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Biocompatible interpolymers complex matrix tablets - an oral sustained release class-III antidiabetic drug

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Abstract. Development of sustained release formulations of Metformin hydrochloride (Met) having low bioavailability and short half-life is one of the frontier areas of research towards achieving novel drug delivery systems. Towards the same, we have prepared interpolymers complexes (IPCs) of chitosan (CH) and two different viscosity grades of hydroxypropyl methylcellulose - HPMC (K4M and K100M) in various ratios, say, 4:6, 2:8, 1:9, respectively. The IPCs are characterized by Fourier transform infrared spectroscopy (FT-IR) and Thermo gravimetric analysis (TGA) techniques. Drug compatibility study is carried out by FT-IR and powder X-ray diffraction (XRD) techniques. The physical properties and drug content of formulated tablets are evaluated and found to be optimum. In addition, in vitro drug release kinetics is carried out at two different pH, say, 1.2 and 6.8. The release pattern from different polymeric matrices is shown in figure below: a) Chitosan, HPMC K4M and HPMC K100M b) IPCs of CH/HPMC K4M in [2:3, 1:4 and 1:9 ratios] c) IPCs of CH/HPMC K100M in [2:3, 1:4 and 1:9 ratios]. From the study, it has been observed that the drug release is sustained for a period of 12h in 1:9 ratio of CH: K100M IPC due to the formation of complex network matrix.

1. Introduction

In many therapies, sustained release preparations are considered desirable due to greater availability of drug over extended period of time. It is chosen as an important area of research in the field of pharmaceutical and health care sectors. Different types, grade and concentration of polymers prolong the release rate of active drug from the formulation. Encapsulation of the drug inside a hydrophobic polymer matrix could controls the release rate of drugs. Thus, it brings about greater bioavailability at a lower dosage of drug. Towards this, a hydrophilic polymer is considered as an ideal drug carrier to arrive at a sustained release oral formulation [1-4].

HPMC is one such hydrophilic polymer that controls drug release by its rapid hydration, gelation, swelling and cross linking properties [5,6]. The importance behind hydroxypropyl methylcellulose based formulations, imparts steady rate of drug release irrespective of processing techniques involving several factors like reduced particle size of a drug, compression and compaction and addition of a lubricant [7]. Another valuable polymeric material is Chitosan, widely used drug carrier; possess bioadhesive, biodegradability, mucoadhesivity, low toxicity and germicidal effect [8-15]. Chitosan broadly used in biomedical field [16,17] and as a hydrogel component in health sector



[18-20]. Due to the presence of amino and hydroxyl functional groups in the structure are favorable for the formation of IPC and can be easily blended with other polymers [21-23]. Metformin is used for treating type II diabetes belongs to biguanide group [24], in its structure and is categorized as Biopharmaceutics classification system (BCS) class III drug showing 40%-60% bioavailability and has shorter half life could be used as anticancer agent [25,26]. Quite a few reports are available regarding the formulation of sustained release metformin tablet with different types and grades of polymers or their combinations. Wadher et al. used combination of hydrogenated castor oil with stearic acid to sustain the metformin release. Sahu Manoranjan reported that HPMC and polyvinylpyrrolidone in a suitable ratio was able to control the release rate of metformin. Several grades of hydroxypropyl methylcellulose are utilized for controlling metformin as reported by Bagyalakshmi et al.

Present study mainly focused on the preparation of IPC matrix of CH/HPMC at different compositions. Metformin loaded IPC matrix tablet is monitored for drug release profile at two different pH values, say, 1.2 and 6.8. Selection of polymers mainly chosen due to their pharmaceutical applications and are designed to arrive an adjustable drug carrier system for sustained release of highly water soluble metformin.

2. Experimental

2.1. Materials

Metformin HCl and HPMC K4M, Mn= 86000, viscosity 4000 cps and HPMC K100M, Mn= 150,000, viscosity 10,000 cps were obtained from Cipla research laboratories. Low molecular weight of CH was obtained from Sigma Aldrich. All excipients used were analytical research grade.

