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Design and *In Vitro* Evaluation of Interpolymer Complex Bound Metformin Sustained Release Tablet

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ABSTRACT: Metformin hydrochloride shows high solubility and incomplete absorption in biological system. To control the release pattern of such a drug, interpolymer complexes (IPCs) have a greater advantage over the individual polymers. In view of that, hydrophilic chitosan and hydroxypropyl methylcellulose (HPMC K4M) IPCs are developed at different ratios (1 : 1, 1 : 2, 1 : 3, and 1 : 4) and characterized by thermogravimetric analysis, Fourier transform infrared spectroscopy, and X-ray diffraction studies. Different formulations (F1–F10) are developed using individual polymers and IPCs of hydrophilic polymers. Addition of hydrophobic shellac and beeswax to IPCs extends the release rate of metformin. The physical properties and drug content values of the tablets were determined and found to be within the standard limits. Based on the results of dissolution study, it is found that formulation F10 containing 1 : 4 IPC and beeswax has shown good sustained release for a period of more than 10 h. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 41018.

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INTRODUCTION

Metformin hydrochloride (Met) is the chosen antidiabetic drug that belongs to biopharmaceutics classification system (BCS) Class III drug. This is the most preferred antidiabetic drug with minimum side effects, reduces glucose production and its subsequent absorption.[1] As it is characterized by high solubility in water[2] low permeability in cell membranes,[3,4] and shorter biological half-life of 1.5–4.5 h with only 40–60% bioavailability,[5,6] sustained release tablets (SRT) are considered to overcome these shortcomings. Thus, SRT is considered as the most desirable dosage form for treating various diseases, such as alzheimer, cancer, tuberculosis, heart disease, and kidney disease including diabetes. These liberate the active drug and provide effective plasma drug concentration over a period of time[7,8] to bring about the desired therapeutic action. In addition, the drug release depends on various factors, such as particle size of active drug, different additives and excipients, drug carriers, and surfactants used.[9–20] The role played by polymeric matrix as a drug carrier is quite significant in extending the drug release pattern. The probable processes that control the release rate of active drug involve swelling of the polymer matrix that facilitates slow and steady diffusion of the active drug and eventually the swollen polymer matrix is removed from the system.[21] The hydrophilic polymer matrix rapidly diffuses the drug molecule that gets completely soluble in water. To overcome this and to facilitate controlled release of the drug over a desired period of time, hydrophobic polymers (waxes) are added as an additive to interpolymer complexes (IPCs).[22]

A few literature reports on Met indicate the use of polymers as such or that is used as a polymeric blend to make it a sustained release form. Corti et al. used the blend of chitosan (CH), hydroxypropyl cellulose, EudragitRL100-55, and other excipients for the sustained release of Met dispersed in hydrophobic triacetyl-β-cyclodextrin.[23] Wadher et al. reported the significance of combinations of hydrophobic polymer (ethyl cellulose) in the presence of hydrophilic polymer (Eudragit RSPO and RLPO) toward controlling the drug release rate of Met as compared to individual hydrophilic polymers.[24] Further, it has also been reported, based on comparison study of different grades of hydroxypropyl methyl cellulose, that hydroxypropyl methylcellulose (HPMC) K100M shows greater effect in controlling the Met release due to its high viscosity.[25] A very few reports are available with regard to the use of IPCs as a drug carrier for other types of drugs and not for Met. The chitosan/Carbopol IPC shows pH-independent sustained release profile of theophylline from the tablets that contain different molecular weight CH. Imwitor 900 K, a hydrophobic waxy retardant polymer used as an efficient matrix forming agent, with hydrophilic IPCs

