *In vitro* dissolution results for all the formulations are evaluated by Zero-order, First-order, Hixson-crowell, Higuchi and Korsmeyer-peppas model. Formulation F1 has shown rapid disintegration (within 60min) in the acidic medium (pH-2). Therefore, the correlation coefficients and the diffusional exponents for these formulations could not be calculated. The release kinetics
follows both the kinetics, say, formulation F2 to F6 fit to korsmeyer-peppas and F7 to F8 to hixson-crowell plots. With reference to diffusional exponent (n) values of korsmeyer-peppas plots, it shows case II transport (values of n is 0.45<n<0.89) (Costa and Lobo, 2001; Abdelbary et al., 2008).

### Table 6 Release kinetics of Met from the prepared formulations (F1-F9)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order plots</th>
<th>First order plots</th>
<th>Hixson-crowell plots</th>
<th>Higuchi plots</th>
<th>Korsmeyer-peppas plots R²</th>
<th>Diffusional exponent (n)</th>
<th>Order of release</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>F2</td>
<td>0.9808</td>
<td>0.9143</td>
<td>0.8484</td>
<td>0.9292</td>
<td>0.9862</td>
<td>0.9508</td>
<td>Erosion</td>
</tr>
<tr>
<td>F3</td>
<td>0.977</td>
<td>0.9887</td>
<td>0.9816</td>
<td>0.9899</td>
<td>0.9916</td>
<td>0.9764</td>
<td>Erosion</td>
</tr>
<tr>
<td>F4</td>
<td>0.9773</td>
<td>0.9161</td>
<td>0.9648</td>
<td>0.9377</td>
<td>0.9867</td>
<td>0.9417</td>
<td>Erosion</td>
</tr>
<tr>
<td>F5</td>
<td>0.9911</td>
<td>0.9178</td>
<td>0.9786</td>
<td>0.9638</td>
<td>0.9927</td>
<td>0.9563</td>
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</tr>
<tr>
<td>F6</td>
<td>0.976</td>
<td>0.7949</td>
<td>0.9514</td>
<td>0.9657</td>
<td>0.9798</td>
<td>0.9533</td>
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<tr>
<td>F7</td>
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<td>0.9428</td>
<td>0.984</td>
<td>0.9595</td>
<td>0.9679</td>
<td>0.9258</td>
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</tr>
<tr>
<td>F8</td>
<td>0.9525</td>
<td>0.9315</td>
<td>0.9907</td>
<td>0.9796</td>
<td>0.9836</td>
<td>0.9736</td>
<td>Diffusion</td>
</tr>
<tr>
<td>F9</td>
<td>0.965</td>
<td>0.9322</td>
<td>0.9903</td>
<td>0.9797</td>
<td>0.9901</td>
<td>0.9827</td>
<td>Diffusion</td>
</tr>
</tbody>
</table>

Formulations F7 and F8 best fit to Hixson-crowell based on the assumption that release rate is controlled by the dissolution rate of drug particle (Costa and Lobo, 2001) whereas F9 best fit to both krosmeyer & Hixson patterns.

### 2.6 SUMMARY

In this Chapter, we have considered two hydrophilic polymers CH and HPMC (HPMC K4M and HPMC K100M) for the formulation of interpolymer complex as a drug carrier for highly water soluble metformin. It is observed from drug dissolution study that CH polymer could not sustain the release of metformin more than 60min. Among the IPCs, matrix of CH/HPMC K100M (1:9) retard the metformin release up to 12h and proved to be a better drug carrier than IPCs of CH/HPMC K4M. The high concentration and high viscosity grade of HPMC K100M are highly advantageous towards formation of complex network matrix favouring sustained release pattern. The release kinetics follows both diffusion and non fickian mechanism.