2.2. Characterization

Fourier transform infrared spectroscopy (FT-IR) conducted for the prepared CH/HPMC IPCs in the wavelength range 500–4000 cm^{-1} . X-ray diffraction (XRD) technique used to analyse individual polymers, IPCs and IPCs with metformin hydrochloride are. Thermal analysis was carried out at the ranges of 30°C to 700°C for CH, K100M and CH: K100M (1:9) by Thermo gravimetric analysis (TGA) techniques. Thickness is measured by Vernier caliper. UV Visible spectrophotometer and dissolution apparatus is used to analyse content of the drug and release of drug from the different formulations respectively.

2.3. IPCs preparation method for CH, HPMC K4 and HPMC K100

A known quantity of CH was dissolved in acetic acid (1% v/v) under stirring condition for 2h till bubble free homogeneous solution obtained. HPMC K4 and HPMC K100 were dispersed in distilled water and agitate for 2h. CH solution mixed with HPMC K4 and K100 solution separately and stirred for 3h. Obtained solution dried under hot air oven at 90°C. Collected IPCs were ground and sieved and stored with air tight closed container for further study. CH and HPMC solutions were prepared at different compositions (4:6, 2:8, 1:9) to prepare IPCs.

2.4. Preparation of sustained release matrix tablet

Weight granulation technique is used to prepare sustained release tablet for formulation F1 to F9. Weighed amount of all ingredients were mixed properly. Binding agent PVPK30 mixed with isopropyl alcohol and added to the mixture to obtained a dough mass. Obtained dough mass pass through 10 mesh sieve and dried at 50°-60°C. Obtained granules again passed through 16 mesh sieve to avoid agglomeration. Granules were weighed as per the prescribed dosage form and compressed in a cadmach single punching machine by 12mm round biconcave punch to obtain 850mg tablet. Each tablet contains 500mg of metformin and other excipients mention in Table 1.

Table 1. Formulation of metformin HCl matrices (850mg) and their composition (mg)

Code	Drug	CH	HPMC		CH/K4M IPC	CH/K100M IPC	Lactose	PVP- K30	Mg Stearate	Talc
			K4M	K100M						
F1	500	227	-	-	-	-	82	30	6	5
F2	500		227		-	-	82	30	6	5
F3	500	-	-	227	-	-	82	30	6	5
F4	500	-	-	-	227(4:6)	-	82	30	6	5
F5	500	-	-	-	227(2:8)	-	82	30	6	5
F6	500	-	-	-	227(1:9)	-	82	30	6	5
F7	500	-	-	-	-	227(4:6)	82	30	6	5
F8	500	-	-	-	-	227(2:8)	82	30	6	5
F9	500	-	-	-	-	227(1:9)	82	30	6	5

2.5. Evaluation of sustained release tablet

2.5.1. Weight variation test for tablet

Randomly selected 20 tablets were taken from each formulation and weighed by digital balance individually. The average weights were calculated and mean values were determined. It should not deviate more than $\pm 5\%$ as per the Indian Pharmacopeia (IP).

2.5.2. Tablet thickness test

To determine the uniformity and physical dimension of prepared tablet, thickness is measured by Vernier callipers for 20 tablets randomly selected from each formulation.

2.5.3. Hardness test

Randomly selected 10 tablets from each group are used to determine the hardness of the prepared tablet using Monsanto hardness tester [27]. This result provides the strength of the tablet.

2.5.4. Tablet friability

Previously weighed 10 tablets were kept inside the Roche's friabilator for 15min under 100 rpm. After friabilation tablets were de-dusted and weight accurately and % of loss was calculated. As per IP limit for friability should be less than 1%.

2.5.5. Drug content of tablet

Randomly selected 10 tablets from each group is crushed and dissolved in water. Obtained solution was filtered and sample was determined under UV Visible spectrophotometer at 232 nm.

2.5.6. In-vitro drug release study

Dissolution apparatus is used to determine drug release rate for all the formulations. Two, different pH like pH-2 and pH-6.8 are used to determine the drug release. Dissolution apparatus contain 900 ml of pH solution at 100rpm and temperature maintain at $37 \pm 0.5^\circ\text{C}$. At regular intervals of time, 5ml sample were withdrawn and replaced by fresh solution and the absorbance was measured at 232 nm.