Table I. Formulation of Met 850 mg Tablets

Batch no	Drug (mg)	CH (mg)	HPMC K4M (mg)	Shellac (mg)	CH-K4M IPCs (mg)	Lactose (mg)	PVP-K30 (mg)	Mg Stearate (mg)	Talk (mg)	Total weight of tablet (mg)
F1	500	226	-	-	-	82	30	5	5	850
F2	500		226	-	-	82	30	5	5	850
F3	500	-	-	-	226(1 : 1)	82	30	5	5	850
F4	500	-	-	-	226(1 : 2)	82	30	5	5	850
F5	500	-	-	-	226(1 : 3)	82	30	5	5	850
F6	500	-	-	-	226(1 : 4)	82	30	5	5	850
F7	500	-	-	113: 113(1 : 4) 1 : 1		82	30	5	5	850
F8	500	-	-	113: 113(1 : 4) 3 : 1		82	30	5	5	850
F9	500	-	-	113: 113(1 : 4) 3 : 1 (IPCs)		82	30	5	5	850
F10	500	-	CH-K4M (1 : 4):Beeswax 1 : 1 (ECM)			82	30	5	5	850

of Chitosan/hyaluronate sodium, pectin, and sodium alginate controls the release rate of nicorandil drug to about 8 h.[26–28]

From the above literature survey, it is obvious that the role of IPCs toward sustained release of Met is yet to be unequivocally proved. Toward the same, in the current study, IPCs of hydrophilic and hydrophobic matrix systems have been designed. In addition, their role as drug carrier for controlled release of Met has been discussed in detail.

EXPERIMENTAL

Materials and Methods

Analytical grade metformin hydrochloride and hydroxypropyl methylcellulose (HPMC, $M_n = 86{,}000$, and viscosity 4000 cps) were obtained from Cipla Research Laboratories, India. Refined bleached Shellac (Food grade) obtained from Mylon, Hyderabad, India. White beeswax was obtained from Nice Chemicals Private Limited, Cochin, India. Chitosan analytical research (AR) grade, low molecular weight, viscosity 20–300 cps was purchased from Sigma Aldrich and used as received. All other excipients were of analytical grade, and they are used as received.

Preparation of CH, K4M, and Shellac IPCs

To about 20 mL of 1% v/v acetic acid solution, added a known quantity of CH slowly with continuous stirring for 2 h, until a clear solution was obtained. A known quantity of K4M solution was prepared separately in 30 mL of water with 2 h stirring. The prepared CH solution was added into K4M solution in stirring conditions for 3 h at room temperature. The resultant solution was dried in a hot air oven at 90°C. Dried samples were ground and sieved (no.80 mess size) and stored in desiccator.

CH–K4M solutions were mixed in different proportions (1 : 1, 1 : 2, 1 : 3, and 1 : 4) to prepare IPCs. Similarly, CH–K4M and shellac or beeswax IPC was also developed.

Thermogravimetric Analysis

Thermal analysis was carried out, using a thermogravimetric analyzer (Perkin Elmer STA 6000, Diamond). The sample (2–6 mg) was analyzed in temperature ranges 25–700°C at the scan rate of 10°/min in nitrogen atmosphere.

Fourier Transform Infrared Spectroscopy

The infrared absorption spectra of CH, K4M, and shellac and their IPCs were analyzed, using a FTIR spectrophotometer (IR-Affinity-1, Shimadzu, Japan).

X-ray Diffraction Studies

X-ray diffraction (XRD) patterns of all individual polymers, IPCs and Met with different IPCs were analyzed using powder X-ray diffractometer (Bruker D8 Advance, Germany) in the angular range of 10–80° with step size 0.02, scanning rate 4°/min.

Preparation of Met Tablets

Formulations F1–F9 was prepared by wet granulation technique and formulation F-10 by emulsion congealing method to avoid poor solubility issue between hydrophobic and hydrophilic polymers. The prepared granules were compressed (CMB4 D-27, Cadmach Engg, Ahmedabad, India) using 12 mm round biconcave punch. Each 850 mg tablet contains 500 mg of Met and other pharmaceutical excipients as listed out in Table I.

Wet Granulation Method (Formulation F1–F9)

Weighed amount of all ingredients (listed in Table I) was passed through sieve no-44 and mixed uniformly for 15 min except PVPK30. Then PVPK30 (binder) dissolved with isopropyl alcohol (as binder solution) was mixed to form a dough mass. The dough mass was passed through sieve no.10 and dried at 50–60°C till the loss on drying is less than 1–2% w/w and again passed through sieve no.16 and the obtained granules were taken for compression of tablet.