3. Results and discussion

FTIR spectra of chitosan, HPMC K4M/ HPMC K100M and their IPCs respectively shown in figure 1 (a,b). 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. Broadening of peaks has been observed at 3444 cm^{-1} which is due to the intermolecular bonding between CH/HPMC polymers during the formation of IPCs [28,29].

The FTIR spectrum in figure 2 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. In the

similar way, XRD pattern in figure 3 confirms that metformin has shown an intense sharp peak due to the crystalline nature of 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 concluded that the peak intensity and position has been changed. This proves that individual polymers and their IPCs are highly compatible with the drug metformin.

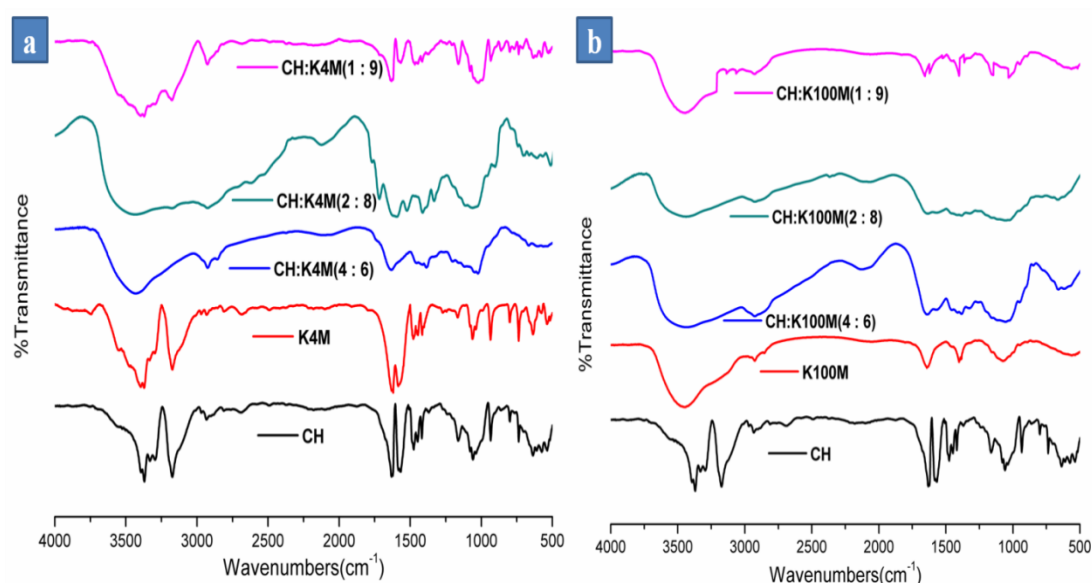


Figure 1. FTIR spectra of a) CH, K4M and IPCs of CH/K4M (4:6, 2:8, 1:9) and b) CH, K100M and IPCs of CH/K100M (4:6, 2:8, 1:9)

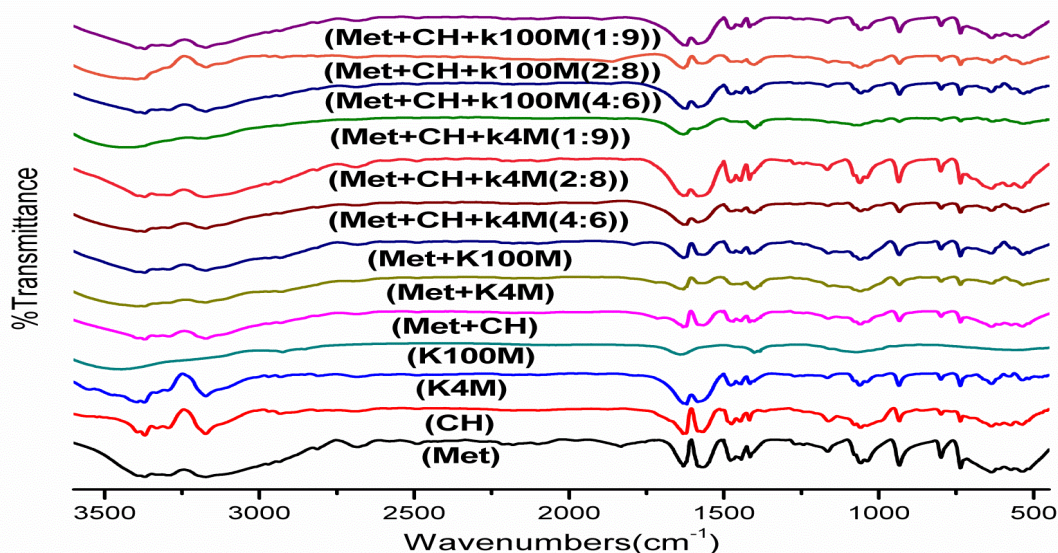


Figure 2. FT-IR spectra of metformin hydrochloride, pure polymers (CH, HPMC K4M/K100M) and metformin with pure polymers and their IPCs in different ratios

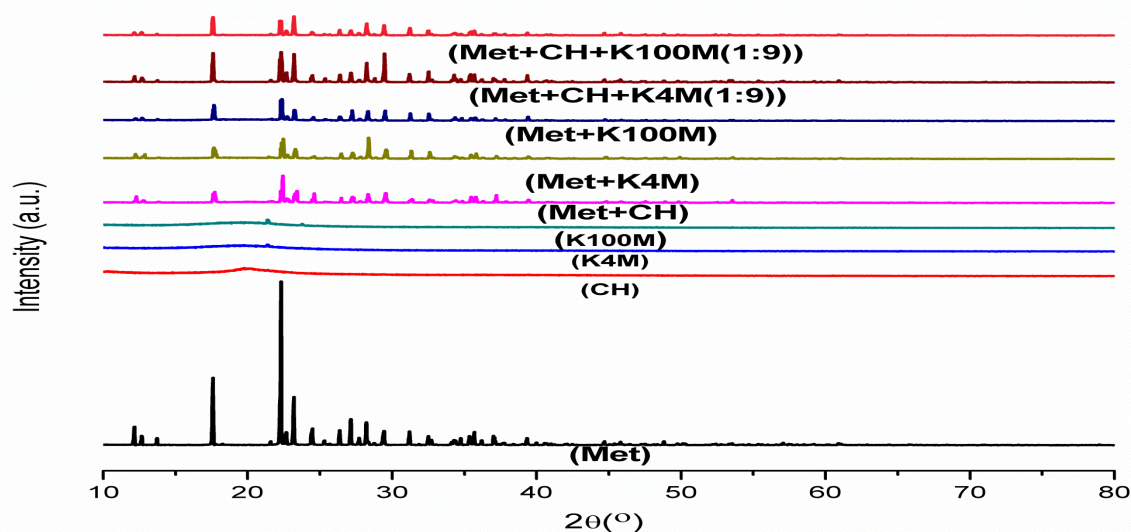


Figure 3. X-ray diffraction pattern of metformin hydrochloride, pure polymers (CH, HPMC K4M/K100M) and metformin hydrochloride with pure polymers and their IPCs in (1:9) ratio

Figure 4 reveals two stages of thermal degradation for CH, K100M and IPCs of CH: K100M (1:9). The first stage of thermal degradation confirms 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 chitosan chains [30,31,32], cellulose ethers dehydration [30] and degradation of CH and K100M in IPC respectively. Thermal behaviour of IPC shows its characteristic changes as compared to individual polymers.

Metformin tablets (Formulation F1-F9) were evaluated for their physicochemical properties that play a vital role in the drug release pattern. The comparison study of physicochemical properties for all formulations has shown in table 2. Obtained results for weight variation was found to be within the prescribed limit such as $\pm 5\%$ as per IP. The average weight for all formulations was found to be in the range of 847.31 ± 1.31 to 850.79 ± 1.03 mg. The uniform thickness was obtained throughout all the formulations and was well within the range of 5.17 ± 0.35 to 5.68 ± 0.15 mm. The formulated tablets passed through the hardness and friability tests as per the standard limits, the hardness ranging from 6.02 ± 0.17 to 7 ± 0.85 and percentage of friability obtained below 1%. Drug content for each formulation was within the standard limit $97.5 \pm 1\%$ to $100.5 \pm 2\%$. The prepared tablets are thus mechanically stable for further study.