Table II. FTIR Absorption Bands of CH, K4M, Shellac, IPCs of CH/K4M and CH/K4M/Shellac

Pure polymers and their IPCs								
Assignment	CH	K4M	CH/K4M (1 : 1)	CH/K4M (1 : 2)	CH/K4M (1 : 3)	CH/K4M (1 : 4)	Shellac	(CH/K4M)/Shellac (1 : 3) IPCs
OH— and NH—stretching	3337	3444	3419	3421	3421	3444	3473	3437
CH—stretching	2878	2932	2885	2926	2924	3178	2931	2927
			2839			2926	2856	2856
C=C stretching							1717	1724
							1641	1631
							1631	
NH—bending (amide II)	1655	1647	1649	1641	1710	1641		
			1548	1535	1535			
CH— and OH—vibrations	1422	1457	1427	1369	1369	1398	1467	1462
	1380	1376	1371			1384	1382	1382
		1316						
C—N stretching	1257							
Antisymmetric stretching of the C—O—C bridge	1157		1155			1120		
Skeletal vibrations involving the C—O stretching	1087		1078	1058	1070	1068	1064	1066
			1060				1035	1001
O—H bending		947	941	943	950	952		
=C—H bending							997	943
							923	723
							723	

Emulsion Congealing Method for formulation (F10)

In this method, appropriate amount of Met was incorporated into beeswax by melting in a water bath at 65°C. The mixture was poured into previously prepared CH and K4M solution in a stirring condition for 3 h to obtain a homogeneous clear solution and dried at room temperature. Dried samples were ground, sieved (no.80 mess size), and stored in desiccator.

Evaluation of the Prepared Tablet

Weight Variation Test. Twenty tablets were randomly selected and weighed individually from each formulation. The average weight of tablet was calculated.

Tablet Thickness Test. Tablet thickness was measured using Vernier calipers for randomly selected 20 tablets. Control of physical dimensions of the tablets such as thickness is essential for consumer acceptance and tablet-to-tablet uniformity.

Hardness Test. Hardness was determined for randomly selected 10 tablets from each formulation by Monsanto Hardness Tester.

Tablet Friability. Ten tablets were weighed and placed in the Roche's friabilator for 15 min/100 rpm. The tablets were removed from the drum, dedusted and accurately weighed. The difference in the weight loss was noted and expressed as percentage. It should be less than 1%.

Drug Content Uniformity. Randomly selected 10 tablets from each formulation were weighed individually, crushed and hydrated in water. The solution was filtered by whatman no.42 (2.5 μm) filter paper, and the drug content was determined by UV spectrophotometer (Jasco V-670, Japan) at 232 nm with a suitable dilution.

***In Vitro* Dissolution Test.** Drug release studies for all formulations were carried out using single bucket USP Type-I basket apparatus (Secor India Lab), at 100 rpm bearing 900 mL of pH 2 or pH 6.8 medium at 37 ± 0.5°C. The samples (5 mL) were withdrawn at required intervals of time and replaced by the same amount of fresh solution (pH 2 or pH 6.8). Absorbance was determined by UV spectrophotometer at 232 nm.

RESULTS AND DISCUSSION

FTIR Characterization of the CH/K4M and CH/K4M/Shellac IPCs

Fourier transform infrared spectroscopy (FTIR) data with all assignment of the absorption bands including pure polymers and IPCs are summarized in Table II.

Figure 1(a) shows a high intense absorption band at 1655 cm^{-1} for $-NH_3^+$ groups present in CH and 3444 cm^{-1} representing —OH groups present in K4M. In case of IPCs, the reduced intensity and broadening of bands at 3444 and 1631 cm^{-1} can be inferred to intermolecular H-bonding between CH/K4M polymers. Reduced intensity and broadening of peaks suggested the formation of IPCs between CH and nonionic K4M polymers.[26,29,30]

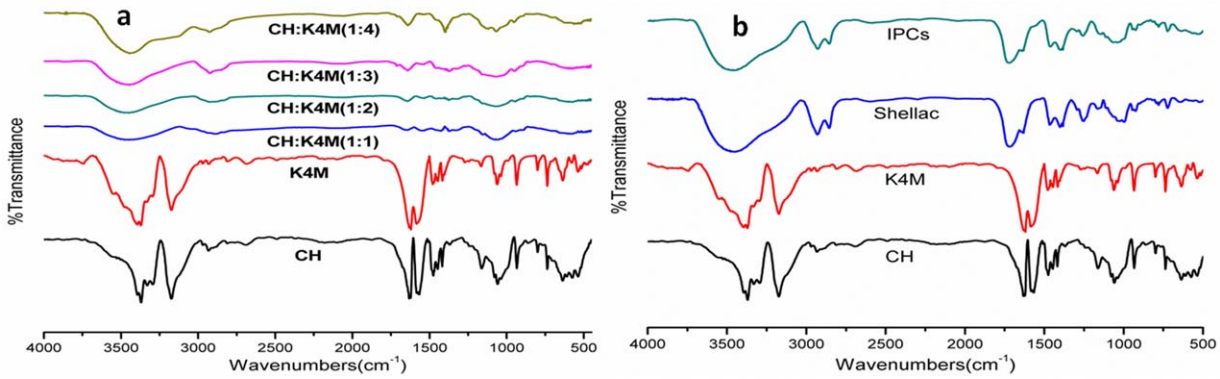

Figure 1. FT-IR spectra of (a) CH, K4M, and IPCs of CH/K4M (1 : 1, 1 : 2, 1 : 3, and 1 : 4) ratios and (b) CH, K4M, and Shellac and their IPCs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 1(b) shows the FTIR spectra of IPC of CH/K4M/shellac. In the spectrum of shellac, OH— stretching at 3473 cm^{-1}; CH stretching at 2931and 2856 cm^{-1}, C═C stretching at 1717, 1641, and 1631 cm^{-1}, CH— vibrations at 1467 and 1382 cm^{-1}, skeletal vibration of C—O stretching at 1064 and 1035 cm^{-1} and ═C—H bending at 997, 923, and 723 cm^{-1} were observed. The intense peak shown in CH and K4M pure polymers were quite different from the peaks observed for IPC spectra. The broadening of bands and intensity of peaks in IPC is same as that of shellac, indicating that the added shellac has no role in the formation of IPC. This may be attributed to poor solubility in aqueous medium, poor mechanical property, and instability.[31,32] Further, it has been extensively reported for its application in pharmaceutical and food industry[33,34] as a coating material rather than as polymeric blend additive.

Thermogravimetric Analysis of the CH, K4M, and CH/HPMCK4M IPCs

Figure 2 shows the results of thermogravimetric analysis of pure polymer and their (CH/ K4M) IPCs in different ratios, say, 1 : 1, 1 : 2, 1 : 3, and 1 : 4. It consists of two stages of thermal degradation the first is attributed to the weight loss of up to 2–8% at the temperature range of 55–80°C due to the presence of moisture in the compound. The initial weight loss for pure CH is 7% at 78°C, whereas K4M shows 3% weight loss at 57°C. The second stage of thermal degradation occurs at the temperature range of 250–410°C for all compounds. The pure CH polymer shows 65% weight loss at 299°C with a residual mass of 19.45% due to the depolymerization of CH chains.[35,36] K4M loses 97% weight at 354°C with zero residual mass due to the degradation of cellulose ethers, along with dehydration.[35] CH : K4M (1 : 1, 1 : 2, 1 : 3, and 1 : 4) IPCs show 75–86% weight loss in the temperature range of 350–365°C with residual mass of 2–7% attributed to the degradation of unsaturated CH and K4M in IPCs.