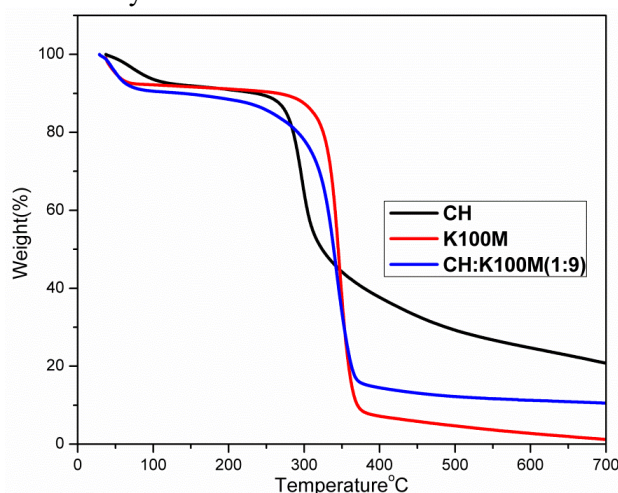


Figure 4. Thermogravimetric curves of CH, K100M and CH:K100M (1:9) IPC

Table 2. Physicochemical properties of prepared tablets

Formulations	Tablet weight variation (mg)	Tablet thickness (mm)	Tablet Hardness (kg/cm^2)	Tablet Friability (%)	Drug content (%)
F1	847.31 \pm 1.31	5.31 \pm 0.72	6.02 \pm 0.17	0.47 \pm 0.02	100.49 \pm 1.78
F2	848.11 \pm 1.3	5.58 \pm 0.69	6.42 \pm 0.14	0.31 \pm 0.32	98.36 \pm 0.32
F3	847.53 \pm 1.9	5.63 \pm 0.09	7 \pm 0.85	0.28 \pm 0.61	98.17 \pm 0.71
F4	848.37 \pm 1.32	5.17 \pm 0.35	6.37 \pm 0.03	0.56 \pm 0.14	99.09 \pm 1.39
F5	849.23 \pm 1.06	5.19 \pm 0.04	6.43 \pm 0.83	0.47 \pm 0.33	98.95 \pm 0.33
F6	850.37 \pm 1.09	5.27 \pm 0.48	6.59 \pm 0.33	0.46 \pm 0.57	97.46 \pm 0.91
F7	849.27 \pm 1.31	5.31 \pm 0.05	6.49 \pm 0.91	0.37 \pm 0.28	99.95 \pm 0.01
F8	850.39 \pm 1.75	5.68 \pm 0.15	6.72 \pm 0.57	0.17 \pm 0.11	98.31 \pm 1.05

Metformin is a hydrophilic drug, incompletely absorbed in gastro intestinal tract [33] and need to be administered twice and thrice in a day to maintain plasma level of drug. Drug act in different ways to maintain the body sugar level such as slowdown the sugar absorption in small intestine reduces glucose production in liver and utilization of insulin present in body. A few reports confirm that orally metformin can target to small intestine [34,35,36]. The sustained release drug delivery is an ideal approach to prolong its activity, patient compliance [33] and also facilitate complete drug release in small intestine and has been developed using different types and grades of polymer in IPC form. *In-vitro* dissolution time for formulation F1 to F9 tablets show variations in release period ranging from 30min to 12h. This may be attributed to the nature of polymer and their grades used in various proportions in IPC. The metformin bound IPC containing a higher proportion of HPMC (F6 to F9) are found to have better control in drug release rate than individual polymers. This can be attributed to cross linking nature of high viscosity grade HPMC forming complex matrix network with chitosan and also due to the intermolecular -H bonding between CH/HPMC. The gel like matrix could retard the drug release. Formulation F1 showed immediate release of metformin (98.26%) at pH-2 within 30min 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 6h and 8h 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 6h, 8h and 9h respectively. Formulation F7 and F8 have shown 95.7% and 98.19% of drug release with in 9h and 11h respectively due to the gradually increasing concentration of HPMC K100M. In case of F9, the higher viscosity grade HPMC K100M present in highest concentration favored retarded drug release of 97.94% till 12h. Figure 5 shows drug release pattern for different formulations (F1- F9).