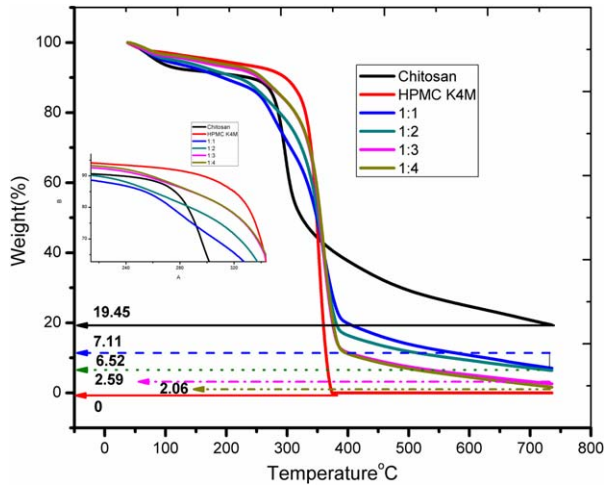

Figure 2. Thermogravimetric curves of CH, K4M, and IPCs of CH/K4M. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

It is observed that IPCs show thermal stability within the range of decomposition temperature of pure polymers. In conclusion, with the increasing ratio of K4M, weight loss of the sample is remarkably increased with decreased residual mass. IPCs show higher decomposition temperature than pure CH and lesser weight loss than K4M. This proves that IPCs show a characteristic thermal behavior different from individual polymers.

XRD Analysis of the CH/K4M IPCs

XRD pattern [Figure 3(a)] of K4M shows a broadened peak that corresponds to the amorphous state, whereas, pure CH shows a dominant sharp peak ($2\theta = 19.91$) confirming the presence of crystalline nature, which is in good agreement with earlier reports.[36] A clear decrease in crystallinity and peak intensity of CH is found in IPCs due to the addition of K4M. The XRD patterns are more comparable to IPCs than pure K4M with the increasing ratio of K4M, indicating that 1 : 4 ratio is more miscible than 1 : 1 ratio proving that physical state of K4M is not much altered during the formation of IPCs.

Figure 3(b) shows high intense sharp peak of Met, whereas, pure polymers (CH and K4M) show broadened peaks. XRD of mixture of Met and IPCs of CH/K4M of different ratios confirm the compatibility of Met with IPC. It also reveals that there is no significant change in peak intensity and peak position. It is confirmed that there is no physical interaction between IPCs and Met thereby proving the role of IPC as an ideal drug carrier.

Physical Properties of the Met Tablet

In the present work, 10 formulations of Met tablets were evaluated for their physical properties to correlate their effect on

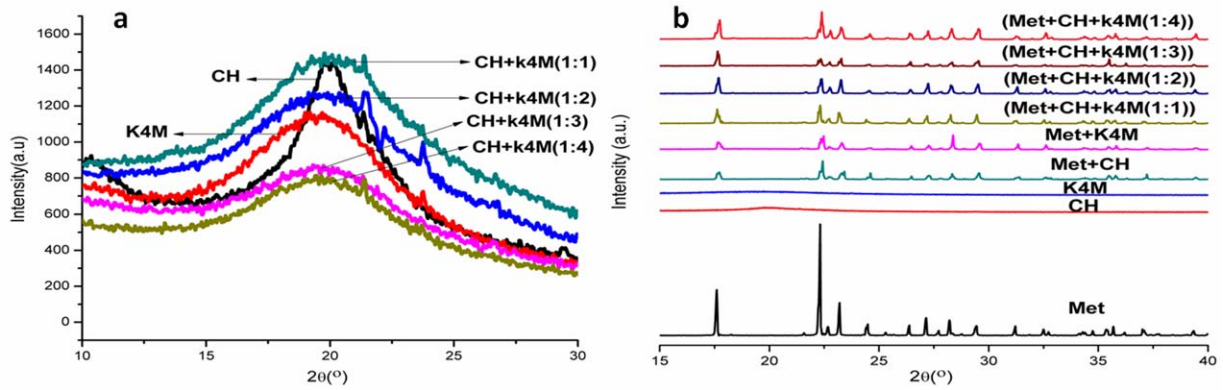

Figure 3. XRD patterns of (a) CH, K4M, and IPCs of CH/K4M and (b) Met, Met with pure polymers and IPCs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the release rate of drug from the tablet. A comparative study of physical properties for all the formulations is given in Table III. The weight variation test proves that the tablet belongs to the specified range. It is clearly shown that all tablets passed the weight variation test ranging from 848.97 to 850.42 mg which lies within the limit of ±5% of average weight as per IP (Indian Pharmacopeia). The thickness of formulated tablets ranges from 4.97 to 5.73 mm.

Hardness is to measure the strength of a tablet, as like friability. It is an important parameter to resist mechanical shocks of handling during manufacture, packaging, and shipping. It is found that hardness of all formulations lies within the range of 9.16 ± 2.22–24.72 ± 1.4 Kg/cm^2. Percentage of friability for all formulations is below 1%, revealing that formulated tablets are mechanically stable as they are within the specified limit.

The drug content in different formulations is found to be uniform and the percentage of drug content is more than 97%. The physical properties of all the formulations are found to be optimum as per the standard limits of IP.

In Vitro Dissolution Study of Met Tablets

Dissolution test determines the amount of drug released in the dissolution media with respect to time. Figure 4(a) represents the percentage of drug release of Met by different formulations at different time intervals. Formulation F1 prepared by pure polymer CH shows immediate drug release (99.69%) within 1 h. HPMC is a pH independent polymer used as tablet binder in film coating and in extended release matrix tablets. We have used K4M in formulation F2 which shows 98.38% release in 4 h. IPCs have been prepared in different ratios say 1 : 1, 1 : 2, 1 : 3, and 1 : 4 between CH and K4M. Increased ratio of K4M was taken for IPCs to prolong the drug release. Formula F3 to F6 is prepared using different IPCs. From the dissolution data, it is found that 1 : 4 ratio of IPCs is able to control the release pattern as compared to other IPCs. It is due to the addition of higher amount of K4M than CH in the ratios. In this study, formulation F3 shows 99.37% of drug release in 4 h and F4, F5 show 97.41 and 92.40% drug release in 5 h, respectively. Formulation F6 is slightly but not significantly able to achieve prolonged drug release for a longer period of time. Formula F6 controls the release of 98.51% of drug for the extended period of 6 h.

Due to the hydrophilic nature of CH, it readily disintegrates the tablet in aqueous buffer solution. K4M is more viscous and forms a gel with aqueous buffer solution. So, it is able to delay the release of Met by forming a gel like structure. In case of IPCs, drug release is controlled better than individual polymers. But to attain a suitable controlled release formulation, we have incorporated hydrophobic polymers (shellac and beeswax) with IPC of CH/K4M (1 : 4) in formulation F7–F10. The matrix surface of waxy polymers acts as a barrier reducing the rate of diffusion of drug.

Table III. Physical Properties of Prepared Tablets

Formulation	Tablet weight variation (mg)	Tablet thickness (mm)	Tablet hardness (kg/cm^2)	Tablet friability (%)	Drug content (%)
F1	848.97 ± 1.67	5.73 ± 0.16	6.17 ± 0.72	0.21 ± 0.06	101.35 ± 2.88
F2	849.4 ± 1.01	5.64 ± 0.32	6.31 ± 0.73	0.16 ± 0.1	97.74 ± 0.54
F3	849.89 ± 1.3	5.67 ± 0.58	7.02 ± 0.69	0.23 ± 0.1	99.09 ± 0.47
F4	850.36 ± 2.04	5.32 ± 0.6	6.68 ± 0.92	0.26 ± 0.09	98.06 ± 0.20
F5	850.23 ± 1.84	5.52 ± 0.44	6.42 ± 0.61	0.11 ± 0.05	98.73 ± 0.47
F6	849.76 ± 2.09	5.37 ± 0.43	6.50 ± 0.73	0.10 ± 0.04	98.46 ± 0.63
F7	850.13 ± 1.95	5.24 ± 0.49	6.47 ± 0.56	0.11 ± 0.05	97.92 ± 0.69
F8	850.42 ± 2 .45	5.2 ± 0.51	6.66 ± 0.8	0.09 ± 0.04	98.82 ±0.6
F9	849.31 ± 1.05	5.37 ± 0.39	6.67 ± 0.78	0.14 ± 0.05	98.87 ± 0.79
F10	849.41 ± 3.05	4.97 ± 0.15	6.21 ± 0.71	0.13 ± 0.02	98.39 ± 0.19