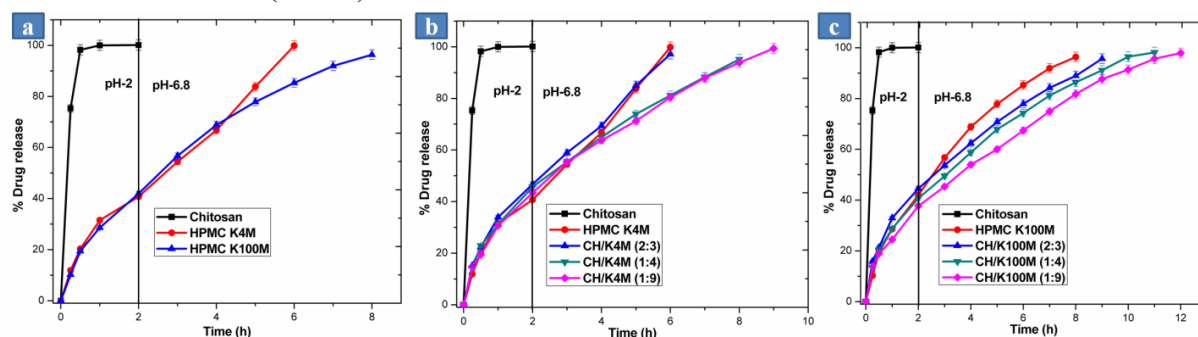


Figure 5. In vitro drug release of metformin from different polymer matrices a) metformin release from polymer Chitosan, HPMC K4M and HPMC K100M b) metformin release from IPCs of CH/HPMC K4M in (2:3, 1:4 and 1:9 ratios) c) metformin release from IPCs of CH/HPMC K100M in (2:3, 1:4 and 1:9 ratios)

3.1. Release kinetic study of Met tablet

The parameters obtained in all the release mechanism of the drug, applied to mathematical models of drug release shows in Table 3. In vitro dissolution results for all the formulations are evaluated by zero-order, first-order, Hixson-crowell, Higuchi and Korsmeyer-peppas release order. Release kinetics follows both the kinetics, say, formulation F1 to F6 fit to Korsmeyer-peppas and F7 to F9 to Hixson-crowell plots. With reference to diffusional exponent (n) values of Korsmeyer-peppas plots, it shows anomalous transport or non Fickian mechanism (values of n is $0.5 < n < 1$) [37]. Formulations F7 to F9 best fit to Hixson-crowell based on the assumption that release rate is controlled by the dissolution rate of drug particle [37].

Table 3. Release kinetic model for metformin from formulations F1 to F9

Batch. no	R ² Values						Release kinetic order
	Zero order plots	First order plots	Hixson- crowell plots	Higuchi plots	Korsmeyer-peppas plots R ²	Diffusional exponent value (n)	
F1	N/A	N/A	N/A	N/A	N/A	N/A	
F2	0.9808	0.9143	0.8484	0.9292	0.9862	0.9508	Non fickian
F3	0.977	0.9887	0.9816	0.9899	0.9916	0.9764	Non fickian
F4	0.9773	0.9161	0.9648	0.9377	0.9867	0.9417	Non fickian
F5	0.9911	0.9178	0.9786	0.9638	0.9927	0.9563	Non fickian
F6	0.976	0.7949	0.9514	0.9657	0.9798	0.9533	Non fickian
F7	0.9672	0.9428	0.984	0.9595	0.9679	0.9258	Diffusion
F8	0.9525	0.9315	0.9907	0.9796	0.9836	0.9736	Diffusion
F9	0.965	0.9322	0.9903	0.9797	0.9901	0.9827	N/A

4. Conclusion

In this study, we have successfully designed biocompatible IPC matrix as a drug carrier for highly water soluble metformin drug in order to control the release rate. Chitosan polymer could not sustain metformin release more than 30min. IPC matrices of CH/HPMC (K4M and K100M) have proved to be a useful drug carrier to retard the metformin release up to 12h. The high concentration and high viscosity grade of HPMC (K100M) are highly advantageous towards formation of complex network matrix favoring sustained release pattern. Thus, the designed IPCs prepared by hydrophilic polymers in varying proportions are quite promising for designing sustained oral drug delivery systems.

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