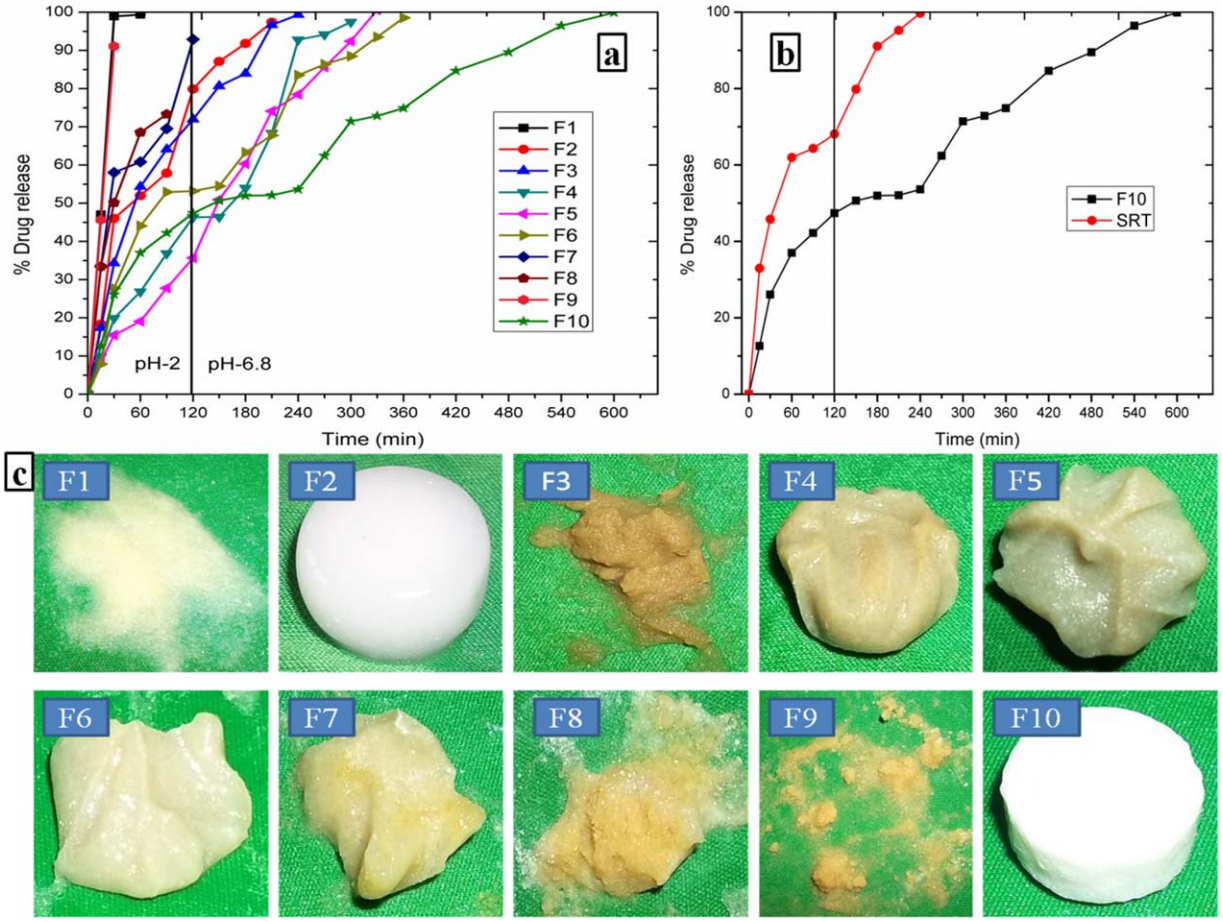

Figure 4. *In vitro* drug release of (a) Met from different polymer matrices (CH, K4M, CH/K4M IPCs, IPC with Shellac and Beeswax), (b) *in vitro* drug release comparison between formulation F10 and SRT, and (c) photograph taken, after 12 h *in vitro* dissolution study of different formulations (F1–F10). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Formulation F7 and F8 contain shellac in gradually increasing ratio with IPC to form a matrix system by wet granulation method. The release rate of Met in formulations F7 and F8 show 92.90 and 81.69% within 2 and 1.45 h, respectively. In formulation F9, shellac is used with CH and K4M to form IPC and shows 91.10% of drug release within 30 min. Immediate release confirms that there is no IPC formed between the polymers as proved by FTIR results. Formulation F10 is prepared by emulsion congealing method with beeswax and IPC of CH and K4M (1 : 4). Formula F10 shows 99.91% of drug release over an extended period of 10 h. Therefore, formulation F10 shows prolonged drug release, probably, due to the reduced penetration of solvent into the matrix and the presence hydrophobic beeswax coated on the surface of drug. Figure 4(b) represents the comparison study between formulation F10 and marketed sustained release Met tablet. SRT shows 99.73% of drug release in 4 h. Figure 4(c) represents the photograph taken after 12 h dissolution study.

Release Kinetic of Met Tablet

The mechanism of the drug release of Met from different matrices shows in Table IV. The release mechanism of Met of different formulations is evaluated based on the theoretical dissolution equations, such as zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer–Peppas model. The obtained results best fit to Korsmeyer–Peppas and Higuchi model. The result reveals that it may be due to the combined effect of diffusion and erosion mechanism.[26] Formula F9 shows immediate drug release in the acidic medium within 30 min and hence the correlation coefficients (R^2) value is not calculated. Thus, the drug release from the different formulations is controlled by both diffusion and erosion processes. The diffusional exponent (n) value obtained for formulation F1, F2, F4, and F5 are greater than 0.89 attributed to erosion control. Thus Met drug release mechanism can be explained well through diffusion and erosion processes.

CONCLUSIONS

This study concludes that IPCs matrix serves as an ideal therapeutic system to control the release of drug better than individual polymers. It acts as an ideal drug carrier for those drugs having poor bioavailability. IPCs were prepared by simple and cost effective technique without crosslinking agent, and can further be optimized and used as an efficient approach for

Table IV. Release Kinetics of Met from the Prepared Formulations (F1–F10)

	R^2 Values						
					Korsmeyer–Peppas plots		
Batch. no	Zero order plots	First order plots	Hixson-Crowell plots	Higuchi plots	R^2	Diffusional exponent (n)	Order of release
F1	0.9992	N/A	0.9156	0.8891	0.9993	0.9095	Erosion
F2	0.9512	0.9041	0.9743	0.9629	0.9922	0.9705	Erosion
F3	0.8897	0.9887	0.9593	0.9916	0.9669		Diffusion
F4	0.9702	0.8693	0.9246	0.9267	0.9928	0.9794	Erosion
F5	0.9911	0.9167	0.9629	0.9182	0.9927	0.9721	Erosion
F6	0.9018	0.8709	0.9638	0.9788	0.966		Diffusion
F7	0.8084	0.7504	0.8563	0.928	0.9269		Diffusion
F8	0.8557	0.9675	0.9382	0.9853	0.9429		Diffusion
F9	N/A	N/A	N/A	N/A	N/A		N/A
F10	0.928	0.6984	0.9327	0.9859	0.9532		Diffusion

industrial preparation. To achieve a suitable sustained release formulation, hydrophobic waxy polymer is added to IPCs to form a suitable matrix that controls the rate of drug release of highly soluble metformin. It is found that formulation F10 shows extended release of Metformin for more than 10 h. It also shows a good fit for Higuchi equation proving diffusion mechanism.

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